Οξεία Καρδιακή Ανεπάρκεια

Νεότερες θεραπευτικές μέθοδοι

Κατερίνα Κ. Νάκα MD, PhD(UK), FESC

Αναπλ. Καθηγήτρια Καρδιολογίας

Πανεπιστήμιο Ιωαννίνων, Σχολή Επιστημών Υγείας, Τμήμα Ιατρικής

2η Καρδιολογική Κλινική, ΠΓΝ Ιωαννίνων

DISCLOSURES

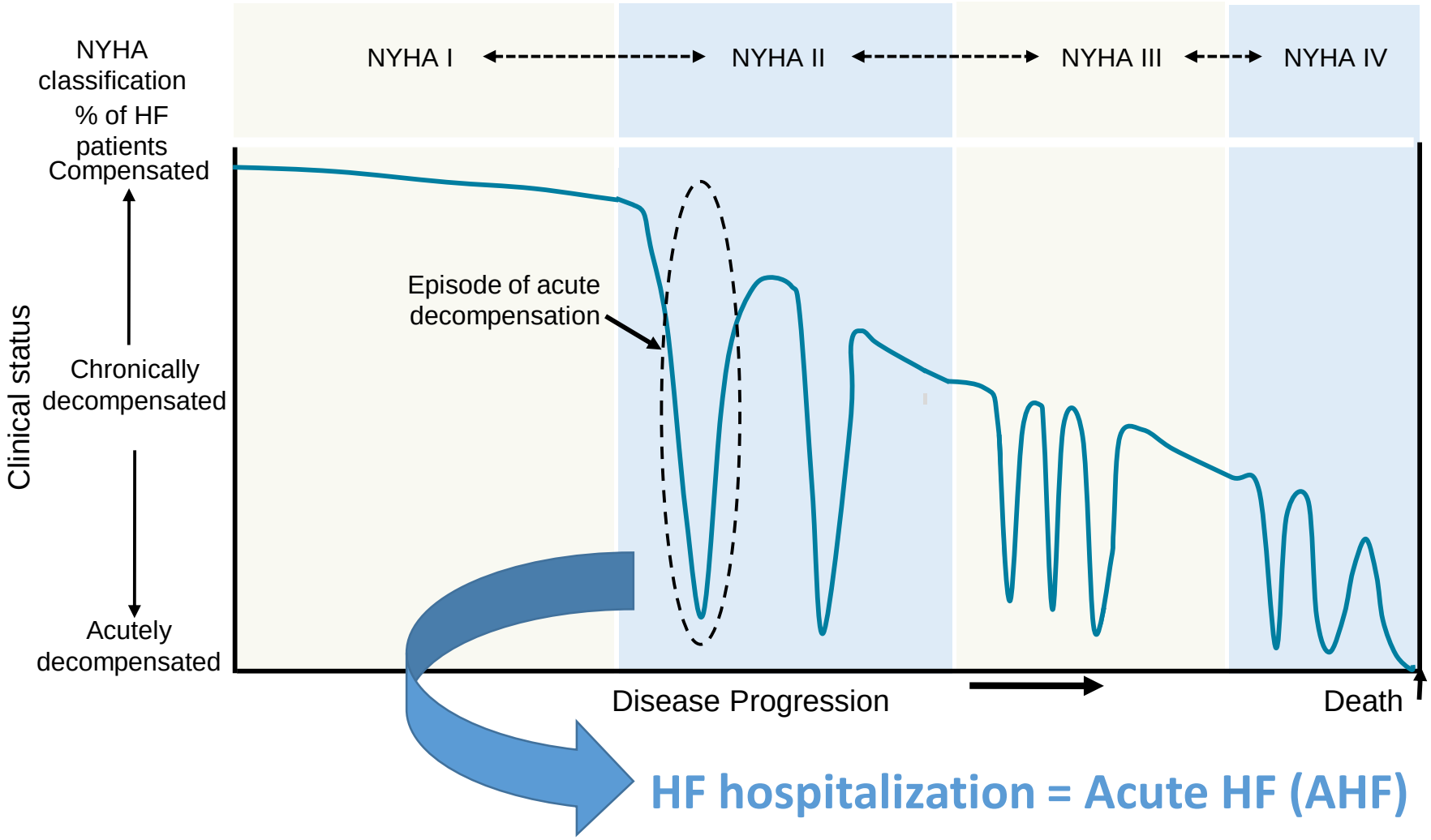
SPEAKER: KATERINA K. NAKA MD, PhD, FESC

RCTs/Registries - *Amgen, Actelion, BMS, Boehringer, CSL Behring, Lexikon, Bayer*

Advisory Boards – *Glaxo, Boehringer*

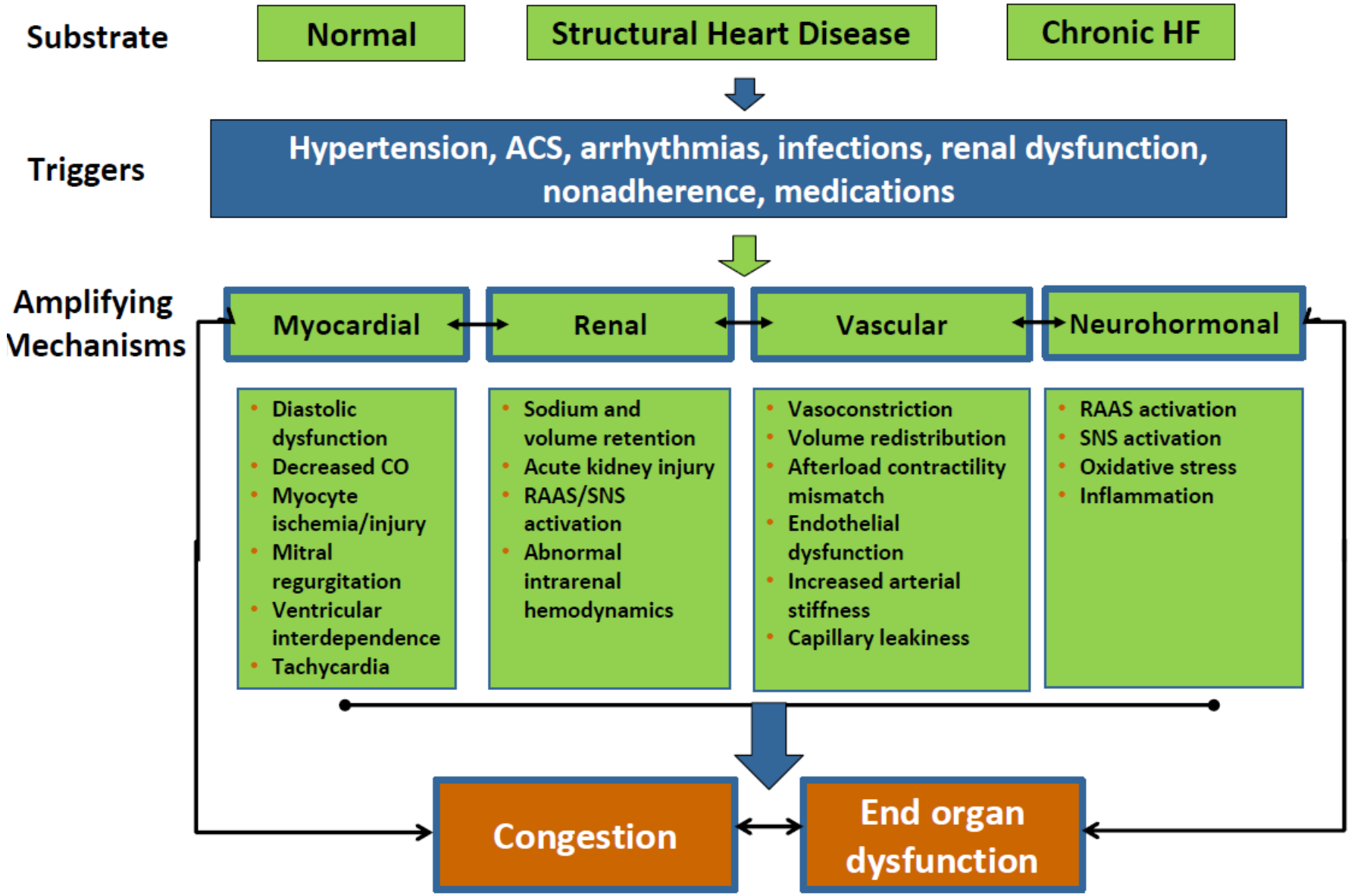
Horizon2020 funding – *KardiaTool, Insilc projects*

HF journey



- With each acute event, myocardial injury and/or renal damage may contribute to progressive LV dysfunction and HF worsening
- **HF hospitalizations =**
  1. **Major predictor of POOR OUTCOMES**
  2. **Major contributor to impaired QOL**
  3. **Responsible for the majority of HF-related COSTS**

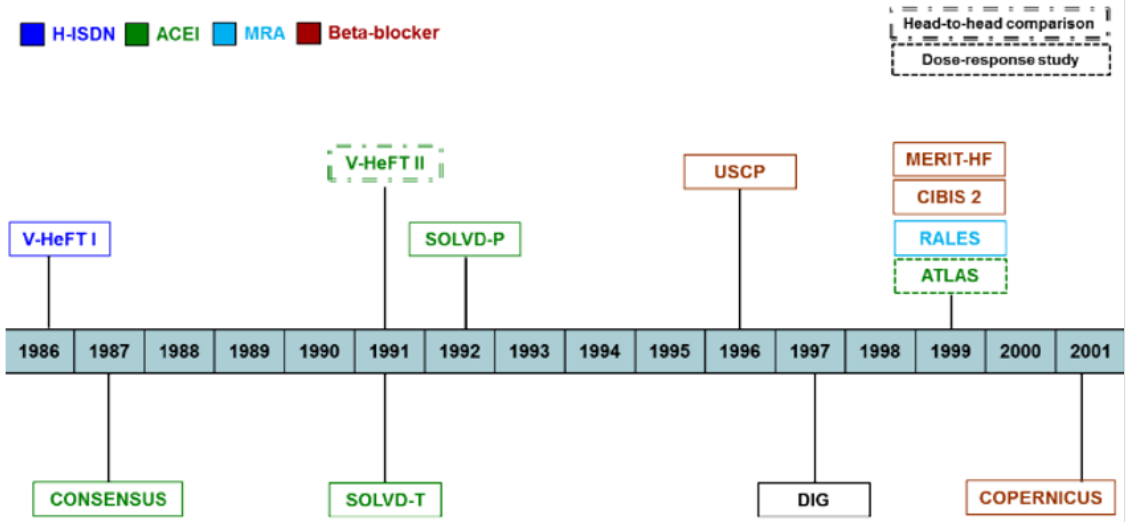
AHF is not a single disease …



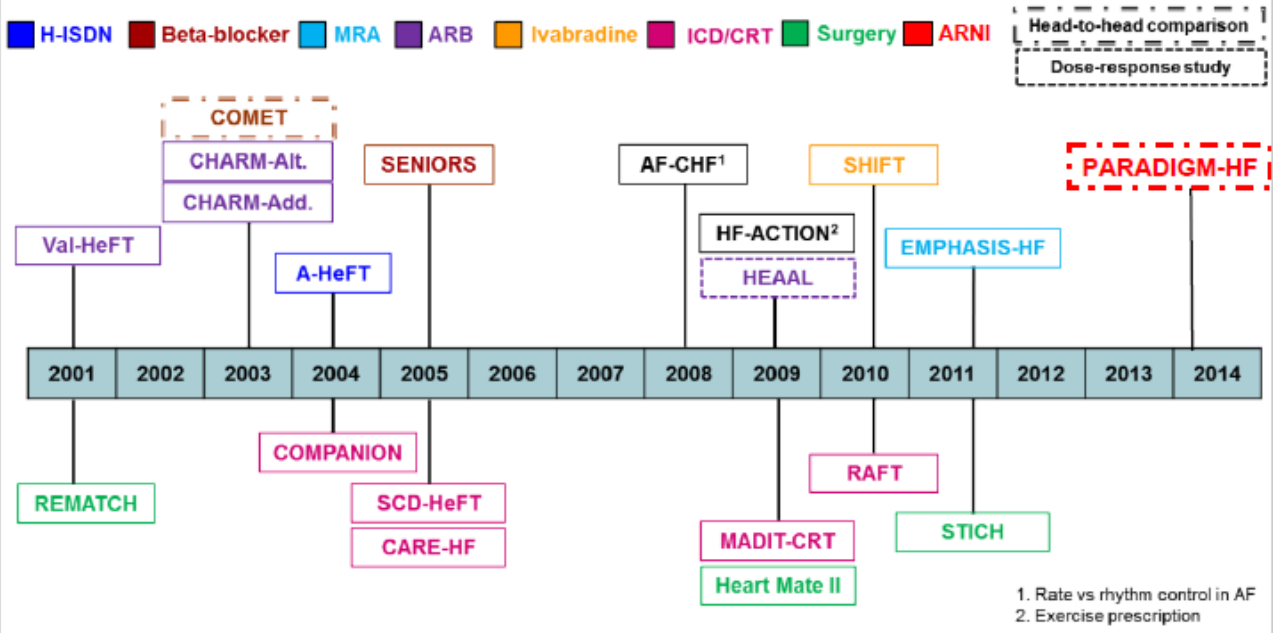
Felker M. Braunwald's Heart Disease, 10th edition

Chronic HFrEF:
Thirty years of progress 1986-2016

Positive drug trials 1986-2001



Positive drug, device and other trials 2001-2014



Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry

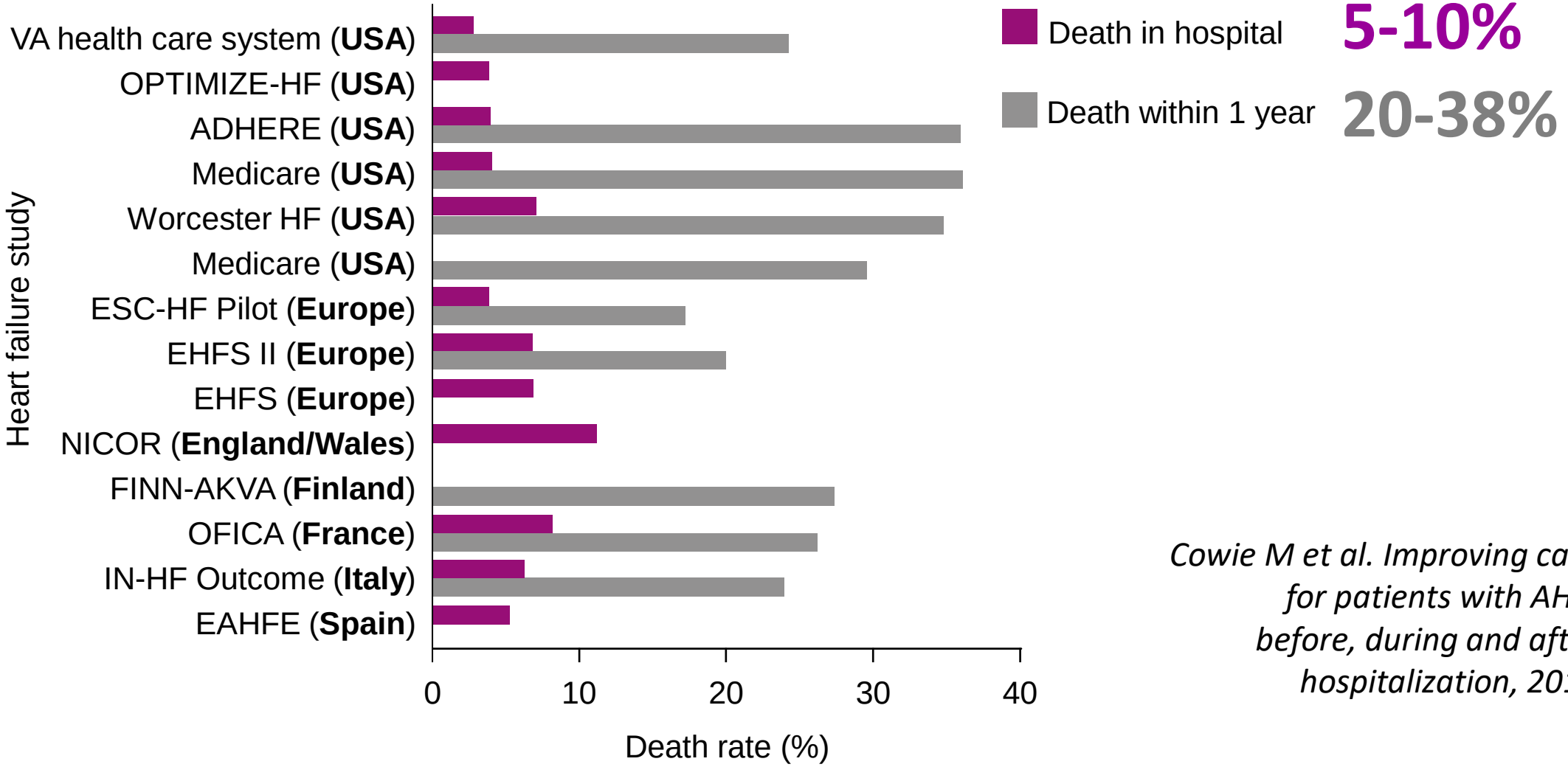
CHRONIC STABLE HF:
still not a 'stable' benign condition

Table 2 Outcomes at 1 year by category of ejection fraction

	All ($n = 9134$)	EF <40% ($n = 5460$)
All-cause death, %	8.1	8.8
Cardiovascular death, %	52.1	53.5
Non-cardiovascular death, %	23.2	20.1
Unknown, %	24.7	26.3
All-cause hospitalization, %	28.1	31.9
HF hospitalization, %	12.4	14.6
All-cause death or HF hospitalization, %	18.6	21.2

Chioncel, …. & Filippatos, EJHF 2017

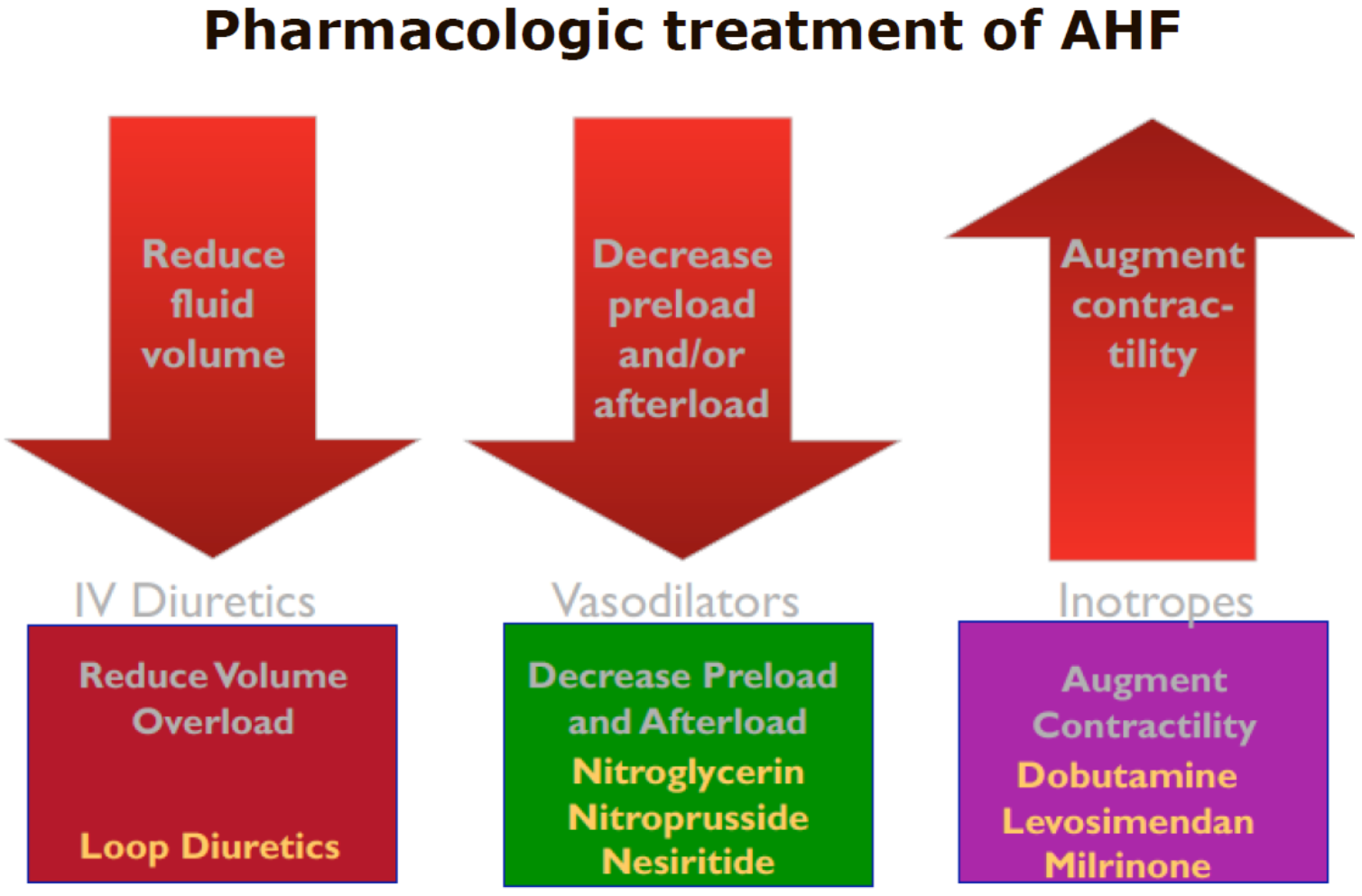
Acute HF: much worse prognosis unacceptably high in-hospital and 1-year mortality

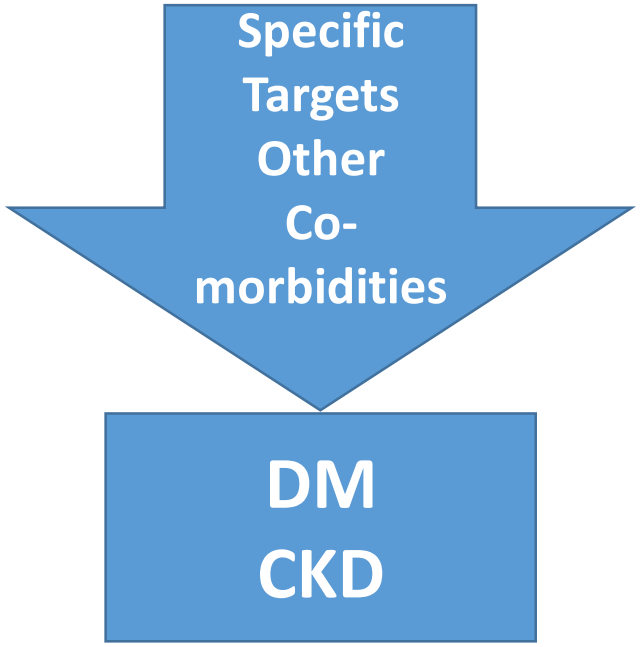


Cowie M et al. Improving care for patients with AHF: before, during and after hospitalization, 2014

Acute HF = In-hospital management

Duration: hours-days
Effect on long-term outcome ???





???

???

BAD

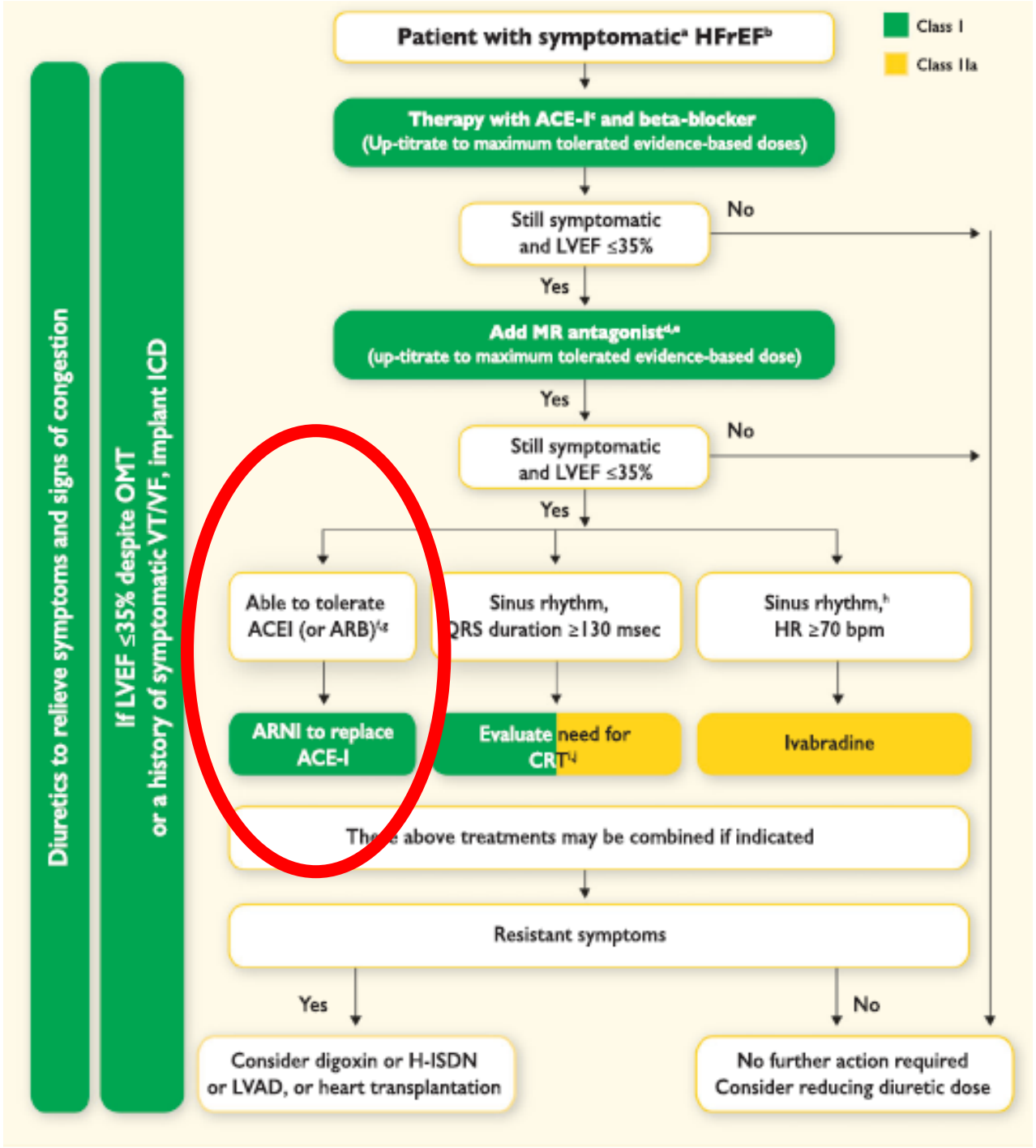
Acute HF = In-hospital management of HF

life-saving chronic HF meds should also be used in the AHF setting

Recommendations	Class [a]	Level [b]
In case of worsening of chronic HFrEF, every attempt should be made to continue evidence-based, disease-modifying therapies, in the absence of haemodynamic instability or contra-indications.	I	C
In the case of de *novo* HFrEF, every attempt should be made to initiate these therapies after haemodynamic stabilization.	I	C

In-hospital management of AHF

Intermediate (in hospital)
Identify aetiology and relevant co-morbidities.
Titrate therapy to control symptoms and congestion and optimize blood pressure.
Initiate and up-titrate disease-modifying pharmacological therapy.
Consider device therapy in appropriate patients.



ESC Guidelines on HF 2016

TRANSITION: Use of Sac/Val early after ADHF

HF treatment optimization in **hospitalized** patients with HFrEF stabilized after an ADHF event*

Recruiting hospitalized HFrEF patients:	Optimization of guidelines recommended HF therapies* at the discretion of the physician	Up-titration and down-titration of Sac/Val according to patient tolerability
• On any dose of ACEI/ARB • Naive to ACEI/ARB • *De novo* (newly diagnosed) HF		

Pascual-Figal et al. ESC Heart Fail 2018

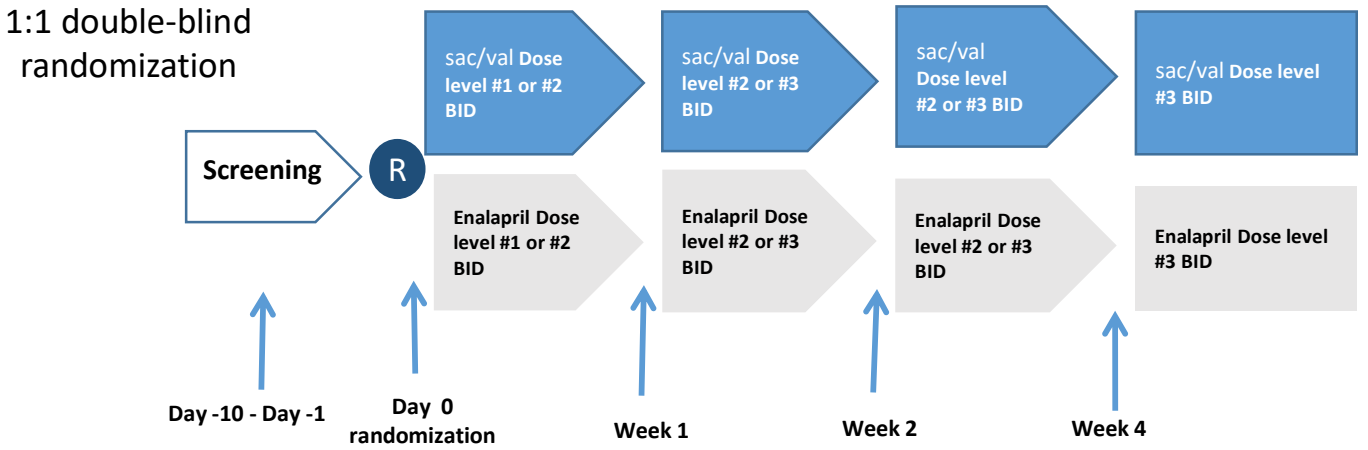
*BBs, MRAs, and replacement of ACEI/ARB by Sac/Val

Initiation of sacubitril/valsartan

in a **wide range** of HFrEF patients, **early after ADHF event,**

in-hospital or **shortly after discharge**, was **feasible** and overall **well tolerated**

PIONEER-HF: Use of Sac/Val in AHF



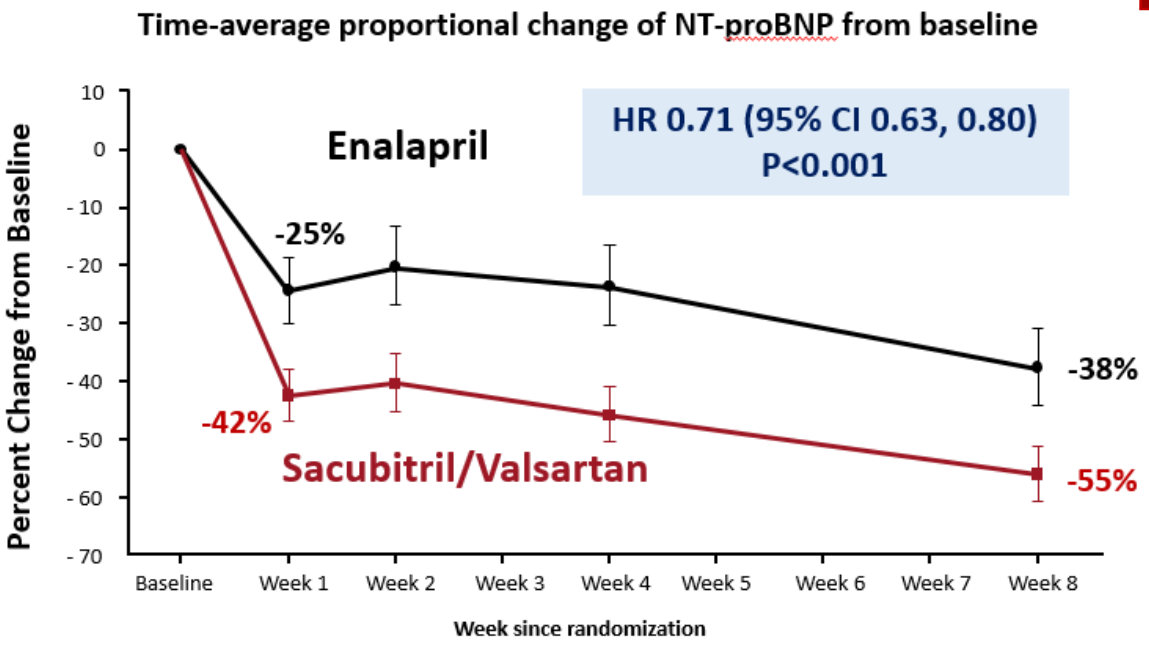
Velazquez et al. N Engl J Med 2018

Dosing: Initial dose of study drug as well as drug titration (at weeks 1, 2, 4 and 6) was determined by SBP criteria

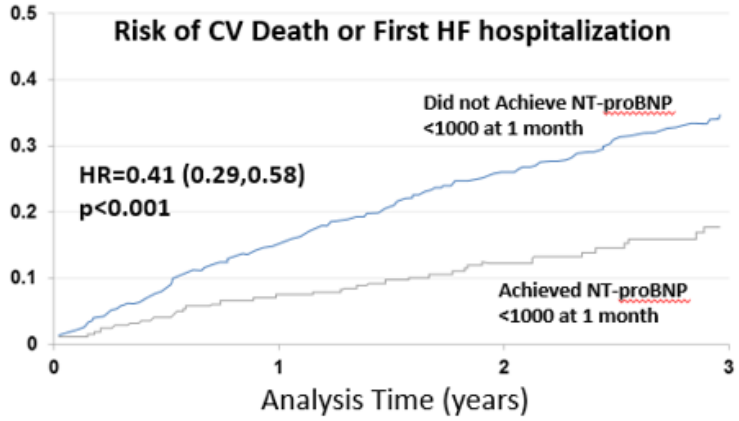
- **SBP ≥100 - 119: start at Dose Level 1** (sac/val 24/26mg or enalapril 2.5mg BID)
- **SBP ≥120 : start at Dose Level 2** (sac/val 49/51mg or enalapril 5mg BID)

- **SBP <110 : remain at the same dose**
- **SBP ≥110 : increase at next dose level** (target is Level 3 sac/val 97/103mg or enalapril 10mg BID)

PIONEER-HF: primary end-point



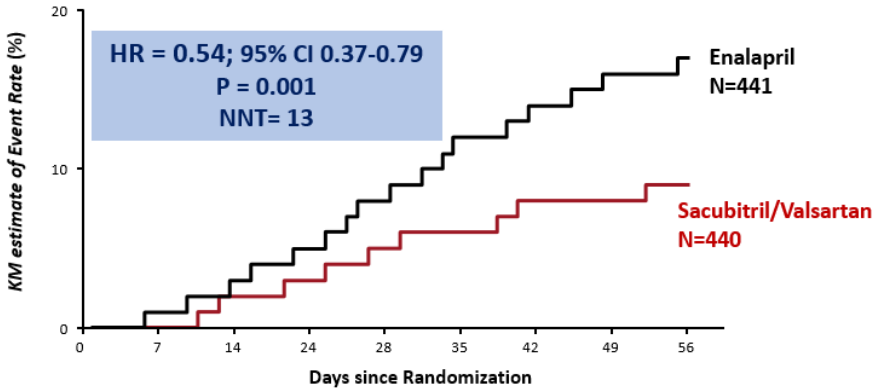
Reduction in NT-proBNP with HF Treatment is Associated with Reduction in CV Death and HF hospitalization (Post hoc Analysis)



Zile et al, JACC 2016

PIONEER-HF: exploratory end-point

Composite of Death, HF re-hospitalization, LVAD, Listing for Transplant

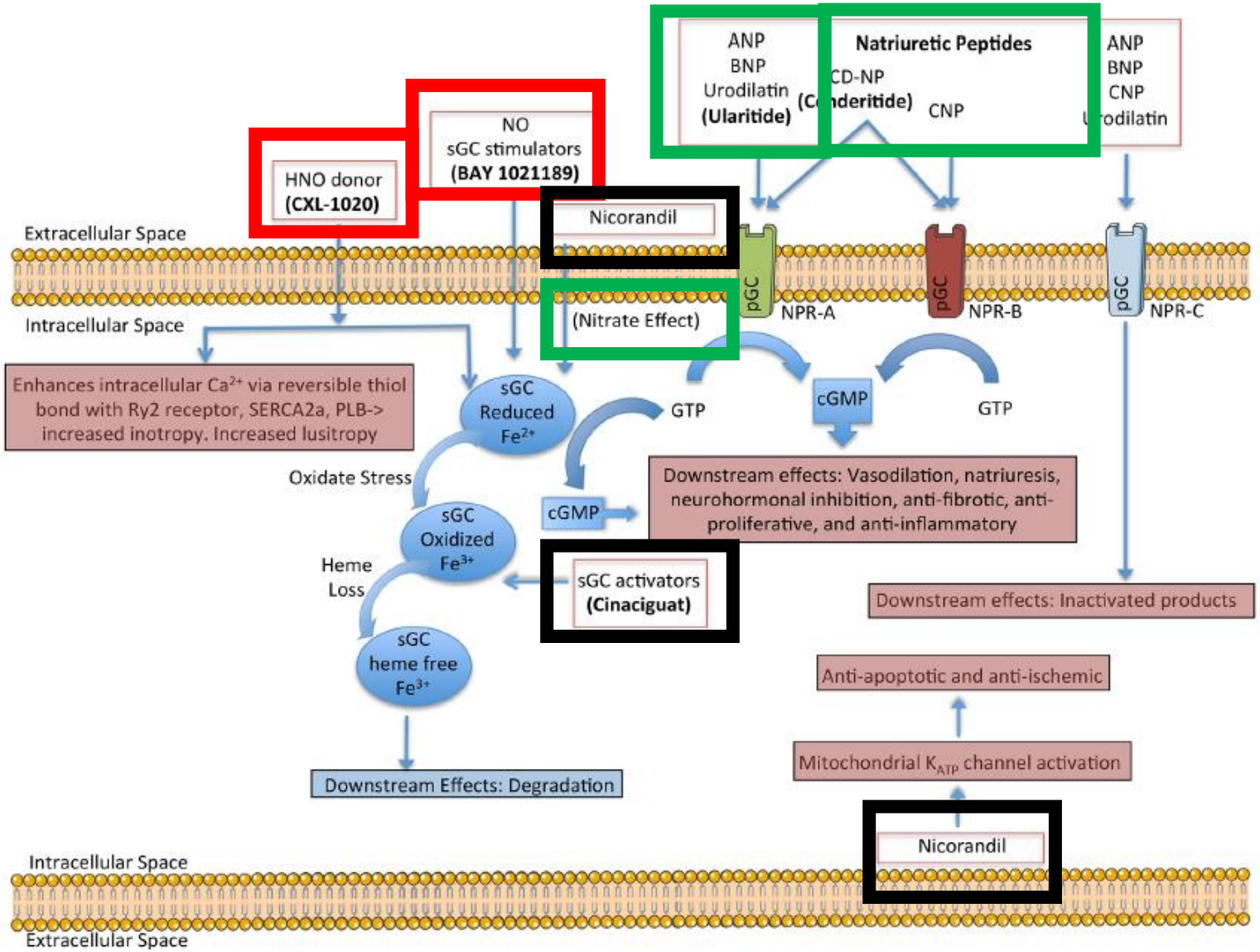


Exploratory Serious Clinical Composite endpoint was driven by **the reduction of HF re-hospitalizations**

Velazquez et al. N Engl J Med 2018

Other agents with vasodilating properties in AHF

(various mechanisms of action)

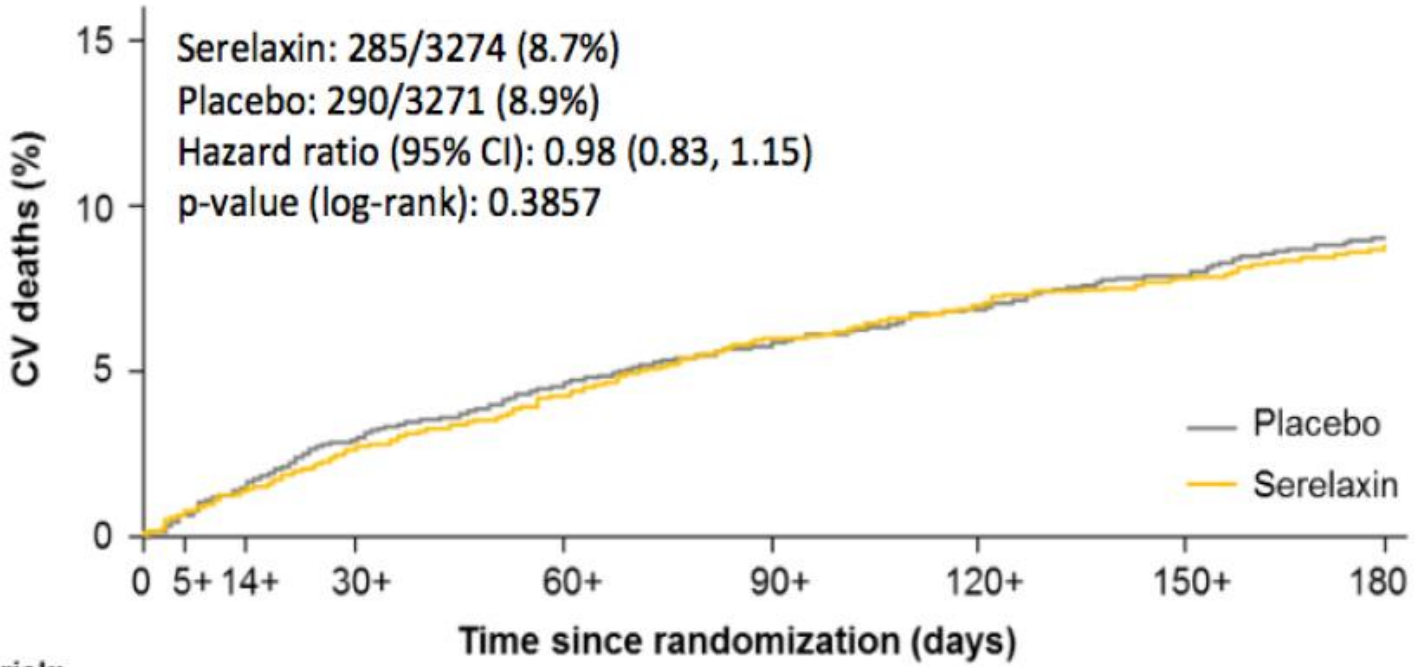


‘DIE HARD’

Singh et al. EHJ 2017

RELAX-AHF-2

Primary endpoint: CV mortality through Day 180



Number at risk:

Placebo	3271	3244	3210	3149	3080	3018	2962	2912	2545
Serelaxin	3274	3247	3218	3165	3100	3032	2988	2949	2548

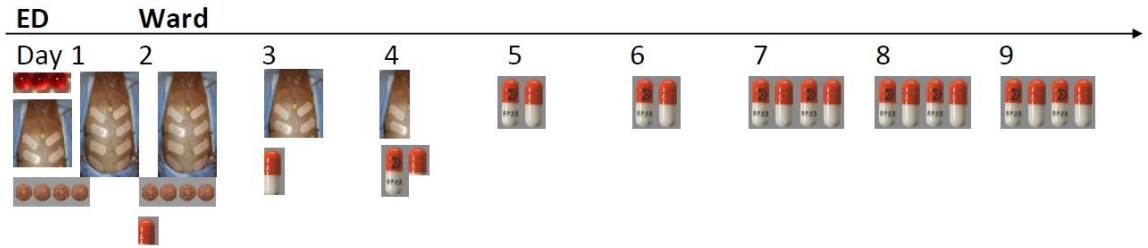
Metra M, Teerlink J et al HFA 2017 Paris

GALACTIC study: Effect of Comprehensive Vasodilation in AHF

- Largest Investigator-initiated RCT in AHF
- Mullens et al
- Presented in HFA 2019

GALACTIC
novel therapy concept in acute heart failure

Methods: Intervention



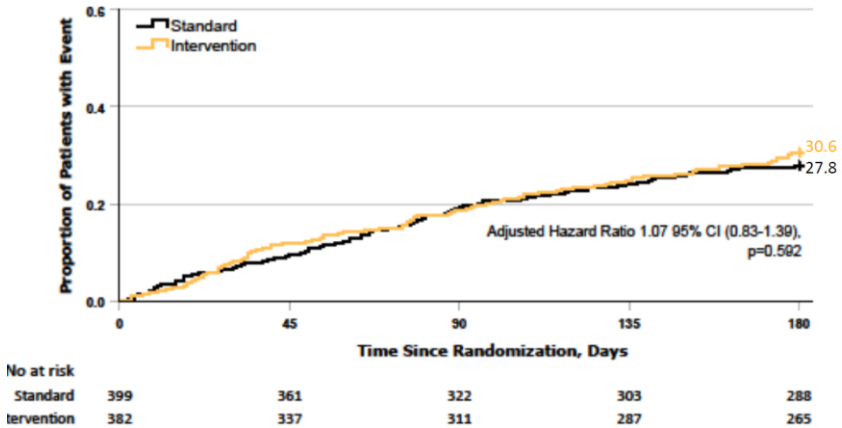
Intervention group continuation	day 4 72 h till 96 h after admission				day 5 96 h till 120 h after admission			
systolic blood pressure [mm Hg]	90 - 110	111 - 130	131 - 150	> 150	90 - 110	111 - 130	131 - 150	> 150
transdermal Glyceryl trinitrate (i.e. Nitroderm® TTS) [mg / 12 h]	25% of day 2	25% of day 2	50% of day 2	75% of day 2			25% of day 2	50% of day 2
Ramipril (i. e. Triatec®) [mg/d][3]	3.75 - 5	3.75 - 5	5 - 7.5	5 - 7.5	5 - 7.5	5 - 7.5	7.5 - 10	7.5 - 10
Lisinopril (i. e. Zestril®) [mg/d][3]	5 - 10	10 - 15	15 - 20	15 - 25	10 - 15	15 - 20	20 - 30	20 - 30
Enalapril (i. e. Reniten®) [mg/d][3]	10 - 15	10 - 15	15 - 20	20 - 30	15 - 20	15 - 20	20 - 30	30 - 40
Captopril (i. e. Capoten®) [mg/d][3]	50 - 75	50 - 75	75 - 100	75 - 100	75 - 100	75 - 100	100 - 150	100 - 150
Candesartan (i. e. Atacand®) [mg/d][4]	12 - 24	12 - 24	16 - 24	16 - 24	16 - 24	24 - 32	24 - 32	24 - 32
Losartan (i. e. Cozaar®) [mg/d][4]	50 - 75	50 - 75	75 - 100	75 - 100	75 - 100	75 - 100	75 - 100	75 - 100

GALACTIC
novel therapy concept in acute heart failure

Conclusion:

In a broad AHF population early intensive and sustained vasodilation with nitrates, hydralazine, ACE-inhibitors, ARB, or sacubitril/valsartan using individualized doses was well tolerated, but **did not improve 180-day all-cause mortality and AHF rehospitalisations**.

Results: Primary Endpoint (Death or AHF)



STANDUP AHF

To evaluate safety and efficacy of iv infusions of HNO (Nitroxyl) Donor

- A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Dose-Ranging
- **Phase 2b Study of the Safety and Efficacy of Continuous 48-Hour Intravenous Infusions of BMS-986231**
- in Hospitalized Patients With HF and Impaired Systolic Function

AVANTI

To Study an Oral Dual V1a/V2 Vasopressin Receptor Antagonist

- A Multicenter, Randomized, Parallel Group, Double Blind, Active and Placebo Controlled Study
- **of BAY1753011, an Oral Dual V1a/V2 Vasopressin Receptor Antagonist**
- in Hospitalised Patients With Congestive Acute HF

Diuretics: Beneficial or investable ?

JACC: HEART FAILURE VOL. 6, NO. 1, 2018
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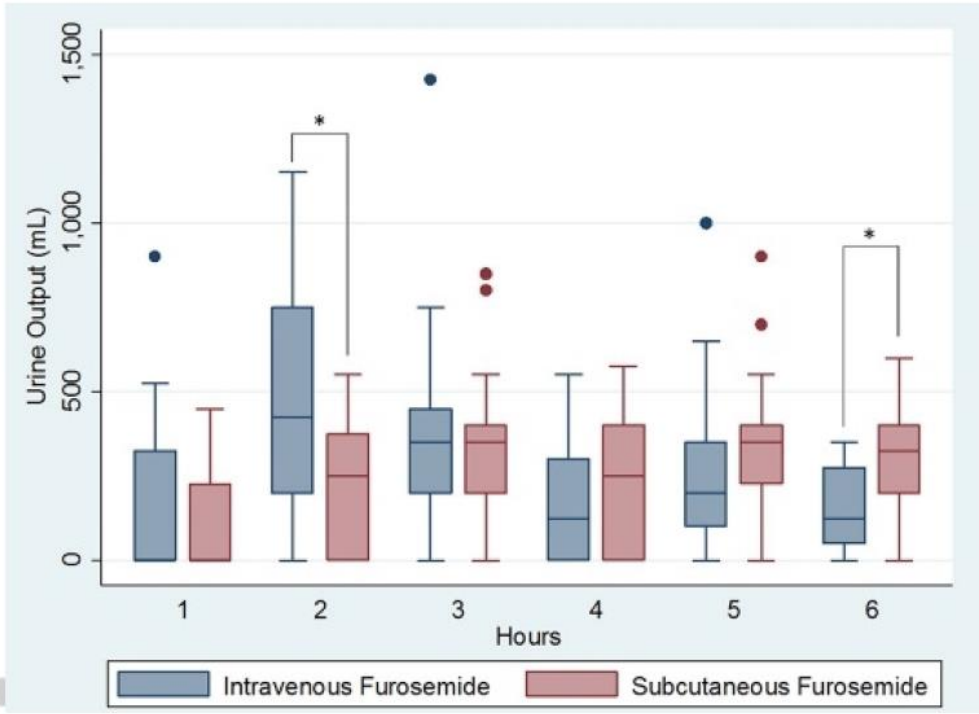
Efficacy of Intravenous Furosemide Versus a Novel, pH-Neutral Furosemid Formulation Administered Subcutaneously in Outpatients With Worsening Heart Failure

Nisha A. Gilotra, MD,[a] Oluseyi Princewill, MD,[b] Bonnie Marino, RN,[a] Ike S. Okwuosa, MD,[a] Jessica Chasler, PharmD,[a] Johana Almansa, DNP,[a] Abby Cummings, CRNP,[a] Parker Rhodes, MS,[a] Julianne Chambers, RN,[a] Kimberly Cuomo, CRNP,[a] Stuart D. Russell, MD[a]

Furosemide: ‘DIE HARD’



Torasemide

The TRANSFORM-HF Trial

6,000 HF Patients

1:1 Randomization

Torsemide Daily | **Furosemide Daily**

≥ 12 months

Routine Clinic Visits
Call Center; NDI

Primary Endpoint:

All-Cause Mortality (12 mos)

Secondary Endpoints:

Health-related Quality of Life over 12 months
All-Cause Mortality + HF Hospitalization at 30 d and 12 months
Survival Time + Total CV Hospitalizations over 12 months

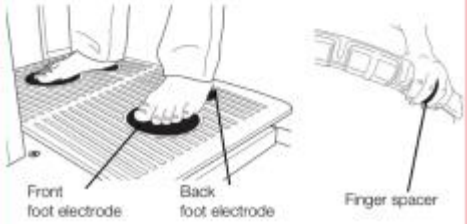
Body-composition analysis of patients with acute heart failure
- preliminary results of the SCALE HF trial -

Switzerland

De Ieso F[1], Mutke MR[1,2], du Fay de Lavallaz J[3], Raichle C[1,4], Brasier N[1], Keller B[1], Sucker C[1], Abdelhamid K[1], Bloch T[1], Reissenberger P[1], Müller C[2,3], Eckstein J[1,2]

a) Body Composition Analyser mBCA 515 Seca® Hamburg, Germany

b) Electrode positions



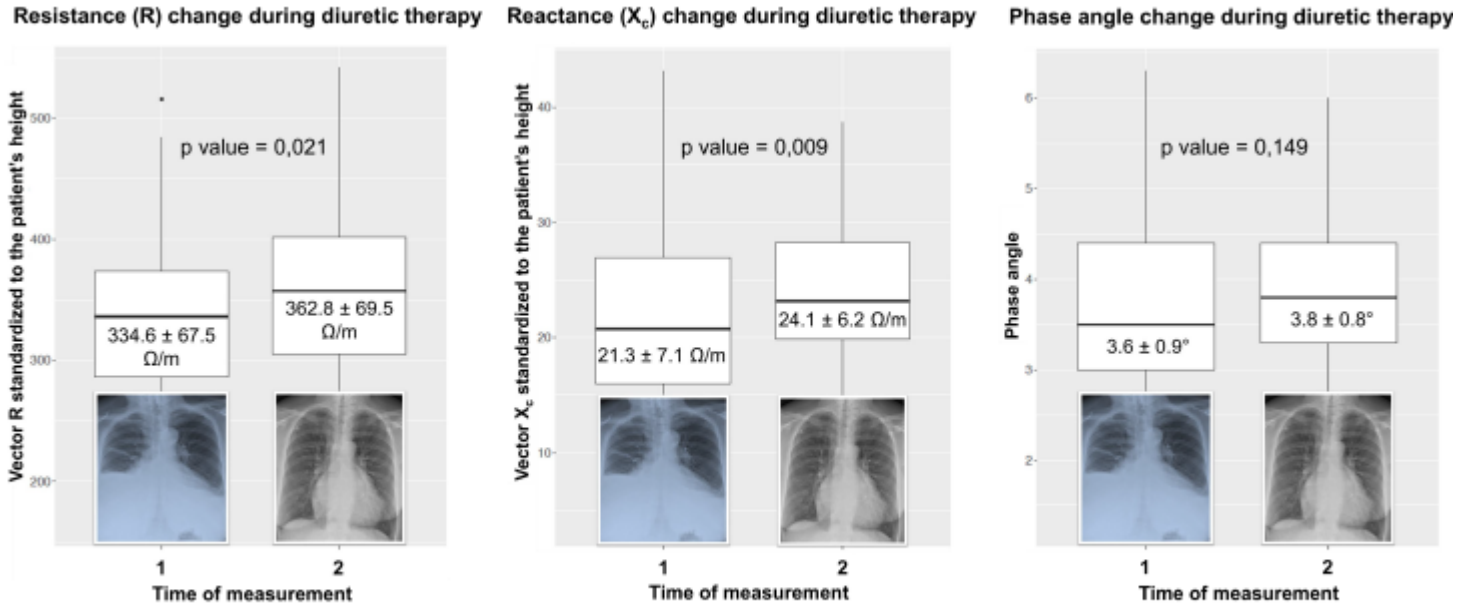


Fig. 3:
Changes in resistance and reactance (standardized to patients height, frequency 50 kHz) and phase angle from admission (1) to last measurement (2) or patient discharge during intensified diuretic therapy

Bioimpedance analysis (BIA) to guide intensified diuresis for AHF

Poster HFA 2019

JAMA Cardiology | Original Investigation

Efficacy and Safety of Spironolactone in Acute Heart Failure
The ATHENA-HF Randomized Clinical Trial

Javed Butler, MD, MPH; Kevin J. Anstrom, PhD; G. Michael Felker, MD, MHS; Michael M. Givertz, MD; Andreas P. Kalogeropoulos, MD, MPH, PhD; Marvin A. Konstam, MD; Douglas L. Mann, MD; Kenneth B. Margulies, MD; Steven E. McNulty, MS; Robert J. Mentz, MD; Margaret M. Redfield, MD; W. H. Wilson Tang, MD; David J. Whellan, MD, MHS; Monica Shah, MD, MHS; Patrice Desvigne-Nickens, MD; Adrian F. Hernandez, MD, MHS; Eugene Braunwald, MD; for the National Heart Lung and Blood Institute Heart Failure Clinical Research Network

INTERVENTIONS High-dose spironolactone (100 mg) vs placebo or 25 mg spironolactone (usual care) daily for 96 hours

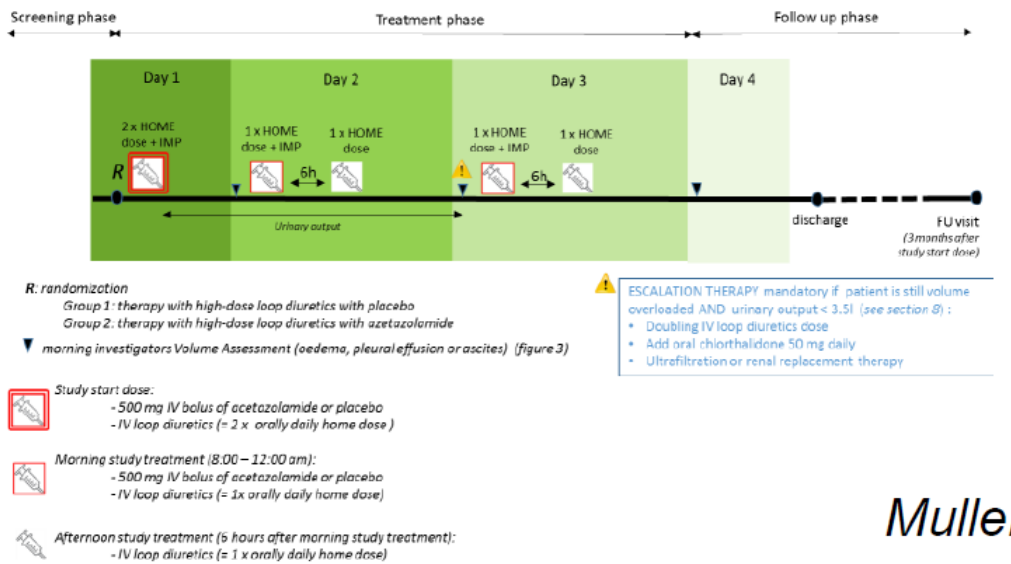
RESULTS A total of 360 patients were randomized, of whom the median age was 65 years, 129 (36%) were women, 200 (55.5%) were white, 151 (42%) were black, 8 (2%) were Hispanic or Latino, 9 (2.5%) were of other race/ethnicity, and the median left ventricular ejection fraction was 34%. Baseline median (interquartile range) NT-proBNP levels were 4601 (2697-9596) pg/mL among the group treated with high-dose spironolactone and 3753 (1968-7633) pg/mL among the group who received usual care. There was no significant difference in the log NT-proBNP reduction between the 2 groups (−0.55 [95% CI, −0.92 to −0.18] with high-dose spironolactone and −0.49 [95% CI, −0.98 to −0.14] with usual care, $P = .57$). None of the secondary end point or day-30 all-cause mortality or heart failure hospitalization rate differed between the 2 groups. The changes in serum potassium and estimated glomerular filtration rate at 24, 48, 72, and 96 hours. were similar between the 2 groups.

CONCLUSIONS AND RELEVANCE Adding treatment with high-dose spironolactone to usual care for patients with AHF for 96 hours was well tolerated but did not improve the primary or secondary efficacy end points.

Acetazolamide in **D**ecompensated heart failure with **V**olume **O**ve**R**load (ADVOR)

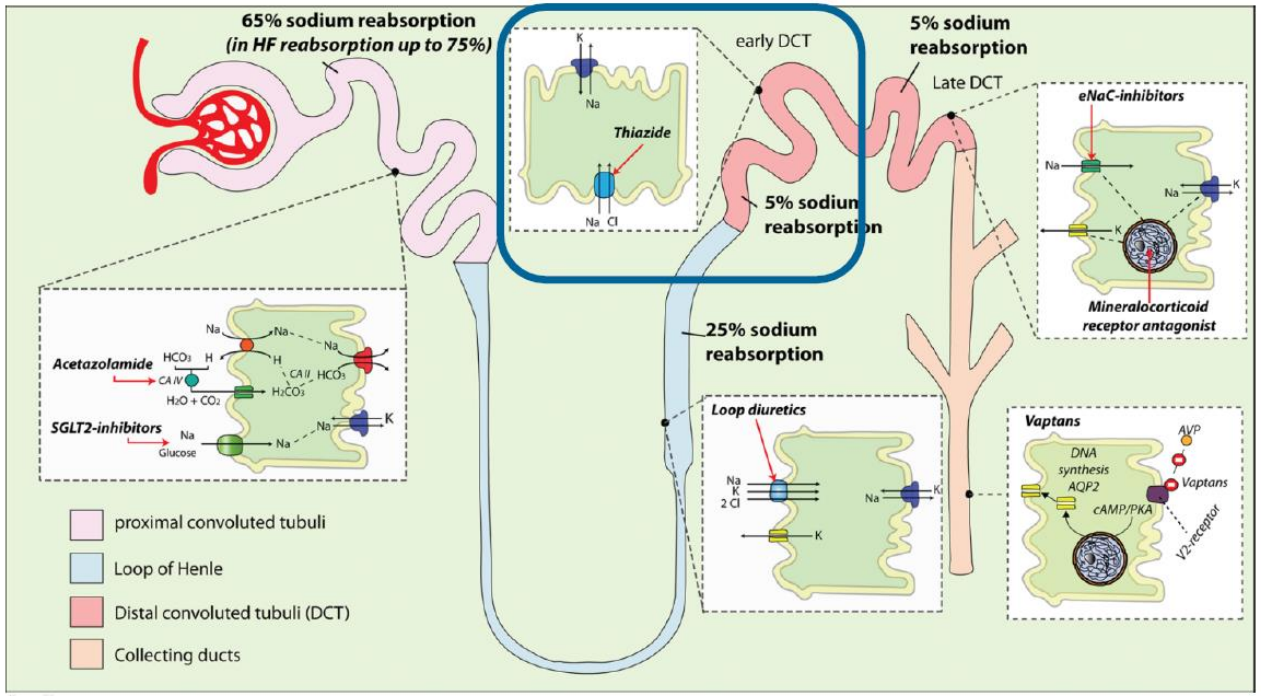
Trial Design
Randomized, multi-center, double blind, clinical trial with 2 treatment arms (n 516)
Acetazolamide + high dose loop diuretics versus *high dose loop diuretics* (=SOC)

Primary endpoint
Treatment success (decongestion achieved) on the morning of day 4 without the need for escalating diuretic strategy (doubling loop diuretic dose, addition of chlorthalidone, or ultrafiltration)



Mullens et al

Sites and mode of action in the nephron of different diuretics



SOLOIST-WHF Trial:

Effect of Sotagliflozin on CV Events in Patients With Type 2 DM Post Worsening HF

Primary Objective: To demonstrate that sotagliflozin reduces CV mortality and morbidity (composite of CV death or hospitalization for HF) compared to placebo **in stable patients with type 2 diabetes and HF after admission for worsening heart failure (WHF)**

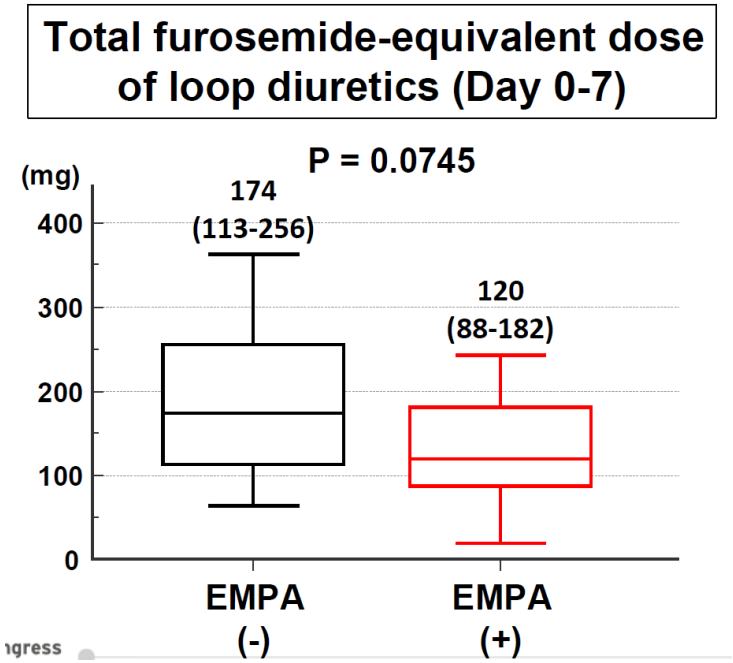
- irrespective of EF

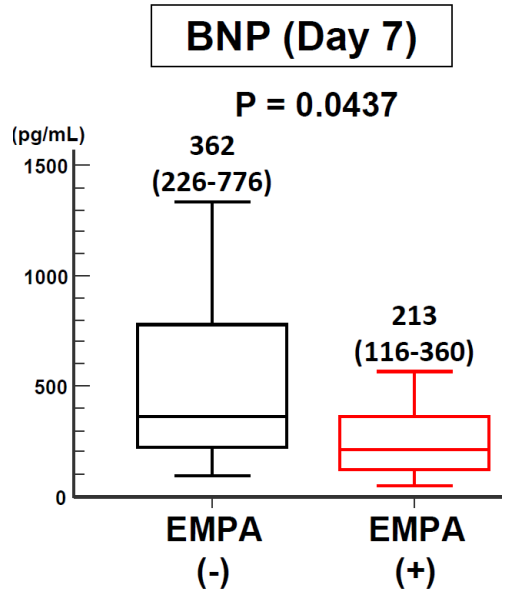
Effect of empagliflozin as add-on therapy on decongestion and renal function in diabetic patients hospitalized for acute decompensated heart failure: *a prospective randomized controlled study*

Shunsuke Tamaki, Takahisa Yamada, Takashi Morita, Yoshio Furukawa, Yusuke Iwasaki,
Masato Kawasaki, Atsushi Kikuchi, Tsutomu Kawai, Masahiro Seo, Makoto Abe,
Jun Nakamura, Kyoko Yamamoto, Masatake Fukunami
Division of Cardiology
Osaka General Medical Center
Osaka, Japan

Empagliflozin as add-on therapy resulted in…

- No significant difference in the change in body weight
- Significantly lower BNP level
- More frequent hemoconcentration
- Larger decrease in %ΔPV
- No difference in the incidence of WRF





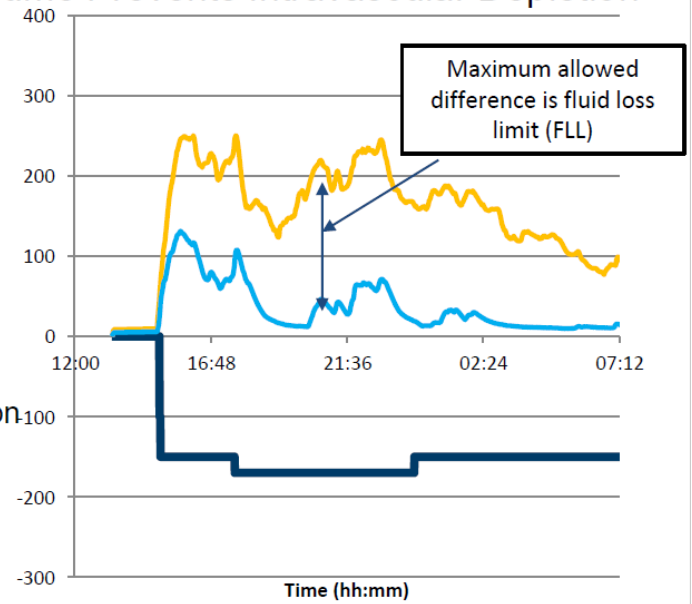
ESC 2019 oral abstract

Controlled decongestion by the Reprieve-System® in acute heart failure: results of the TARGET-1 and TARGET-2 Studies

Piotr Ponikowski, MD, PhD, FESC
Centre for Heart Disease, University Hospital,
Department for Heart Disease, Medical University, Wroclaw, Poland
Military Hospital, Wroclaw, Poland
On behalf of TARGET-1 and TARGET-2 investigators

Heart Failure 2019
#HeartFailure2019

Automated Maintenance of Intravascular Volume Prevents Intravascular Depletion



- Patient given bolus and then started on continuous IV infusion of furosemide
- Rate of **urine production (yellow line)**
- **Fluid loss limit (FLL; dark blue line)** set by physician
- System continuously monitors urine production & automatically maintains FLL by **infusing fluid (blue line)**

- **hospitalized** with primary diagnosis of **acute heart failure**
- clinical signs of **congestion**
- elevated natriuretic peptides:
  BNP ≥500pg/ml, NTproBNP ≥2000pg/ml;
  BNP ≥750pg/ml, NTproBNP ≥3000pg/ml
  for patients ≥75years of age or with AF
- SBP ≥100mmHg
- eGFR 25-90 ml/min/1.73m^2
  calculated using the MDRD equation

1. **Primary endpoint**
   (preventing excess fluid loss – actual FL not exceeding the target FL at conclusion of the Reprieve-System® based therapy)
   was met in all 19 (100%) patients

2. **Safety endpoints**
   procedure **well tolerated,** none of the patients had **any signs of infection nor any other procedure related complication** during and after the treatment phase;
   blood pressure remained **stable;**
   neither deaths nor any serious adverse events reported until day 30.

Recommendations regarding renal replacement therapy in patients with acute heart failure

Recommendations	Class [a]	Level [b]	Ref [c]
Ultrafiltration may be considered for patients with refractory congestion, who failed to respond to diuretic-based strategies.	IIb	B	578–580
Renal replacement therapy should be considered in patients with refractory volume overload and acute kidney injury.	IIa	C	

ESC guidelines on HF 2016

pure·HF | Peripheral Ultrafiltration for the Relief from Congestion in Heart Failure

New gentle·UF concept: *gentle* ultrafiltration complementary to *low-dose i.v. diuretics* with *peripheral* single needle access

Constanzo MR.
Presented in HFA 2018

Patient cohort in pure·HF : Symptomatic HF patients admitted to the hospital due to congestion, not fully responsive to diuretic therapy.

➔ 864 patients in 30 centers in 7 countries

Ultrafiltration group	**Control group**
Peripheral UF + low-dose i.v. diuretics 1-7 UF sessions (6-10h/ day-time session, 1-10 days)	Guideline-directed medical therapy incl. i.v. diuretics Treatment algorithm based on the current dose at index hospitalization, urine output and clinical assessment

Follow-up: 30- and 90-days

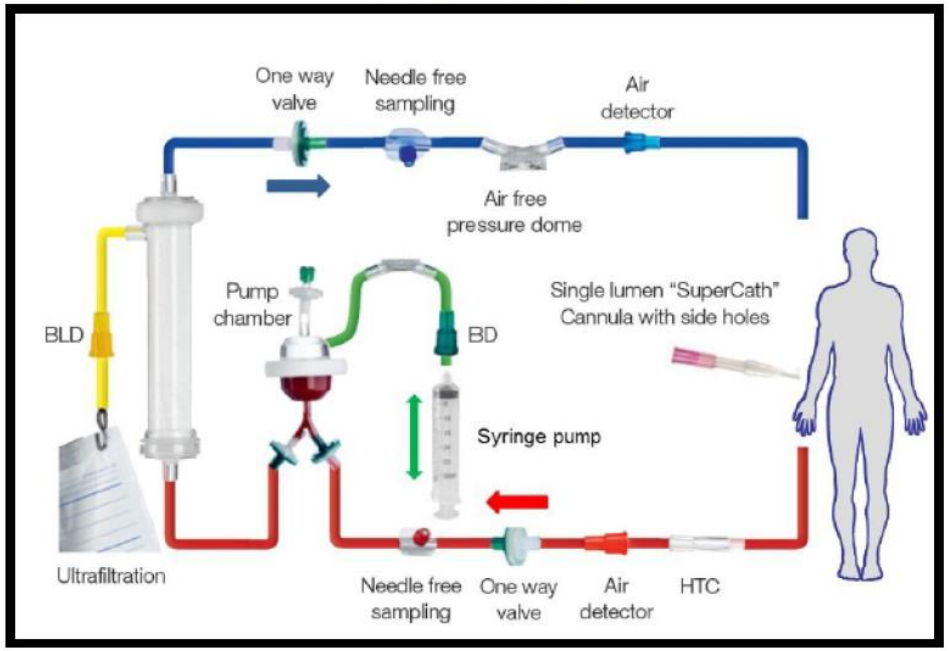
Primary endpoint:

→ Heart failure event in 90 days after discharge

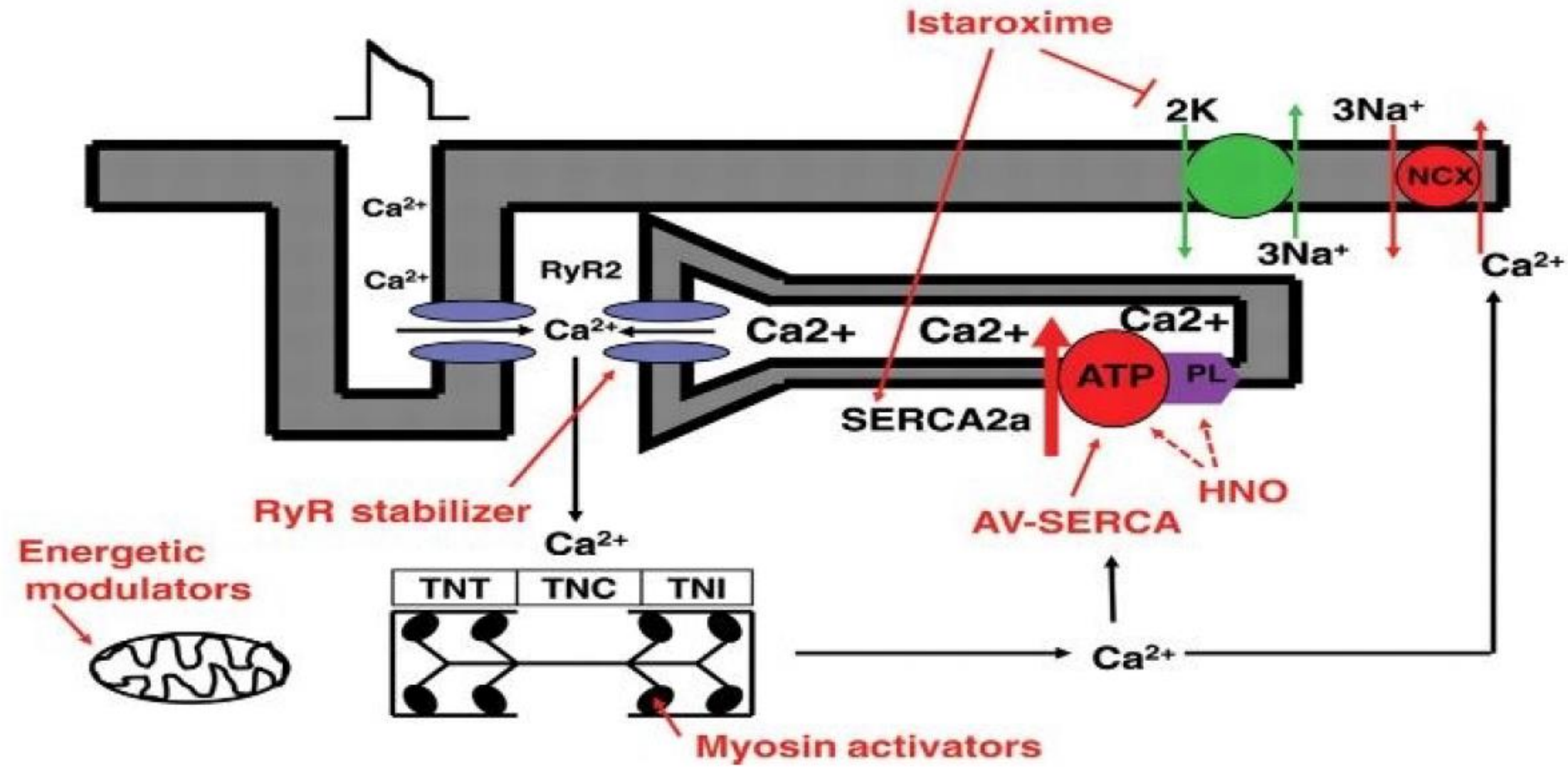
→ Cardiovascular death in 90 days after randomization

HF event: a HF rehospitalization OR unscheduled outpatient visit OR emergency room treatment with i.v. diuretics or UF

CHIARA Device

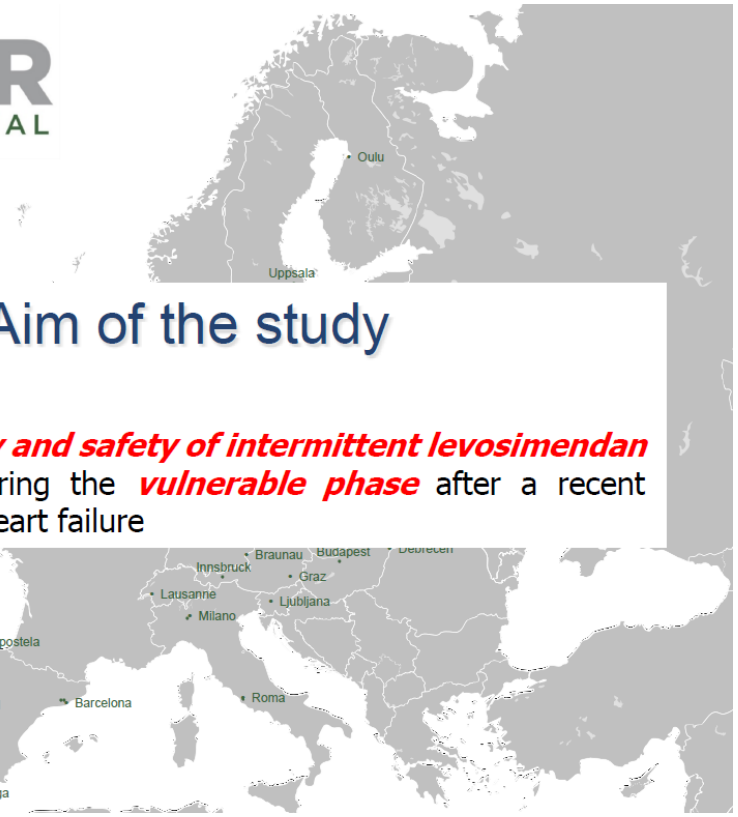


Inotropes: new & old molecules



Hasenfuss G and Teerlink JR. EHJ 2011

LEODOR TRIAL



Aim of the study

To test the ***efficacy and safety of intermittent levosimendan*** therapy started during the ***vulnerable phase*** after a recent hospitalisation for heart failure

The hypothesis will be tested based on a global rank endpoint in which all participants are ranked across three hierarchical groups:

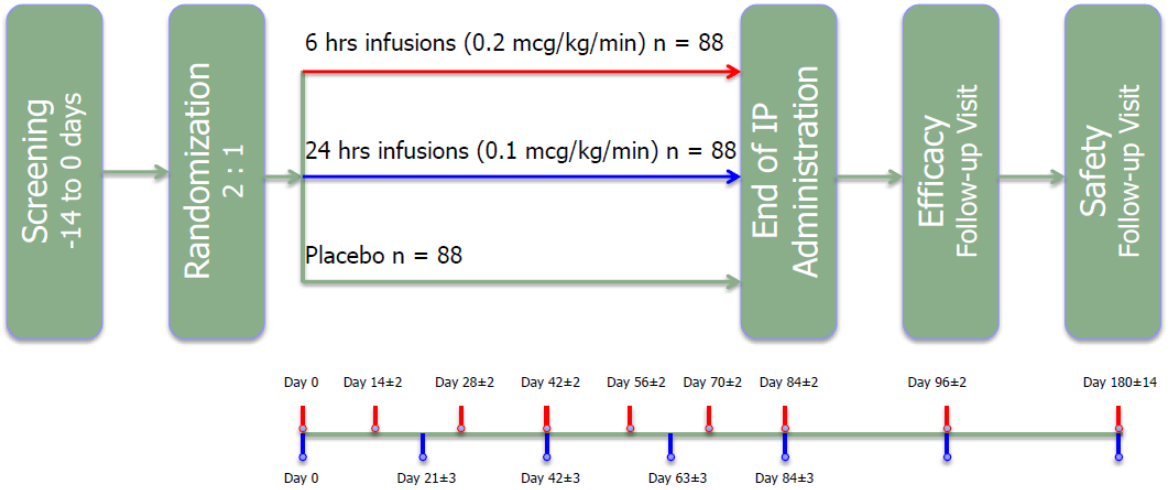
1) *time to death or transplantation / VAD implantation*
2) *time to acute heart failure event* requiring i.v. vasoactive therapy
3) *time-averaged proportional change in N-terminal pro-B-type natriuretic peptide* (NT-proBNP) (from baseline to 14 weeks).

Poelzl et al.
Presented at HFA 2019

LeoDOR Trial
REPETITIVE LEVOSIMENDAN IN ADVANCED HEART FAILURE

Study procedures

Study schedule



Omecamtiv mecarbil

- **The first-in-class cardiac myosin activator, omecamtiv mecarbil,** augments the speed of ATP hydrolysis, thus accelerating the production of a strong actin-myosin complex, which leads to increased force production. It produces dose-dependent increases in SET, SV, EF and FS

- **The ATOMIC-AHF trial: IV omecamtiv mecarbil in a high-dose group of AHF**
  - **did not improve dyspnoea overall but may have improved it**
  - it did, however, increase SET, decrease LVESD and was well tolerated

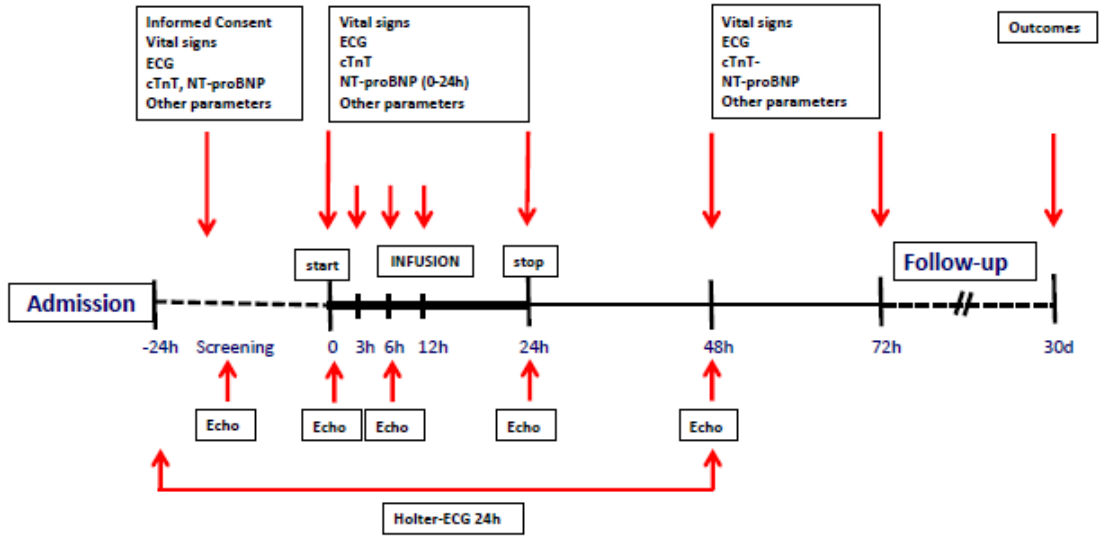
- **The COSMIC-HF trial: pharmacokinetic-based dose-titration strategy**
  - **improved cardiac function and reduced LV diameters vs placebo**
  - had a similar safety profile (minimal troponin release without evidence of ischaemia)
  - significantly reduced plasma NT-proBNP compared with placebo

- **The GALACTIC-HF phase III trial: oral omecamtiv mecarbil vs placebo in patients with chronic HFrEF** (added to current HF standard treatment), expected to be completed in January 2021

The ISTAROXIME-AHF trial: Safety and efficacy of 24-hour istaroxime infusion in patients hospitalized for AHF

- Carubelli et al
- Performed in China
- Presented in HFA 2019
- **1st in class luso-inotropic therapy**
- A phase II study for 2 doses of infusion vs placebo (n=120)
- **PROMISING RESULTS**

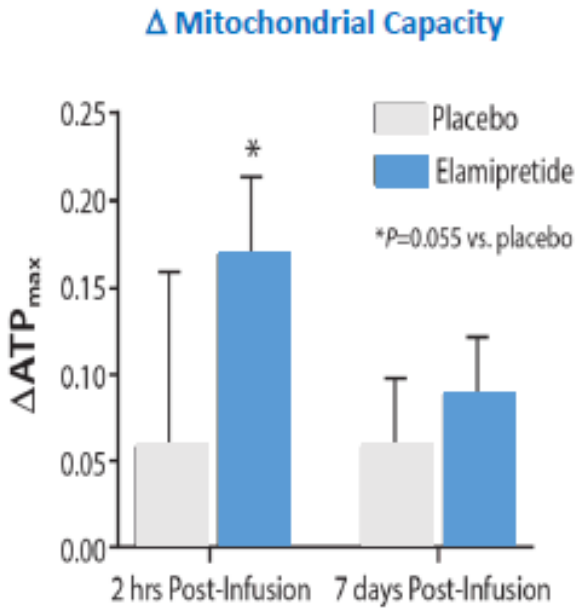
Study Flow Chart



- A 24-hours infusion of istaroxime at doses of 0.5 and 1.0 μg/Kg/min was associated with significant improvements in diastolic and systolic cardiac function
- Istaroxime reduced HR and maintained / increased systolic blood pressure; renal function also tended to improve
- Istaroxime was generally safe and no major concerns related to arrhythmias and cTnT were observed; pain at infusion site was reported with short catheters and GI symptoms primarily with high dose

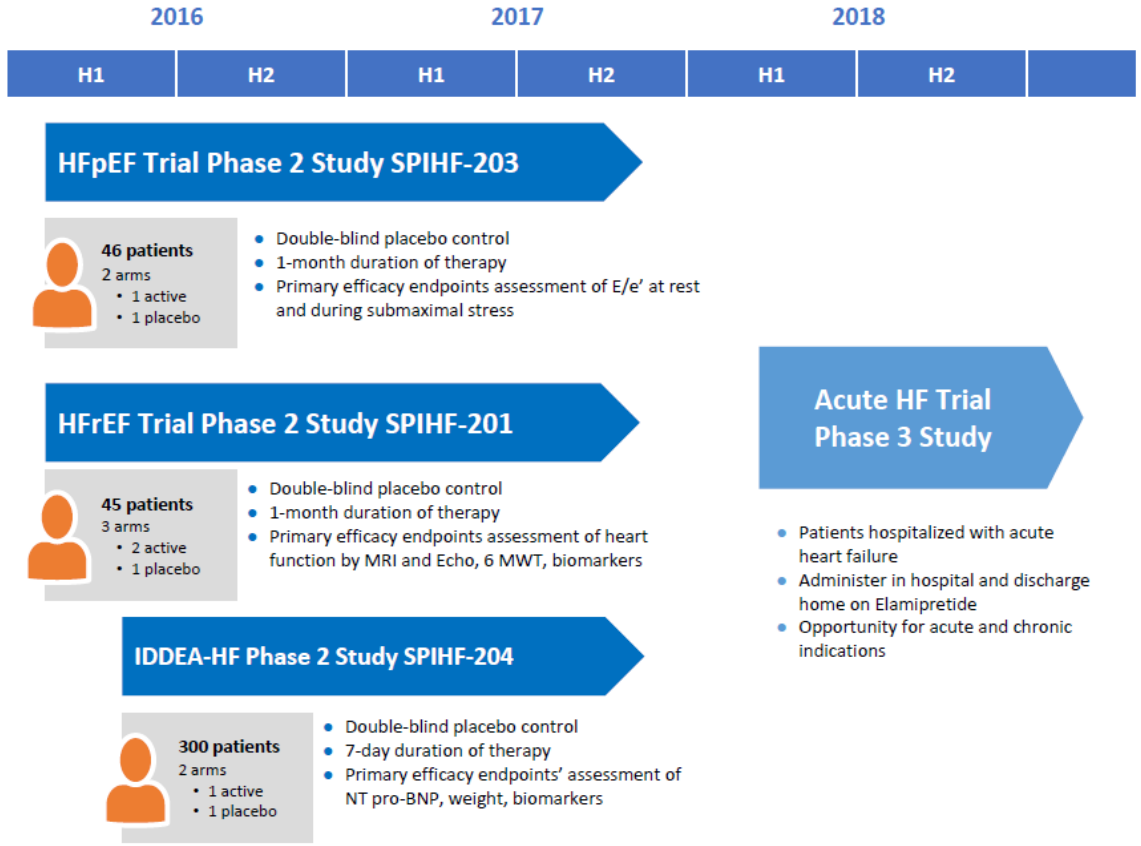
Elamipretide

- Bendavia, SS-31, MTP-1 peptide
- Crosses the mitochondrial membrane and associates with cardiolipin, that stabilizes the respiratory supercomplexes and helps to retain cytochrome C
- **Enhances ATP synthesis in multiple organs (heart, kidney, neurons, skeletal muscle)**
- **MOTION results:** elamipretide improves mitochondrial function by increasing ATP production



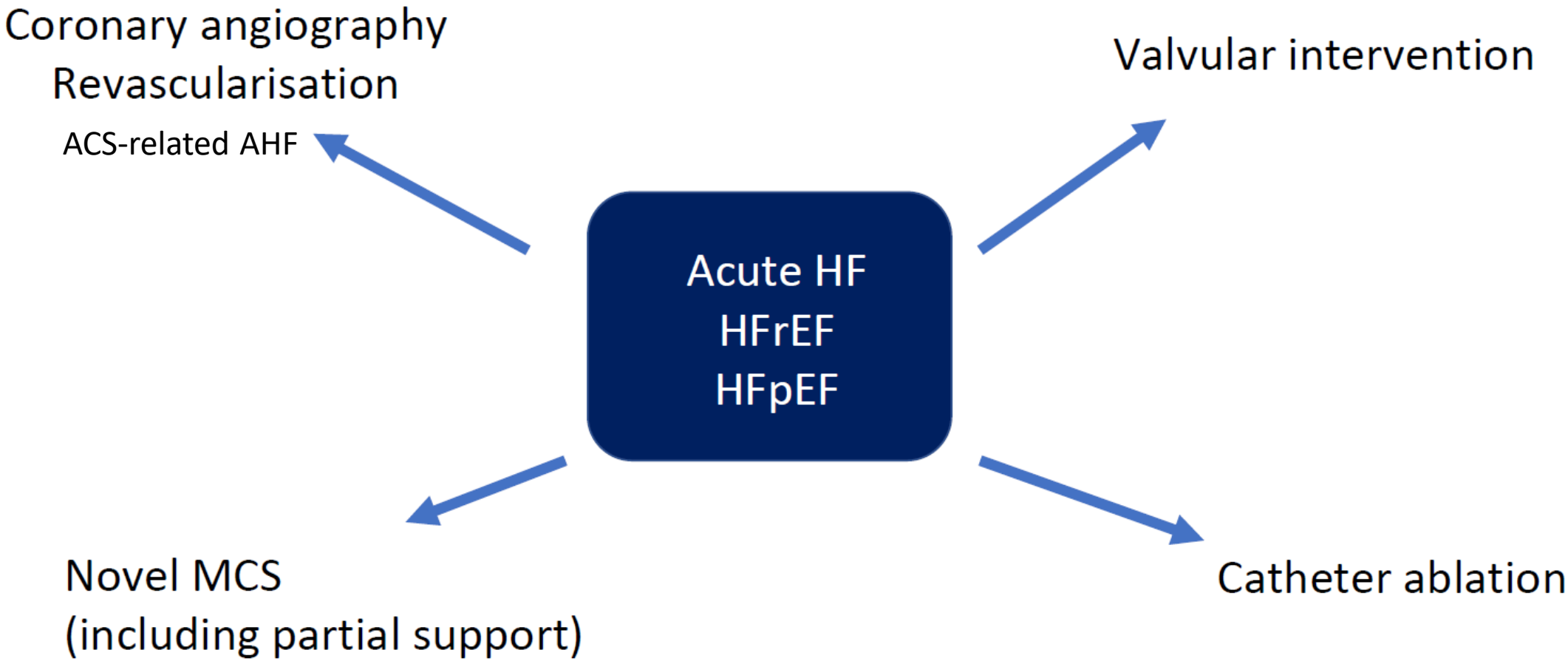
Conley et al, HFSA 2016 poster

Elamipretide Heart Failure Program



G Filippatos, HFA 2018

Interventional Cardiology may also help (some of the) AHF in the future …



Mechanical Circulatory Support in AHF (not shock)

Adjuncts for PCI in acute HF

- IABP
- IMPELLA
- ECMO
- TANDEM HEART

NOT TESTED in AHF

4 studies in shock

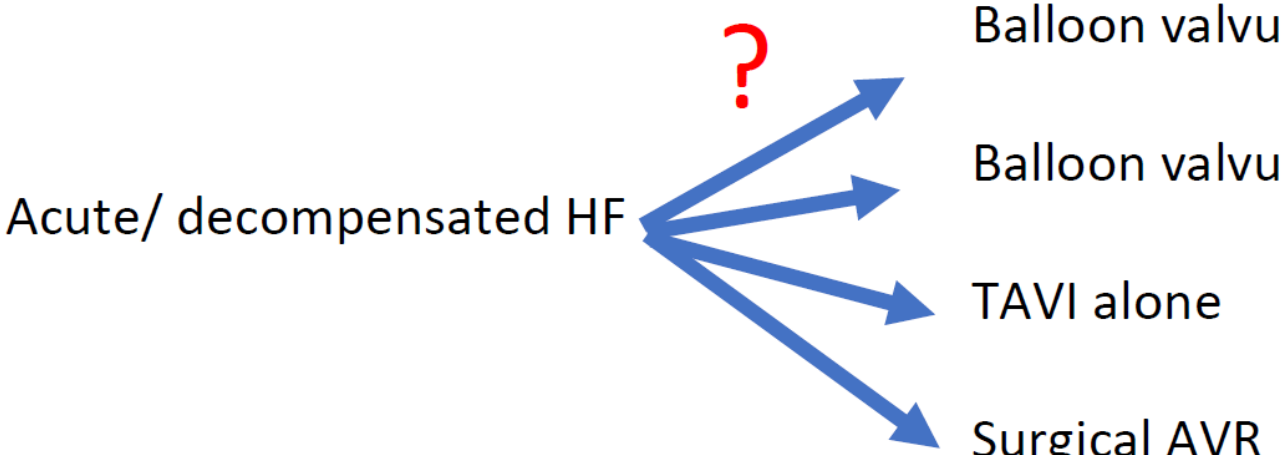
Trials that are necessary in acute/ decompensated HF

- Angiogram v no angiogram in acute HFrEF or HFpEF (without shock)
- PCI v no PCI in acute HFrEF or HFpEF
- CABG v no CABG in acute HFrEF or HFpEF
- IABP v no IABP (in subgroups with acute decompensated HF without STEMI)
- Impella v no Impella (in subgroups with acute decompensated HF without STEMI)
- ECMO v no ECMO (in subgroups with acute decompensated HF without STEMI)

Modified from Mark Petrie, HFA 2018

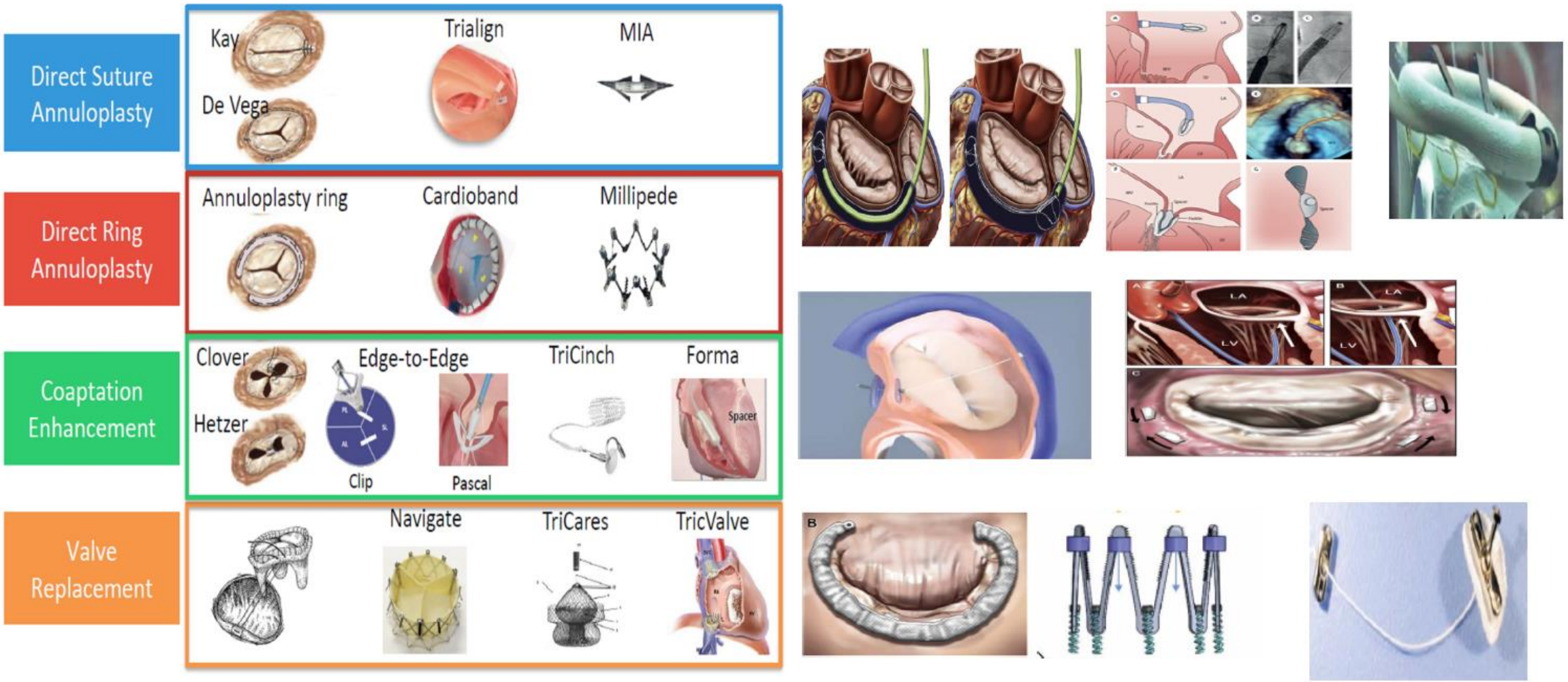
Valvular interventions in AHF

Acute heart failure – aortic stenosis



- No RCTs (small or large)
- No registries
- Very little data
- No data in acute/ decompensated HF
- 2 small studies of emergency BAV or TAVI

Interventions for MR and TR in acute heart failure



Modified from Mark Petrie, HFA 2018

Another approach: Prevent AHF before it happens !!!

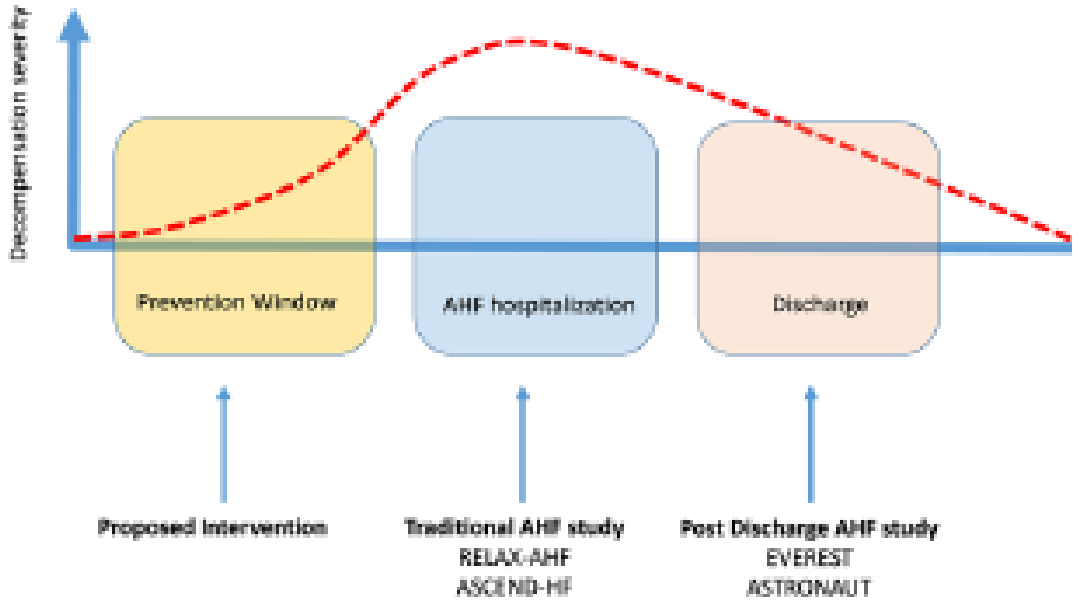
Hemodynamic congestion precedes clinical congestion

JAMA Cardiology | Review

Outpatient Worsening Heart Failure as a Target for Therapy
A Review

2019

Stephen J. Greene, MD; Robert J. Mentz, MD; G. Michael Felker, MD, MHS

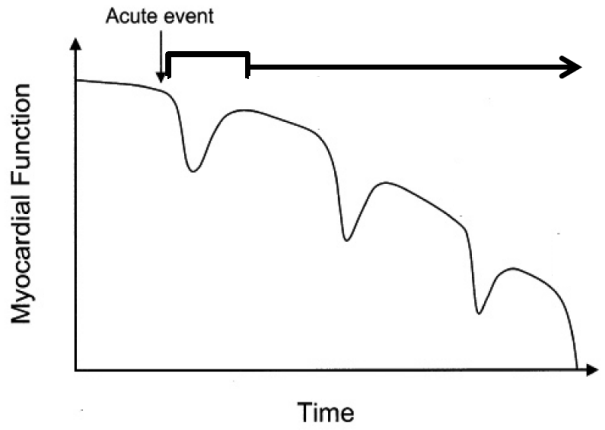


Have we been looking in the wrong place ?

Felker M, 2019

Acute Heart Failure: MORE research is underway

Long-term effects of short-term treatment?



European Journal of Heart Failure (2017)
doi:10.1002/ejhf.932

Heart failure oral therapies at discharge are associated with better outcome in acute heart failure: a propensity-score matched study

Etienne Gayat[1,†*], Mattia Arrigo[1,2†], Simona Littnerova[3], Naoki Sato[4], Jiri Parenica[5], Shiro Ishihara[4], Jindrich Spinar[5], Christian Müller[6], Veli-Pekka Harjola[7], Johan Lassus[8], Òscar Miró[9], Aldo P. Maggioni[10], Khalid F. AlHabib[11], Dong-Ju Choi[12], Jin Joo Park[12], Yuhui Zhang[13], Jian Zhang[13], James L. Januzzi Jr[14], Katsuya Kajimoto[15], Alain Cohen-Solal[16], and Alexandre Mebazaa[1], on behalf of the GREAT Network

Mechanical interventions: costly but a good investment

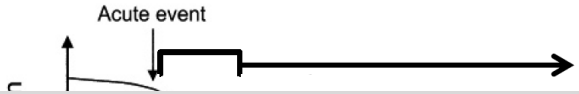
- Cardiac
- Coronary
- Valvular
- Arrhythmias
- Others

AHF phenotyping needed

Avoid the 'one-size fits all' approach

Acute Heart Failure: MORE research is underway

Long-term effects of short-term treatment?



Cost limit ?

Age limit ?

When should palliative care start ?

costly but a good investment

- Cardiac
- Coronary
- Valvular
- Arrhythmias
- Others

European Journal of Heart Failure (2017)
doi:10.1002/ejhf.932

Heart failure oral therapies at discharge are

Avoid the 'one-size fits all' approach

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Σας ευχαριστώ για την προσοχή σας

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