University Hospital Basel

Effect of Comprehensive Vasodilation in Acute Heart Failure: The GALACTIC Randomized Clinical Trial

1. Largest Investigator-initiated RCT in AHF
2. Comprehensive **strategy** of early intensive & sustained vasodilation
3. Individualized doses of well-characterized, widely available, and mostly inexpensive drugs

Disclosures

- Swiss National Science Foundation
- Schweizerische Herzstiftung
  Fondation Suisse de Cardiologie
  Fondazione Svizzera di Cardiologia
- University Hospital Basel
- Foundation for Cardiovascular Research Basel
- Stanley Thomas Johnson Foundation

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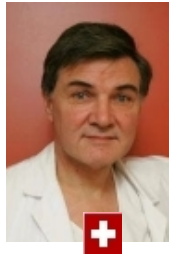


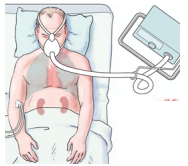




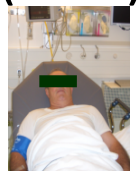


Background I: Acute Heart Failure (AHF)

- Very common, ≈ 2'000'000 patients /year
- **Mortality & morbidity** remain unacceptably high
- Death or AHF rehospitalisation in 40-50% within 180 days

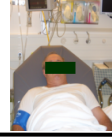


- Optimal treatment: largely unknown
- IV nitrates: ↑ outcome in severe pulmonary edema (≈5% of all AHF)
- **??** Aggressive vasodilation also ↑ outcome in less severe AHF (95%)
- 48h, fixed-dose, single drug infusions did NOT ↑ outcome
- ED → general cardiology/medical ward



Cotter G, et al. Lancet 1998; Sharon A, et al. JACC 2000; Mebazaa A, et al. Intensive Care Med 2010; Levy P, et al. Ann Emerg Med 2007
Metra M, et al. NEJM 2019, Packer M, et al. NEJM 2017; OConner C, et al. NEJM 2011

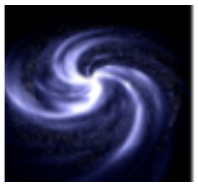
Background II



Hypothesis: **STRATEGY** > single drug

PCWP↓ Organ perfusion↑ + ACE-I/ARB/ARNI↑

- **Comprehensive approach** of **early intensive + sustained vasodilation**
- individualized doses
- combining well-characterized, widely available & inexpensive drugs with complimentary hemodynamic profile → ↑ outcome



GALACTIC

novel therapy concept in acute heart failure

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT00512759

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Methods: Design

Investigator-initiated, randomized, multinational, multicenter, open-label, blinded-endpoint trial

Inclusion Criteria:

- Adult patients presenting with AHF to the ED
- Acute dyspnea NYHA III or IV
- BNP ≥ 500 or NT-proBNP ≥ 2000 ng/L
- Written informed consent
- Negative pregnancy test in females < 60years

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Methods: Design

Exclusion Criteria:

- Need for ICU admission or urgent coronary intervention
- Systolic blood pressure < 100 mmHg
- Creatinine > 250 µmol/l
- Cardiopulmonary resuscitation
- Known severe aortic or mitral stenosis
- Adult congenital heart disease
- Hypertrophic obstructive cardiomyopathy
- Isolated right ventricular failure due to pulmonary hypertension

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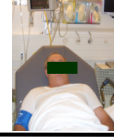
Methods: Design



according to ESC guidelines

Vasodilation

early intensive + sustained

All other therapies including loops diuretic dose and duration, beta-blockers, aldosterone antagonists, cardiac devices, and follow-up care were according to ESC guidelines + at the discretion of the treating physician in both groups

*stratified for site and BNP/NT-proBNP

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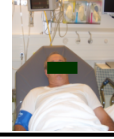
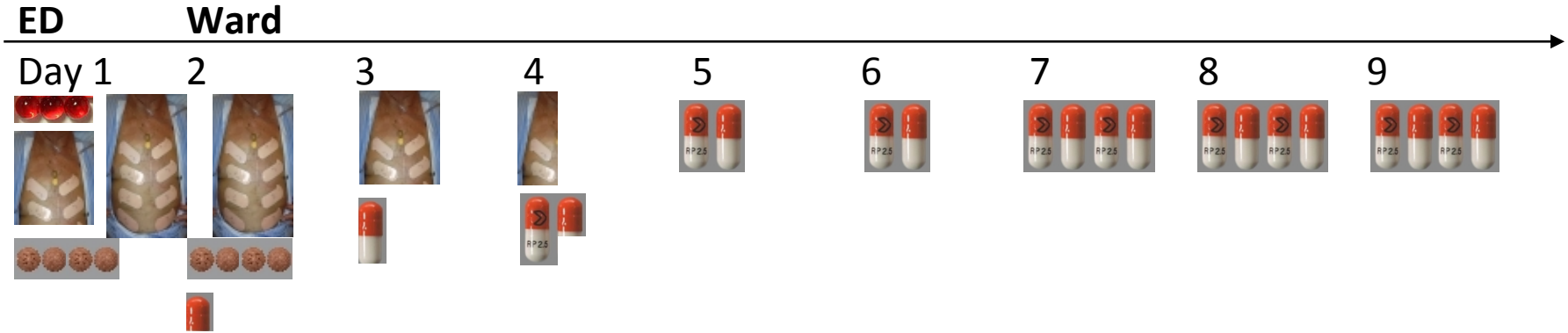
Methods: Intervention





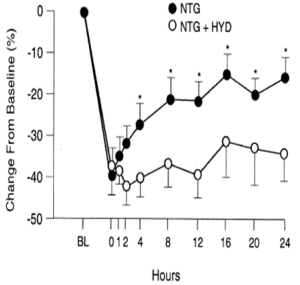
-Complimentary hemodynamic profile of sublingual & transdermal nitrates

-Favorable safety data of high-dose transdermal nitrates on a general ward

-Complementary hemodynamic profile of nitrates & hydralazine

+ Prevention of nitrate tolerance

-↑ outcome of high-dose ACE-I/ARB in chronic HF



Gogia H, et al. JACC 1995; Cohn JN, et al. NEJM 1993; Taylor AL, et al. NEJM 2006; Breidthardt T, et al. JIM 2010; Packer M, et al. Circulation 1999; Konstam MA, et al. Lancet 2009

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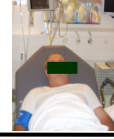
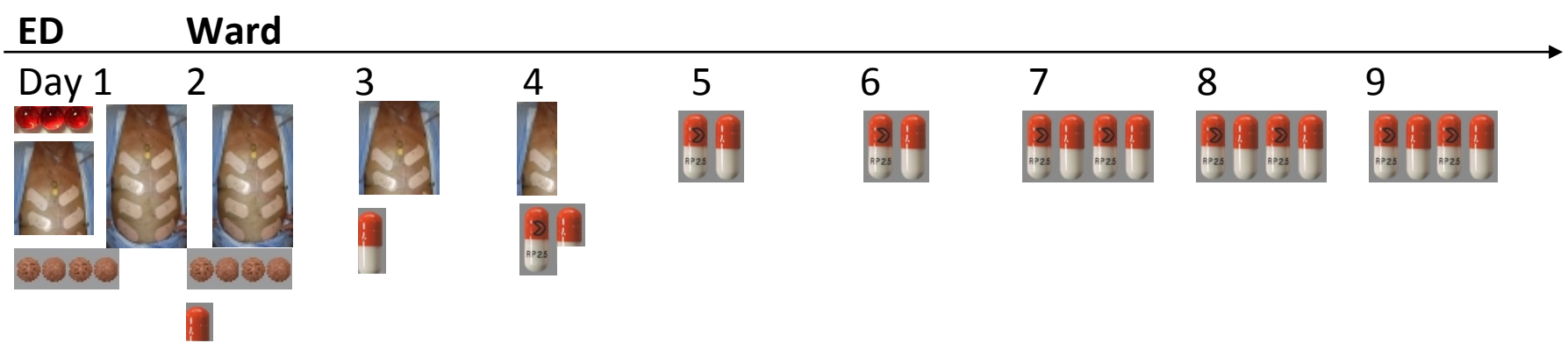
Methods: Intervention





Intervention group	day 1 at hospital admission		day 1 6 h after admission		
systolic blood pressure [mm Hg]	< 130	> 130	90 - 110	111 - 130	> 130
per oral Glyceryl trinitrate capsule (i e. Nitroglycerin Streuli®) 0.8 mg or Spray (i.e. Corangin Nitrospray®)0.4mg	3 or 6 applic.	3 or 6 applic.			
transdermal Glyceryl trinitrate (i.e. Nitroderm® TTS) [mg / 24 h]	40 - 60	60 - 80	+ 0	+ 20 - 40	+ 20 - 60
Hydralazine (i. e. Hydrapres®) 25 mg	1 - 1 - 1 - 1	1 - 1 - 1 - 1	1 - 1 - 1 - 1	1 - 1 - 1 - 1	1 - 1 - 1 - 1
ACE-inhibitor, ARB, or ARNI					

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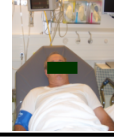
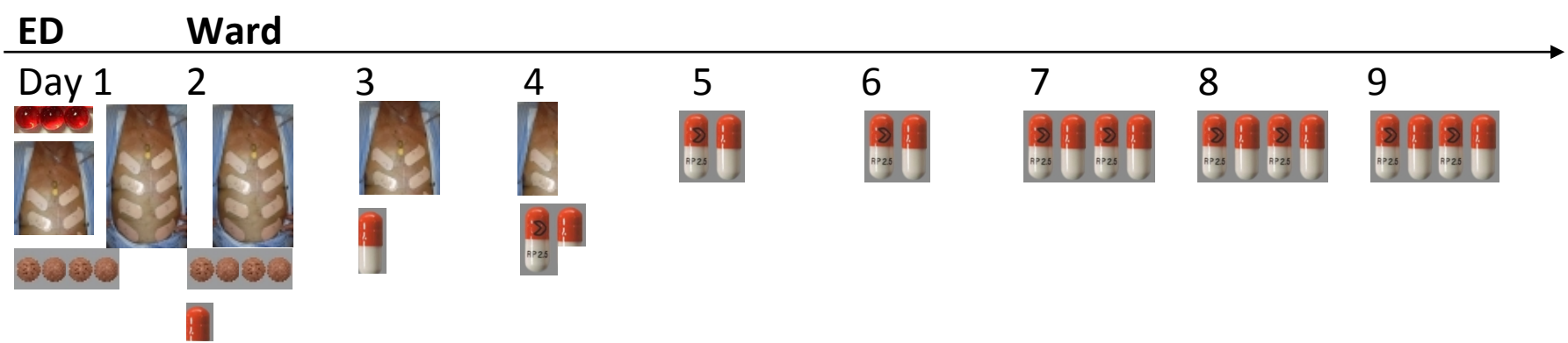
Methods: Intervention





Intervention group continuation	day 2 24 h till 48 h after admission				day 3 48 h till 72 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]**	+ 20 - 40	+ 20 - 60	+ 40 - 80	+ 40 - 80	50% of day 2	50% of day 2	75% of day 2	100% of day 2
Hydralazine (i. e. Hydrapres®) **25 mg**	1 - 1 - 1 - 1	1 - 1 - 1 - 1	1 - 1 - 1 - 1	1 - 1 - 1 - 1				
Ramipril (i. e. Triatec®) **[mg/d]**[3]	1.25	1.25	2.5	2.5	2.5 - 3.75	2.5 - 3.75	2.5 - 5	2.5 - 5
Lisinopril (i. e. Zestril®) **[mg/d]**[3]	2.5	2.5	5	5	2.5 - 5	5 - 7.5	10- 15	10 - 20
Enalapril (i. e. Reniten®) **[mg/d]**[3]	5	5	10	10	5 - 10	5 - 10	10 - 15	10 - 20
Captopril (i. e. Capoten®) **[mg/d]**[3]	37.5	37.5	50	50	37.5 - 50	37.5 - 50	50 - 75	50 - 75
Candesartan (i. e. Atacand®) **[mg/d]**[4]	4	4	8	8	8 - 16	8 - 16	16 - 24	16 - 24

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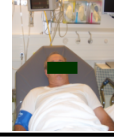
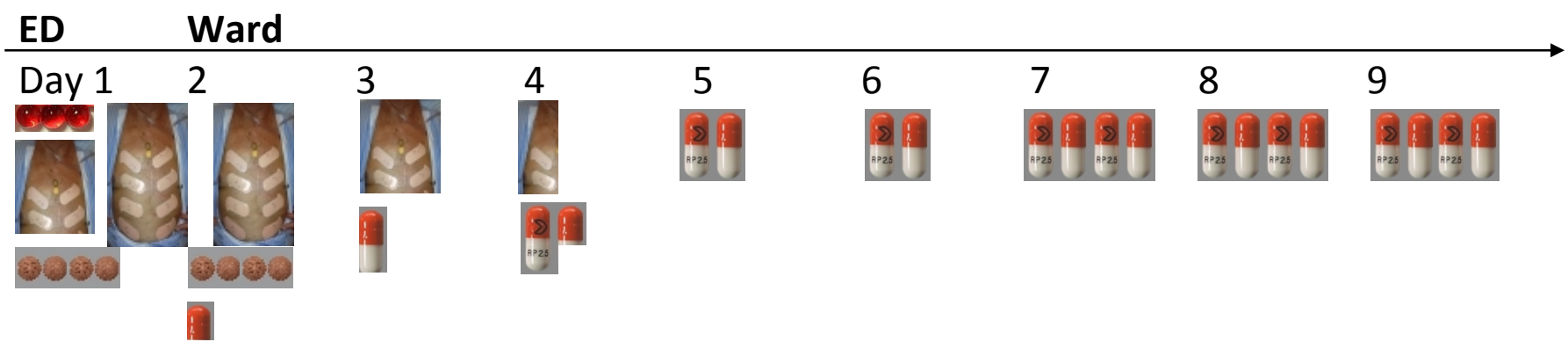
Methods: Intervention





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

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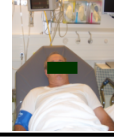
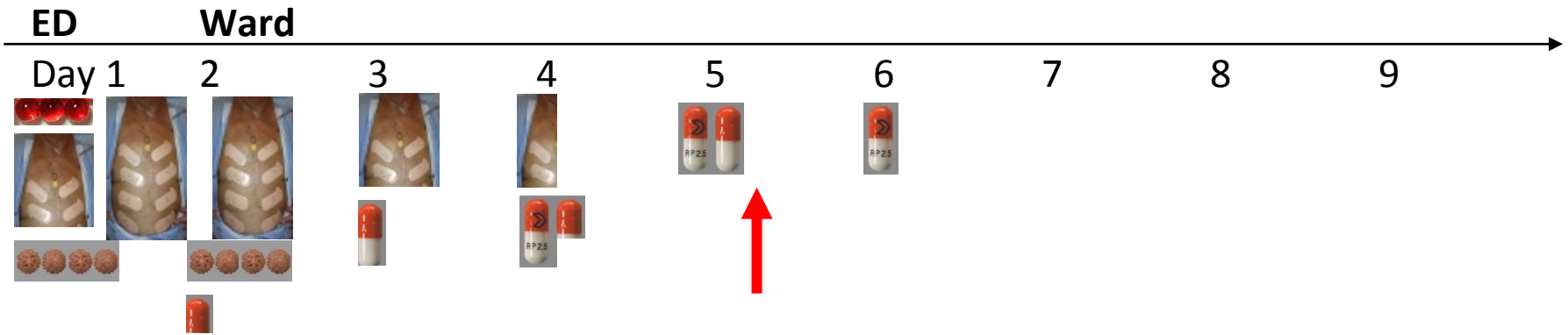
Methods: Intervention





Predefined de-escalation scheme for:

- **Hypotension**
- **Renal function ↓**
- Hyperkalemia

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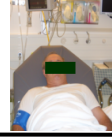
Methods: Statistics



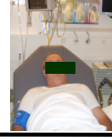
Primary endpoint*: **All-cause mortality or AHF rehosp** within 180 days

Secondary endpoints: Quantitative assessment of dyspnea at day 2 + 6 at 60° (sitting) and 20° (lying)
Time to discharge
Adverse events

Primary analysis: adjusted for four predefined strong predictors of the primary endpoint: age, AHF hospitalization in last year, systolic blood pressure, serum creatinine

*adjudicated by a CEC blinded to group assignment

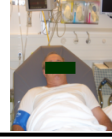
Methods: Statistics



Sample size: superiority hypothesis, based on a prior AHF study (Mueller C, et al. NEJM 2004)
A hypothesized 20% reduction of the primary endpoint was expected to require **385 patients per treatment arm** to obtain, with a probability of 80%, a log rank test result that is statistically significant at the 5% level.
To compensate for an expected 1-2% of patients in whom the primary endpoint could not be assessed at 180 days due to loss to follow-up or complete withdrawal of informed consent, it was planned to enroll approximately **785** patients.
No interim analyses were performed.

Primary and secondary efficacy outcomes were compared between treatment groups on an **intention-to-treat basis** with inclusion of all randomized patients, irrespective of whether and how much of the interventional strategy they received.

Methods: Statistics

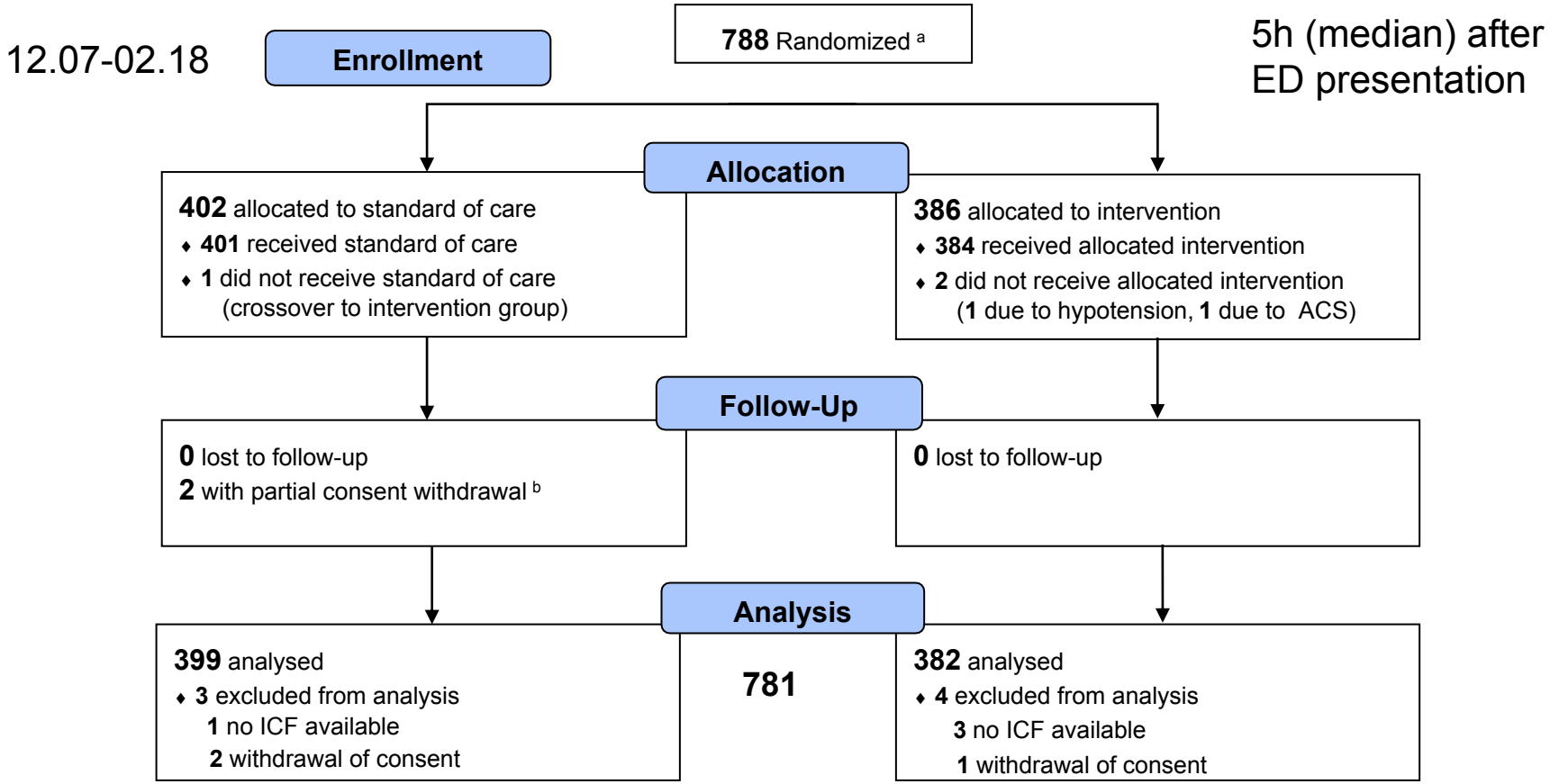


The primary endpoint was analyzed by using survival analysis for cumulative event rates including **Kaplan-Meier estimates** and **Cox regression** for calculation of adjusted hazard ratios.

Interaction test (*p*-value) were conducted between the treatment group and the sub-group variables using Cox regression models with tests for interaction to evaluate the consistency of treatment effects.

Pre-specified subgroups included:
1) women versus men
2) <75y versus >75y
3) reduced LVEF (<40%) versus mid-range LVEF (40-49%) versus preserved LVEF (≥50%)

Results: Patient flow



Results: Baseline characteristics I

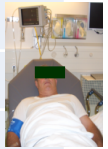
	Standard of Care (N=399)	Intervention (N=382)
Age, median [IQR], y	77.0 [69.0, 84.0]	78.0 [70.0, 85.0]
Women, No. (%)	148 (37)	140 (37)
BNP, median [IQR], ng/l	1272 [845, 2146]	1249 [849, 2254]
NT-proBNP, median [IQR], ng/l	5336 [3021, 9517]	6135 [3359, 9899]
LVEF, median [IQR], %	37 [26, 51]	36 [26, 50]
CV Risk Factors:		
Hypertension, No. (%)	339 (85)	326 (85)
Diabetes mellitus, No. (%)	139 (35)	122 (32)
Structural Heart Disease:		
Chronic Heart failure, No. (%)	229 (57)	231 (60)
Hypertensive heart disease, No. (%)	174 (44)	177 (46)
Coronary artery disease, No. (%)	233 (58)	220 (58)
Myocardial infarction, No. (%)	141 (35)	127 (33)
Atrial Fibrillation, No. (%)	200 (50)	192 (50)

Results: Baseline characteristics II

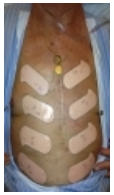
	Standard of Care (N=399)	Intervention (N=382)
Chronic Comorbidities:		
COPD/ Asthma, No. (%)	88 (22)	83 (22)
Renal insufficiency, No. (%)	196 (49)	205 (54)
eGFR, median [IQR], mL/min per 1.73 m^2	53 [37, 72]	52 [38, 69]
Symptoms & Signs: NYHA class, No. (%)		
III	218 (55)	208 (54)
IV	181 (45)	174 (46)
Weight gain, No. (%)	193 (48)	189 (49)
Parox. nocturnal dyspnea, No. (%)	218 (55)	211 (55)
Coughing, No. (%)	199 (50)	180 (47)
Pulmonary Rales, No. (%)	348 (90)	331 (89)
JVP ↑, No. (%)	190 (48)	197 (52)
Positive HJR, No. (%)	92 (23)	98 (26)
Peripheral edema, No. (%)	280 (70)	287 (75)

Results: Baseline characteristics III

	Standard of Care (N=399)	Intervention (N=382)
Vital signs		
Systolic BP, median [IQR], mmHg	131.0 [118.0, 150.0]	130.0 [117.2, 145.0]
Respiratory rate, median [IQR], rpm	20.0 [18.0, 24.0]	20.0 [18.0, 24.0]
Oxygen saturation, median [IQR], %	96 [94, 98]	96 [93, 97]
Triggers of the Current AHF Episode		
Arrhythmia (Afib, …), No. (%)	103 (26)	102 (27)
Hypertension, No. (%)	53 (13)	40 (10)
Myocardial ischemia / MI, No. (%)	21 (5)	22 (6)
Infection, No. (%)	48 (12)	56 (15)
Non-compliance, No. (%)	46 (12)	25 (7)
Medication (NSAID, diuretics↓), No. (%)	32 (8)	24 (6)
Unknown, No. (%)	84 (21)	109 (29)

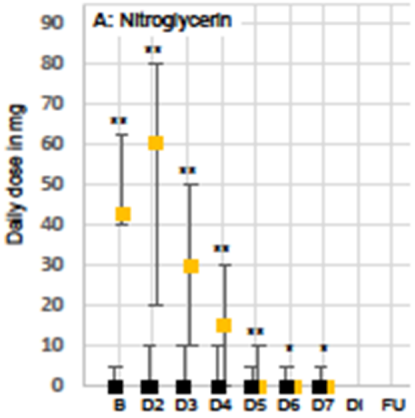


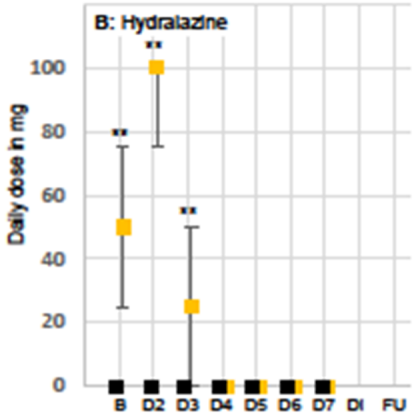
Results: Implementation of Intervention

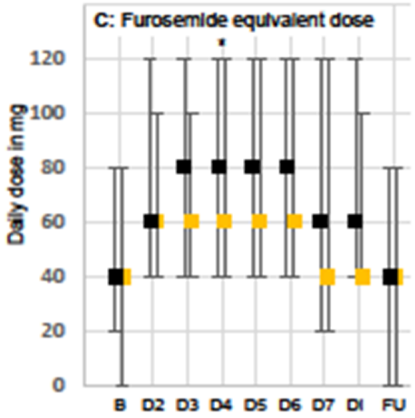


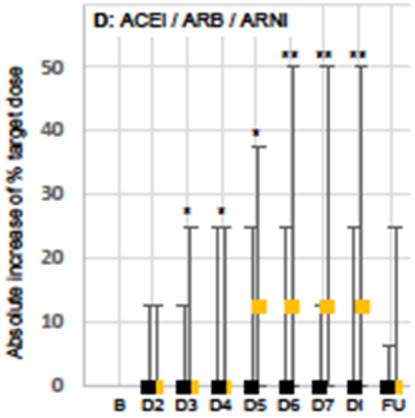
Baseline
% target dose
SOC: 33%
Inter: 25%

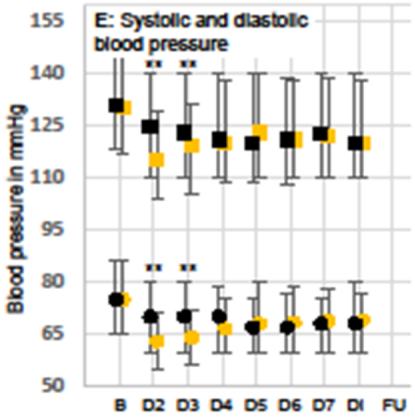
180-days
% target dose
SOC: 22%
Inter: 16%

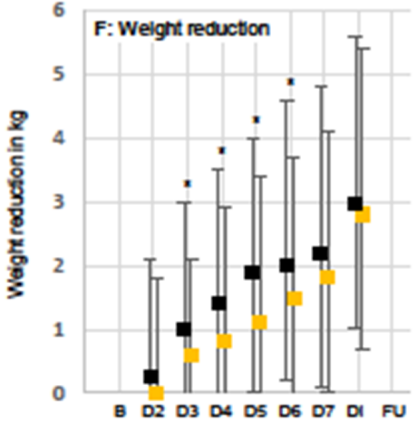




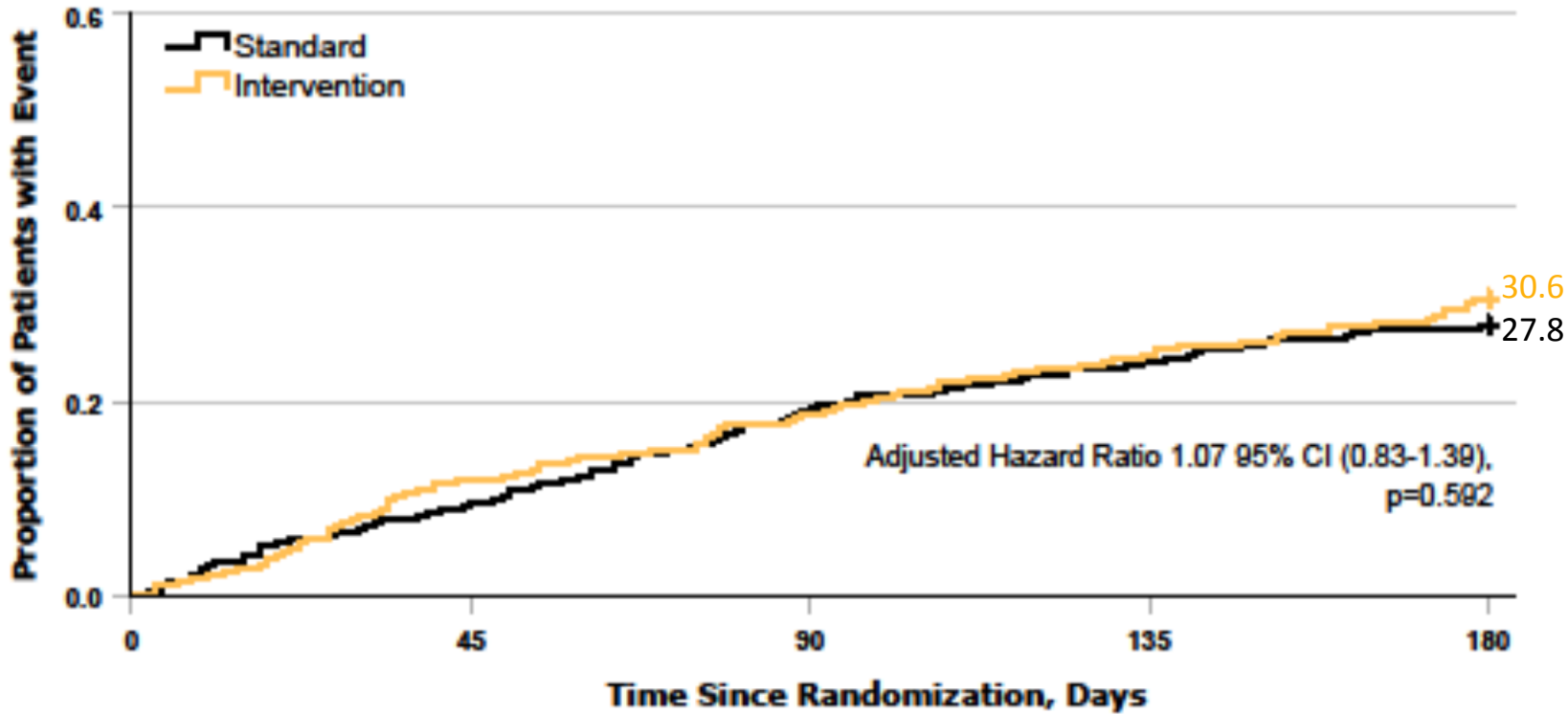








Results: Primary Endpoint (Death or AHF)



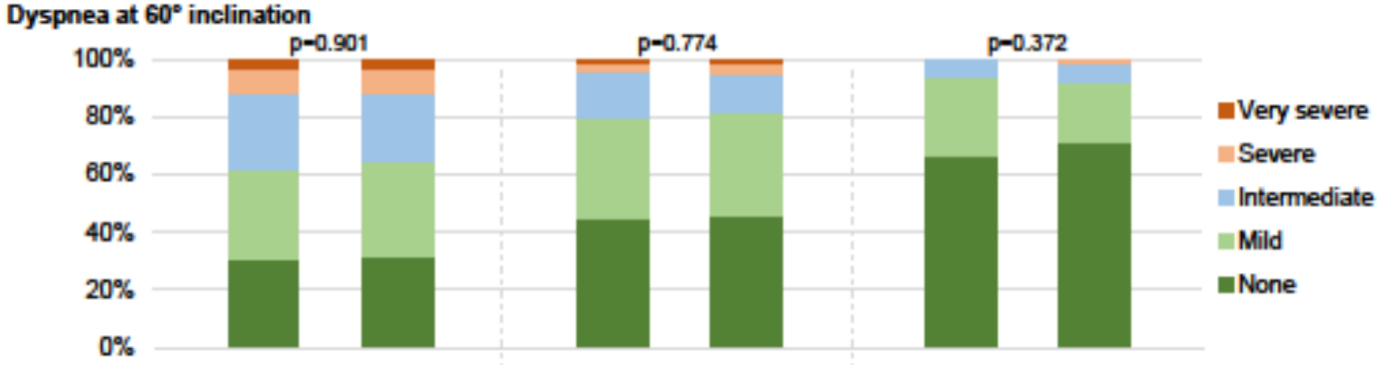
No at risk					
Standard	399	361	322	303	288
Intervention	382	337	311	287	265

Results: Primary Endpoint (Death or AHF)

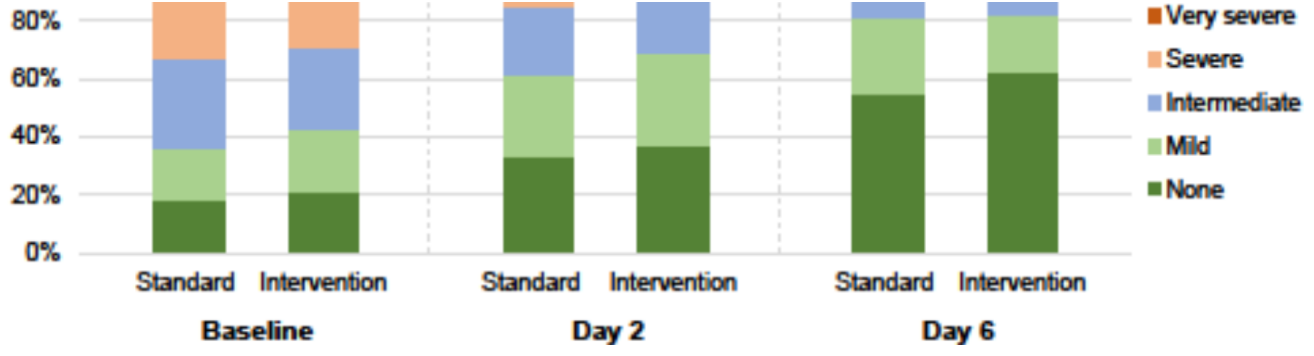
	Standard of Care (N=399)	Intervention (N=382)	Ad. HR (95%CI)	*P* Value	*P* Value for Interaction
Gender					**0.022**
Female	34/148	53/140	1.67 (1.08-2.59)	0.022	
Male	77/251	64/242	0.85 (0.61-1.19)	0.346	
Age					0.288
<75 years	34/159	43/144	1.23 (0.78-1.95)		
≥75 years	77/240	74/238	0.97 (0.70-1.34)		
LVEF					0.208
<40%	44/191	56/175	1.34 (0.90-1.99)		
40-49%	23/59	23/63	0.89 (0.50-1.60)		
≥50%	29/102	22/96	0.76 (0.43-1.33)		

Results: Secondary Endpoint Dyspnea

Dyspnea improved in both groups to a similar extent.



Length of stay (median): 9 days vs 9 days



Results: Adverse Events

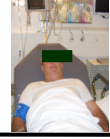
	Standard of Care (N=399)	Intervention (N=382)	P Value
Any (Serious) Adverse Event	300 (75)	315 (82)	0.017
Adverse Events			
Headaches, No. (%)	38 (10)	101 (26)	<0.001
Fall, No. (%)	7 (2)	14 (4)	0.153
Worsening renal function [a], No. (%)	80 (20)	81 (21)	0.757
Hypokalemia < 3.5 mmol/l, No. (%)	98 (25)	88 (23)	0.677
Hyperkalemia > 5 mmol/l, No. (%)	28 (7)	41 (11)	0.089
Systolic arterial hypotension [b], No. (%)	9 (2)	29 (8)	0.001
Others[c], No. (%)	29 (7)	48 (13)	0.018
Serious Adverse Events			
Death, No. (%)	61 (15)	55 (14)	0.803
Transfer to the intensive care unit, No. (%)	16 (4)	14 (4)	0.948
Cardiopulmonary resuscitation, No. (%)	4 (1)	5 (1)	0.948
In-patient hospitalization, No. (%)	167 (42)	167 (44)	0.650

[a] defined as creatinine increase > 30% of baseline [b] defined as systolic arterial pressure < 80 mmHg over 30 minutes
[c] itching of the skin due to the nitrate patch

Limitations:

1) Cannot comment on patients with severe renal dysfunction and patients with SBP < 100mmHg, as they were excluded.
2) Enrolment was slow. As treatment of AHF at large remained unchanged, findings should still apply to current clinical practice.
3) The open-label design, which was mandated by the aim to test a strategy, not a single drug, may have introduced a bias in the unblinded assessment of dyspnea at day 2 and day 6, but not in the primary endpoint, which was assessed by an independent clinical events committee blinded to group assignment.

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**.