Serelaxin: current perspectives

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Presenter Disclosure

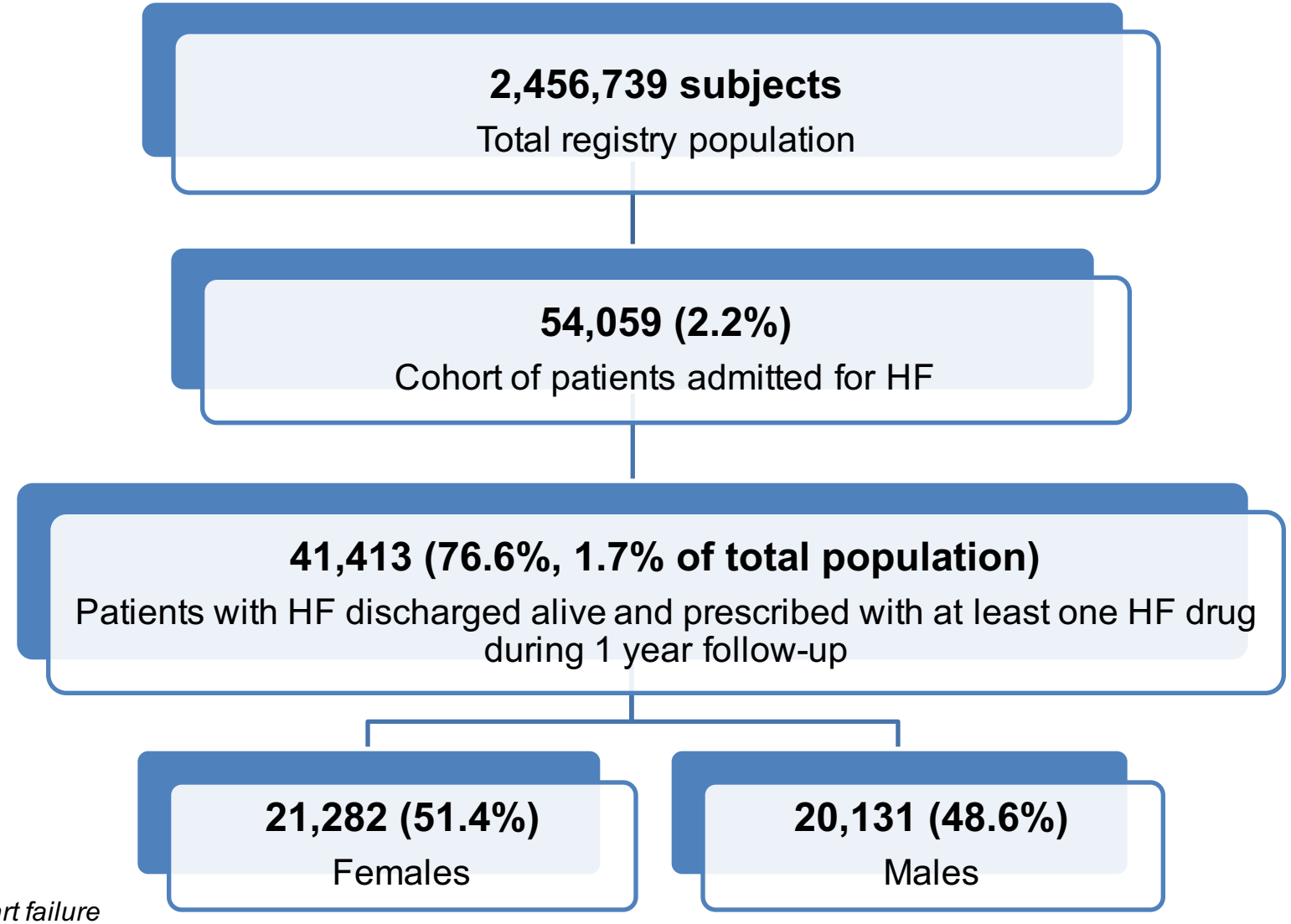
Dr. Maggioni:

- *Serving in Committees of studies on Heart Failure sponsored by:* Bayer, Cardiorentis, Novartis Pharma AG

Acute Hospitalized Heart Failure

- The problem

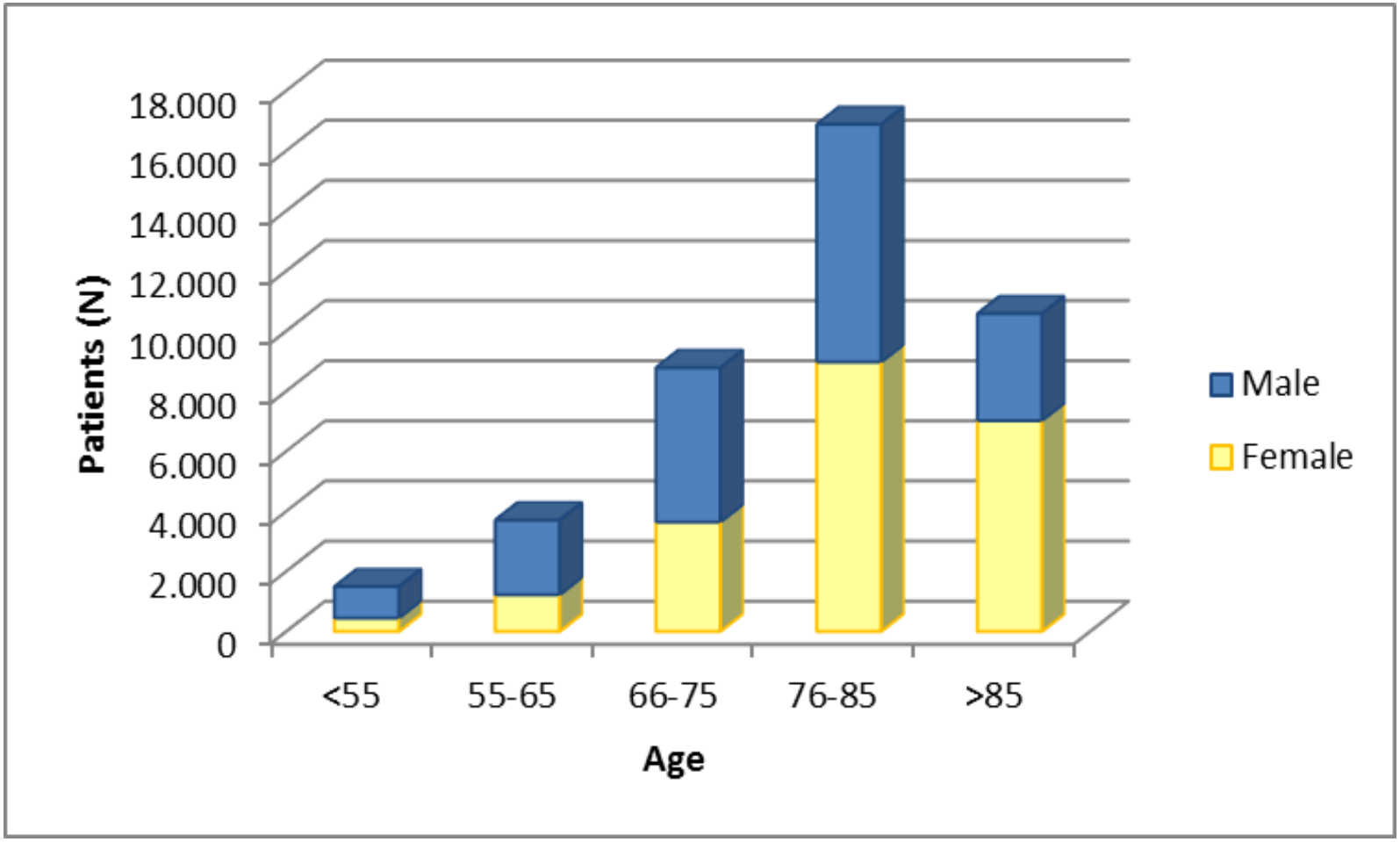
Real World Evidence on HF



HF=heart failure

Maggioni et al. European Journal of Heart Failure (2016) 18, 402–410

Patients distribution by age and gender

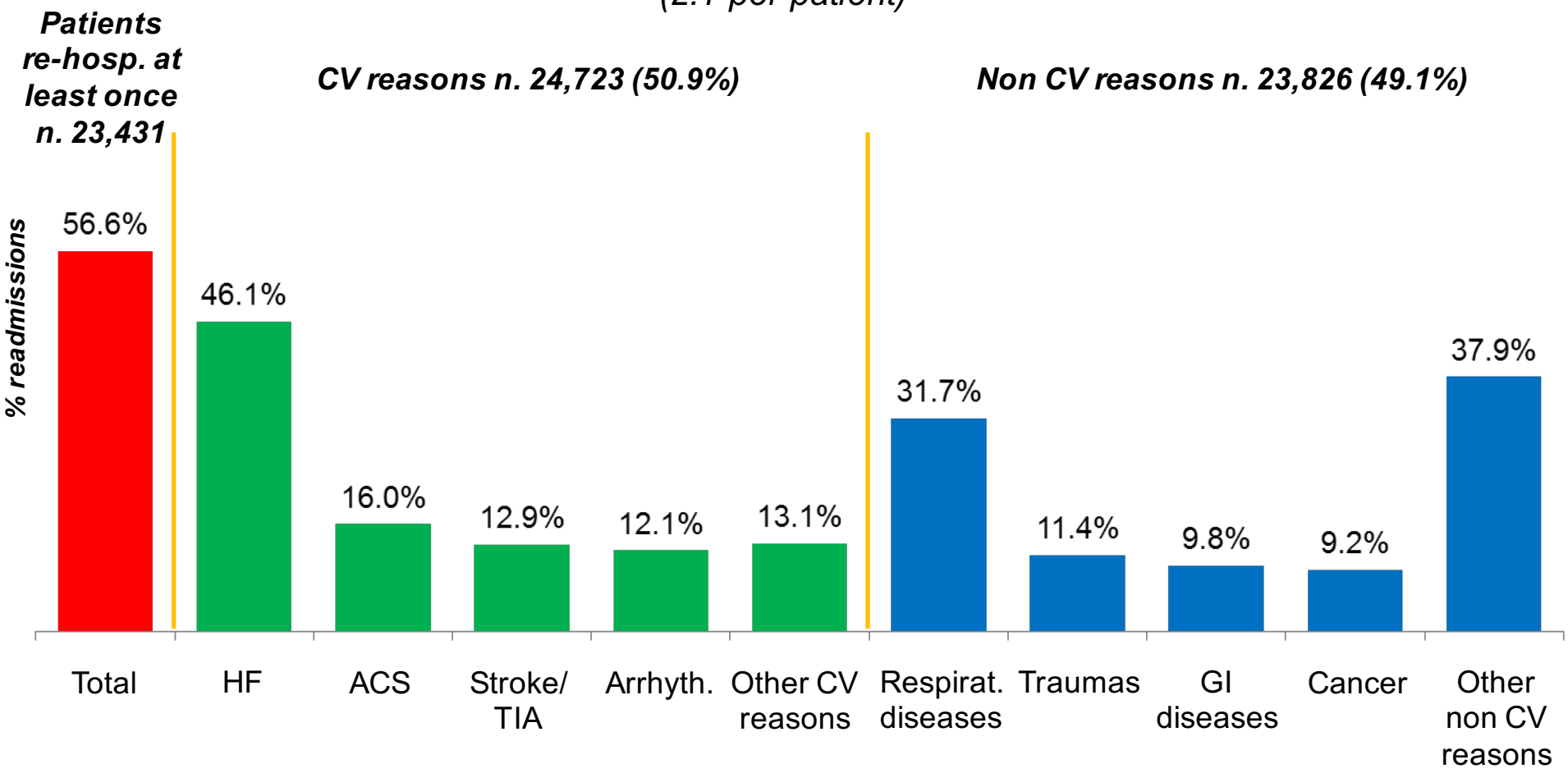


Maggioni et al. European Journal of Heart Failure (2016) 18, 402–410

Rate and causes of hospital re-admissions

Total number of re-admissions = 48,549

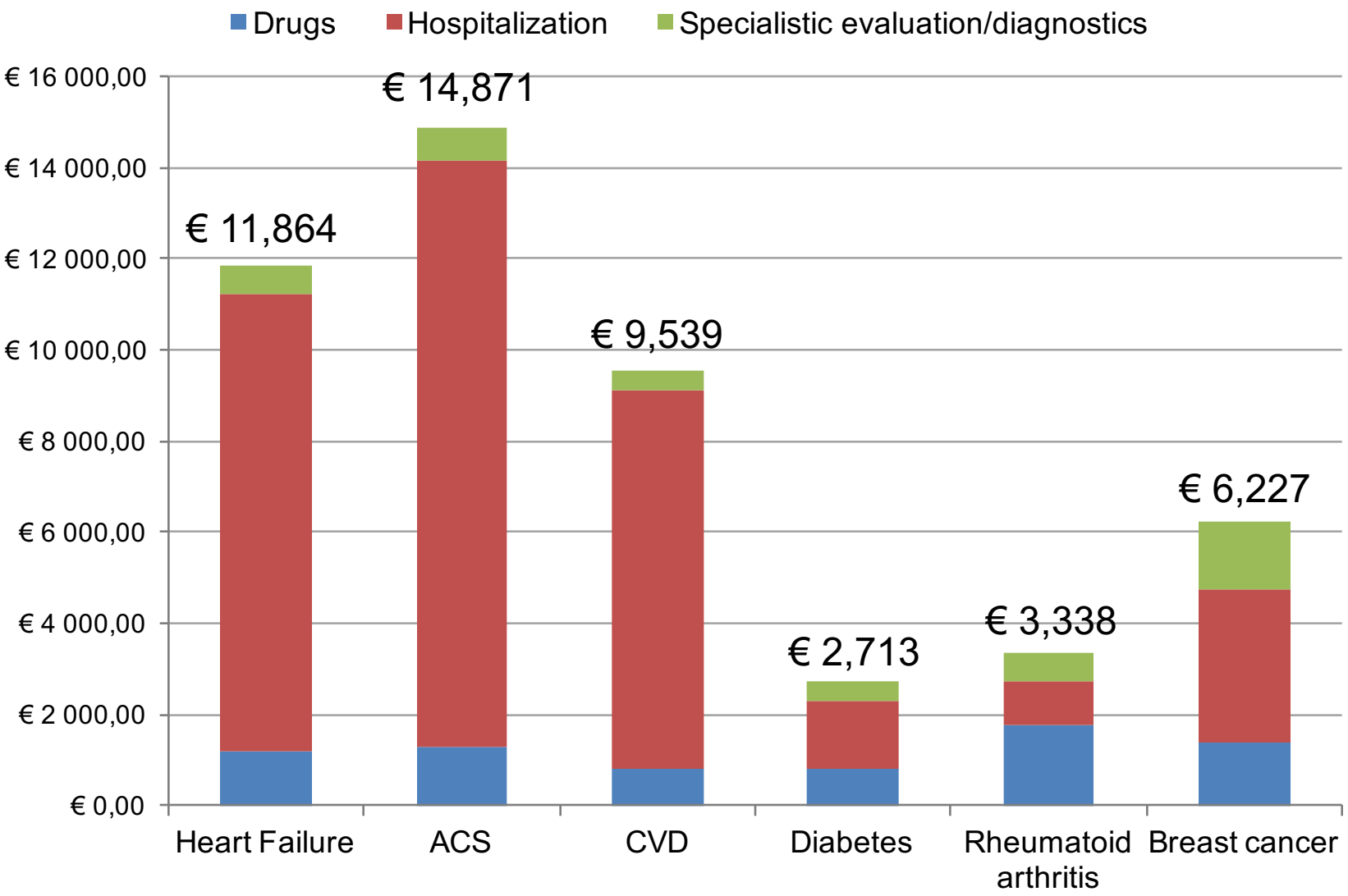
(2.1 per patient)



HF=heart failure; ACS=acute coronary syndrome; TIA=transient ischemic attack; CV=cardiovascular; GI=gastrointestinal

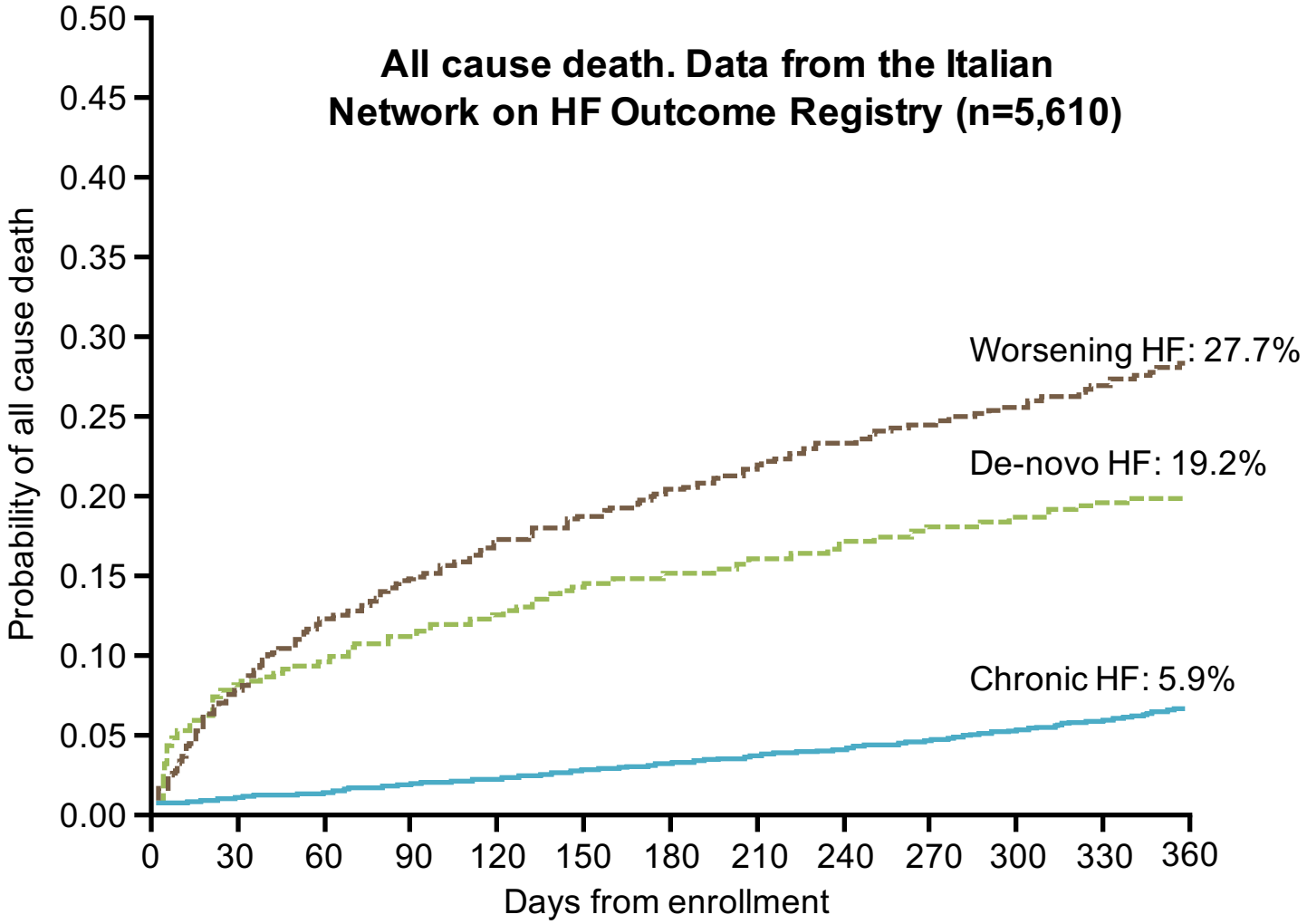
Maggioni et al. European Journal of Heart Failure (2016) 18, 402–410

Costs per patient per year



Maggioni et al. European Journal of Heart Failure (2016) 18, 402–410

Risk of death is higher in patients hospitalized for AHF compared with patients with chronic HF



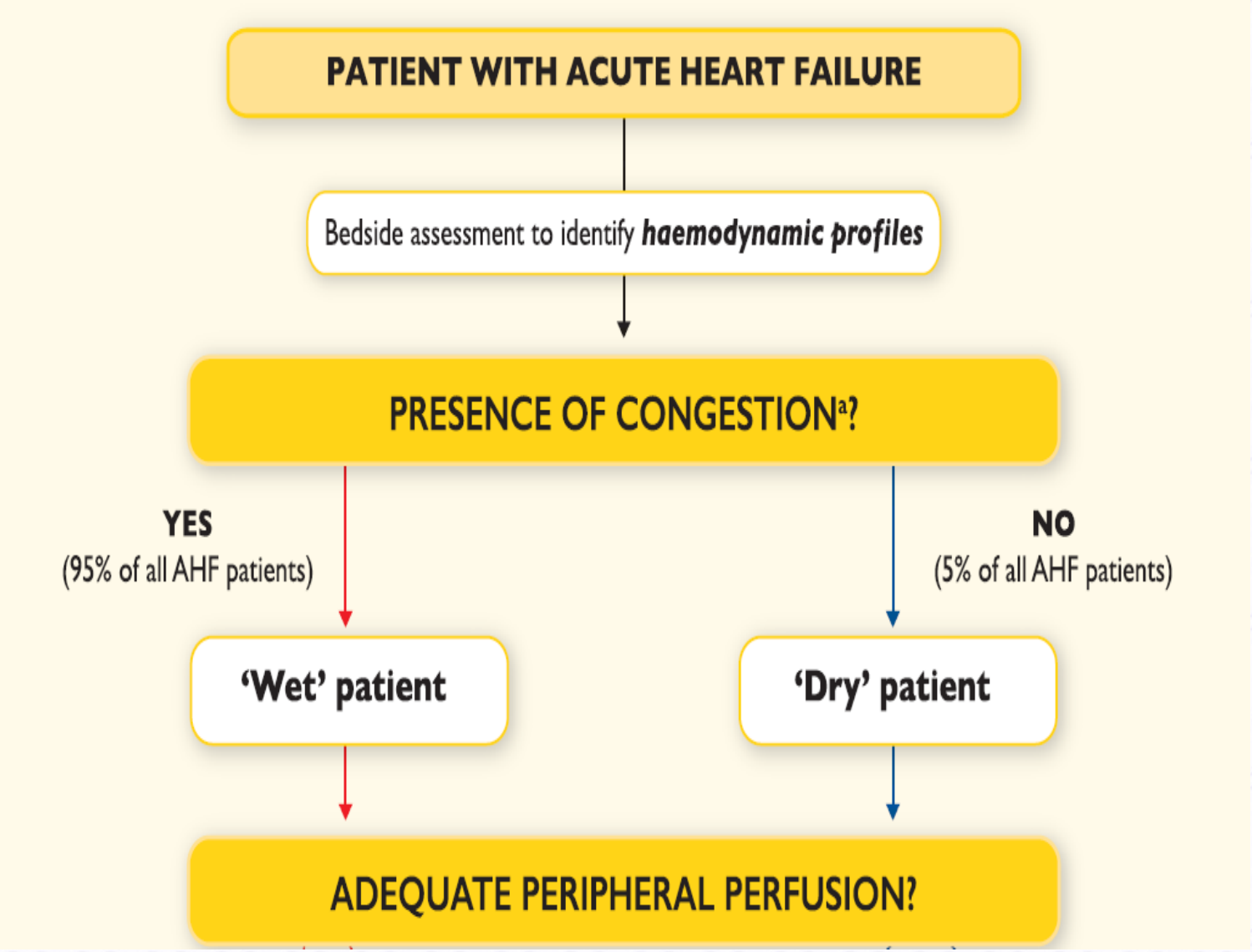
HF=heart failure

Tavazzi et al. Circ Heart Fail 2013;6:473–81

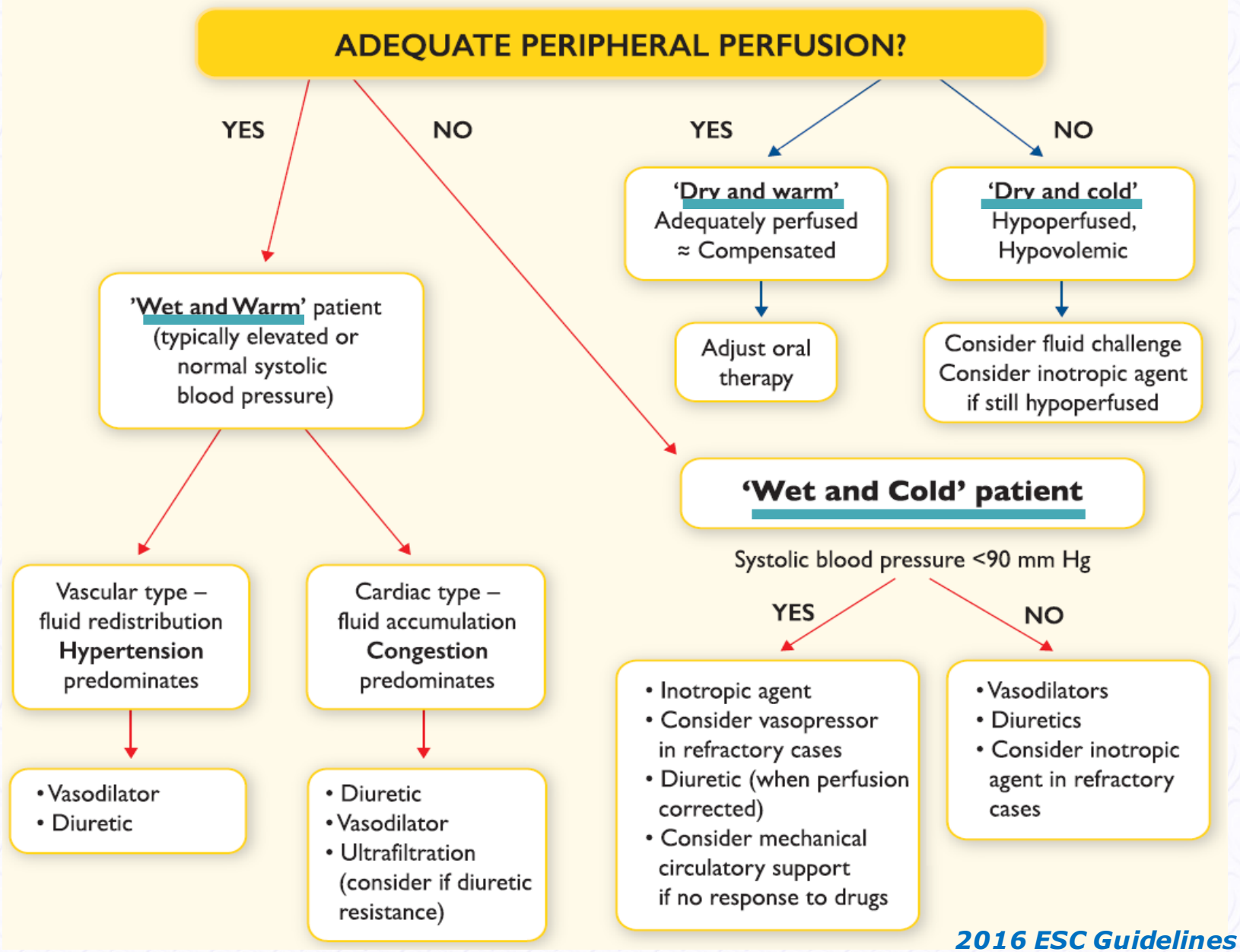
Acute Hospitalized Heart Failure

- The problem
- How to manage it

Management of patients with acute heart failure based on clinical profile during an early phase



Management of patients with acute heart failure based on clinical profile during an early phase



EUROPEAN SOCIETY OF CARDIOLOGY®

2016 ESC Guidelines on HF

Large randomized controlled trials in AHF have failed to demonstrate outcome benefits

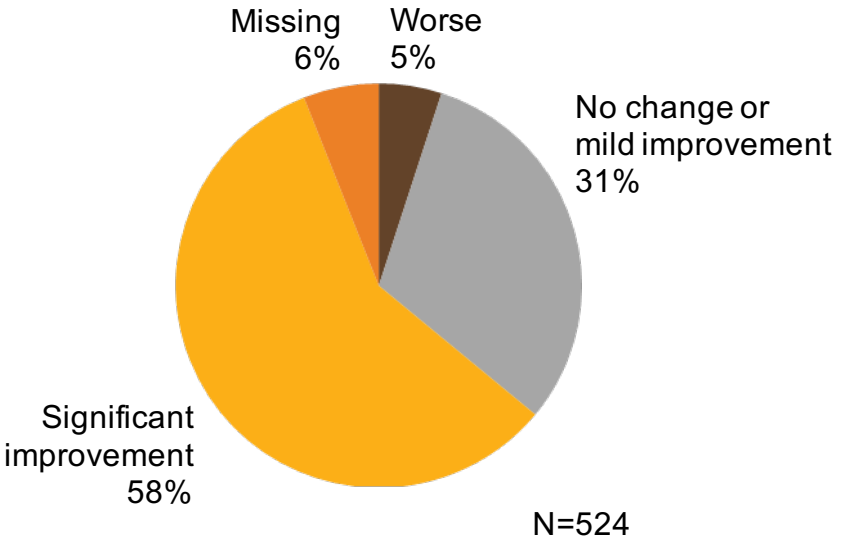
Trial name	Patient population	Intervention	Primary endpoint	Significant effect?
OPTIME-CHF[1]	951 patients admitted with exacerbation of systolic HF	i.v. **milrinone** vs pbo for 48 hours	Length of hospitalization for CV causes	✗
VERITAS[2]	1,448 patients hospitalized with AHF	i.v. **tezosentan** vs pbo for 24–72 hours	Change in dyspnea, incidence of death and worsening HF at 7 days	✗
SURVIVE[3]	1,327 patients hospitalized with AHF	i.v. **levosimendan** vs dobutamine	All-cause mortality at 180 days	✗
EVEREST[4]	4,133 patients hospitalized with AHF	**Tolvaptan** 30 mg once-daily vs pbo for 60 days	All-cause mortality and CV death or hospitalization for HF	✗
ASCEND-HF[5]	7,141 patients hospitalized for AHF	i.v. **nesiritide** vs pbo for 24 hours–7 days	Change in dyspnea and 30-day all-cause mortality or HF hospitalization	✗
PROTECT[6]	2,033 patients hospitalized for AHF	i.v. **rolofylline** vs pbo for up to 3 days	Composite of survival, HF status and renal function	✗

AHF=acute heart failure; CV=cardiovascular; HF=heart failure; pbo=placebo

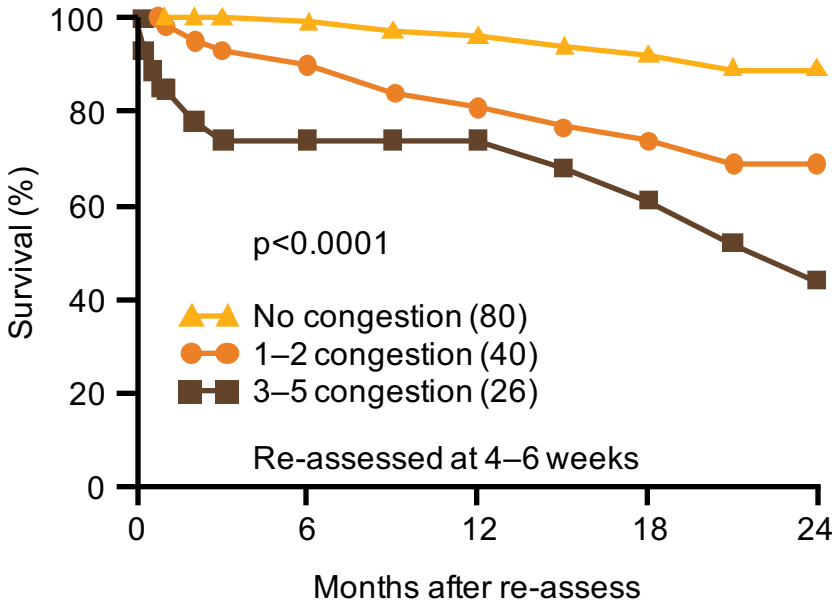
1. Cuffe et al. JAMA 2002;287:1541–7; 2. McMurray et al. JAMA 2007;298:2009–19;
3. Mebazaa et al. JAMA 2007;297:1883–91; 4. Konstam et al. JAMA 2007;297:1319–31;
5. O'Connor et al. N Engl J Med 2011;365:32–43; 6. Massie et al. N Engl J Med 2010;363:1419–28

Current therapies do not provide optimal relief from AHF signs and symptoms

Only 58% of patients hospitalized for acute HF show good symptom relief with standard therapy at 6 hours[1,2]



Signs and symptoms of congestion after hospitalization predict poor survival‡[3]



- **24% of patients hospitalized for HF in Europe have signs of congestion at discharge[4]**

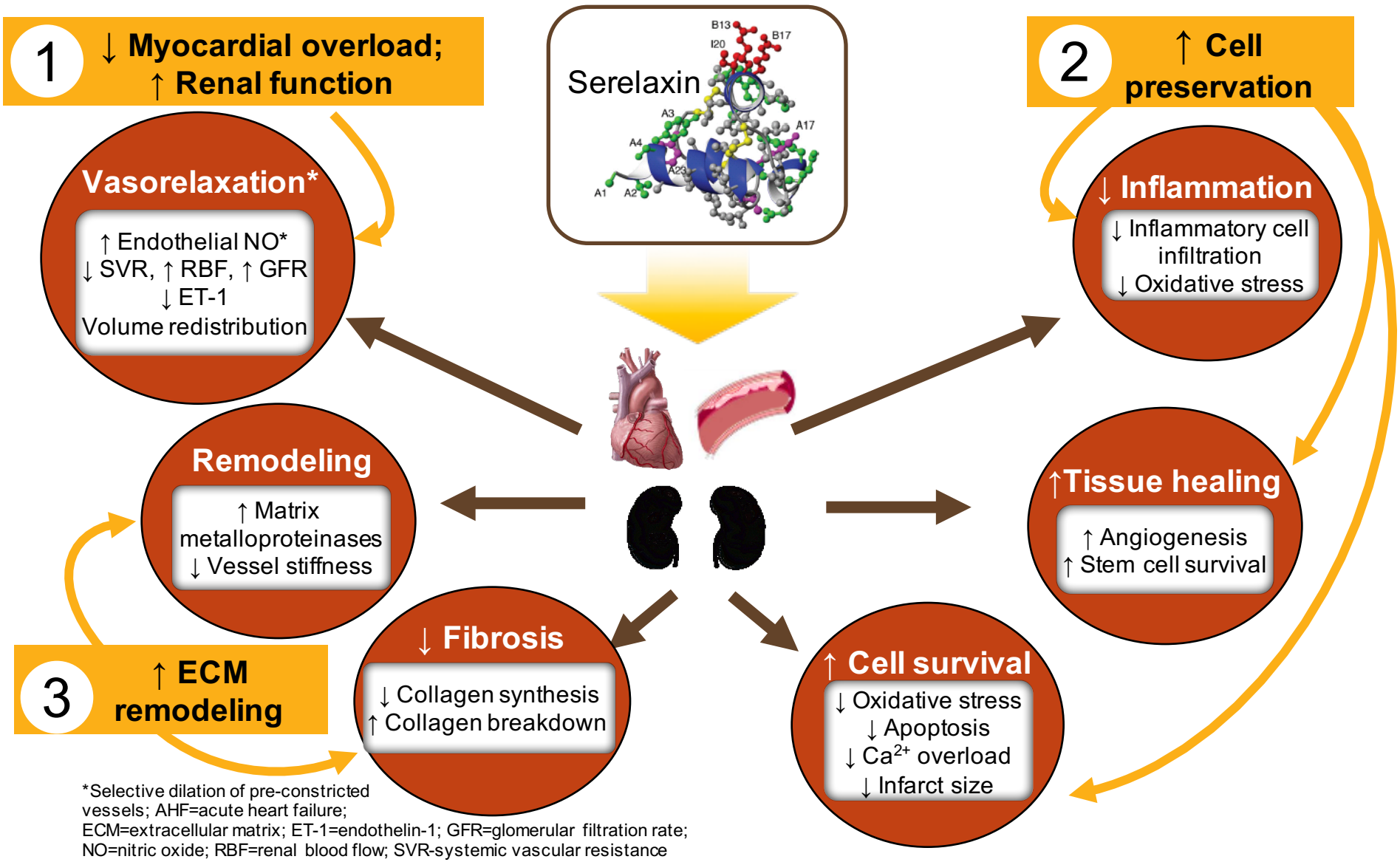
‡Patients with New York Heart Association class IV HF (n=146) were re-assessed for signs of congestion 4–6 weeks after discharge. Criteria for congestion were orthopnea, raised jugular venous pressure, the need to increase the dose of diuretic during the past week, and attending staff assessment of weight;
AHF=acute heart failure; HF=heart failure

1. Mebazaa et al. Eur Heart J 2010;31:832–41; 2. Hogg & McMurray. Eur Heart J 2010;31:771–2; 3. Lucas et al. Am Heart J 2000;140:840–7; 4. Maggioni et al. Eur J Heart Fail 2010;12:1076–84

Acute Hospitalized Heart Failure

- The problem
- How to manage it
- The potential role of serelaxin in the context of this unmet need

Serelaxin has potential multi-mechanistic effects, which may address the pathophysiology of AHF

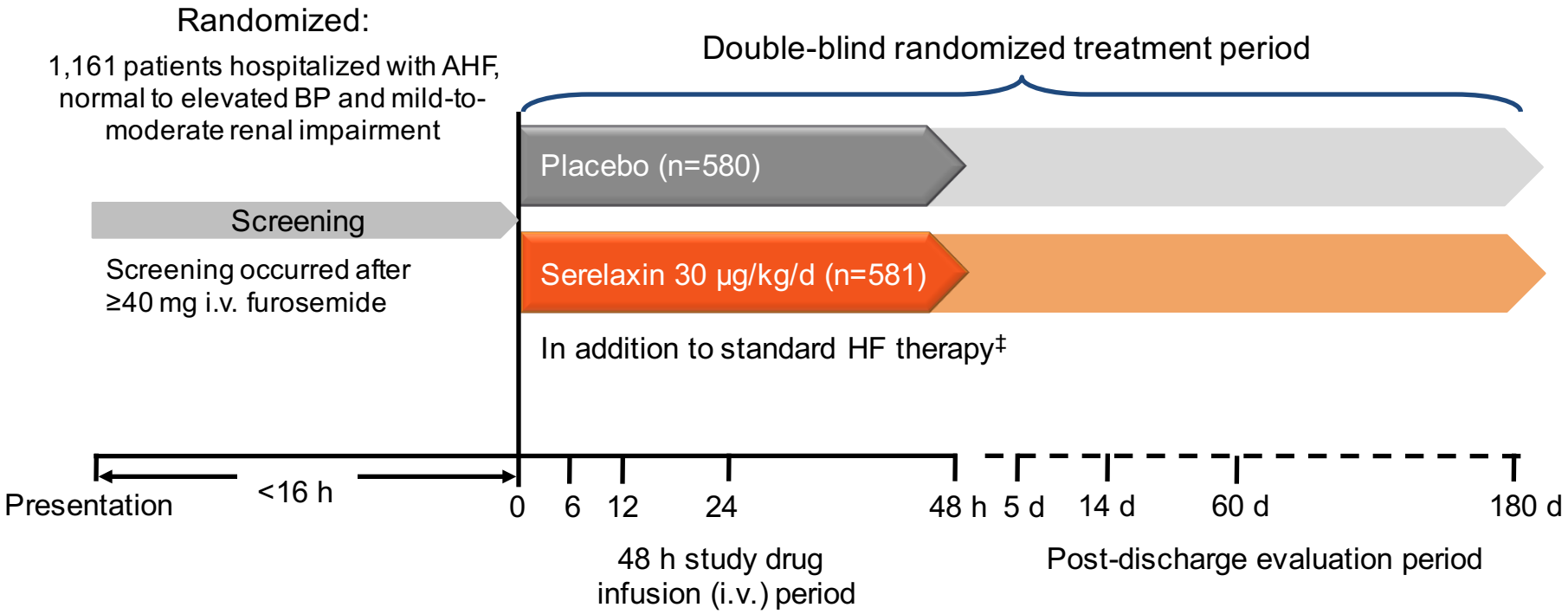


*Selective dilation of pre-constricted vessels; AHF=acute heart failure; ECM=extracellular matrix; ET-1=endothelin-1; GFR=glomerular filtration rate; NO=nitric oxide; RBF=renal blood flow; SVR-systemic vascular resistance

Adapted from Du et al. Nat Rev Cardiol 2010;7:48–58

RELAX-AHF: study design

- A Phase III, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of serelaxin, in addition to standard therapy, in subjects hospitalized for AHF



‡Standard HF therapy permitted at physician's discretion
AHF=acute heart failure; BP=blood pressure; d=day; h=hour; i.v.=intravenous; RELAX-AHF=RELAXin in Acute Heart Failure
Teerlink et al. Lancet 2013;381:29–39; Ponikowski et al. Am Heart J 2012;163:149–55.e1

Serelaxin clinical trial program addresses the four essential endpoints for assessing AHF therapies

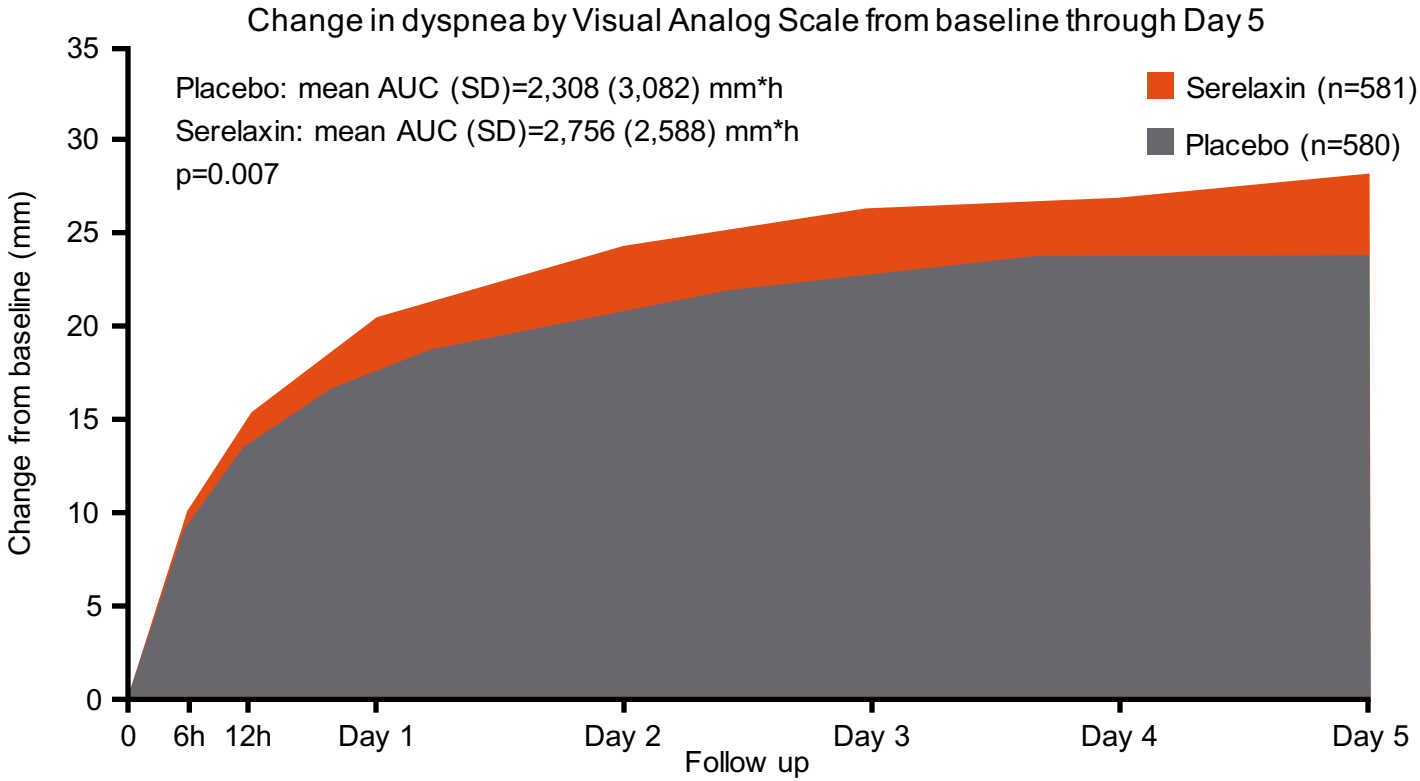
1. **Effects on signs and symptoms**
2. Effects on in-hospital measures
3. Effects on end-organ damage
4. Effects on post-discharge events

AHF=acute heart failure

RELAX-AHF: significant improvement in dyspnea with serelaxin versus placebo (Visual Analog Scale) in patients with AHF

Primary endpoint

- Serelaxin significantly improved the primary efficacy endpoint of dyspnea relief through Day 5 assessed by the Visual Analog Scale AUC compared with placebo (448 mm*h, 95% CI 120, 775; p=0.007)

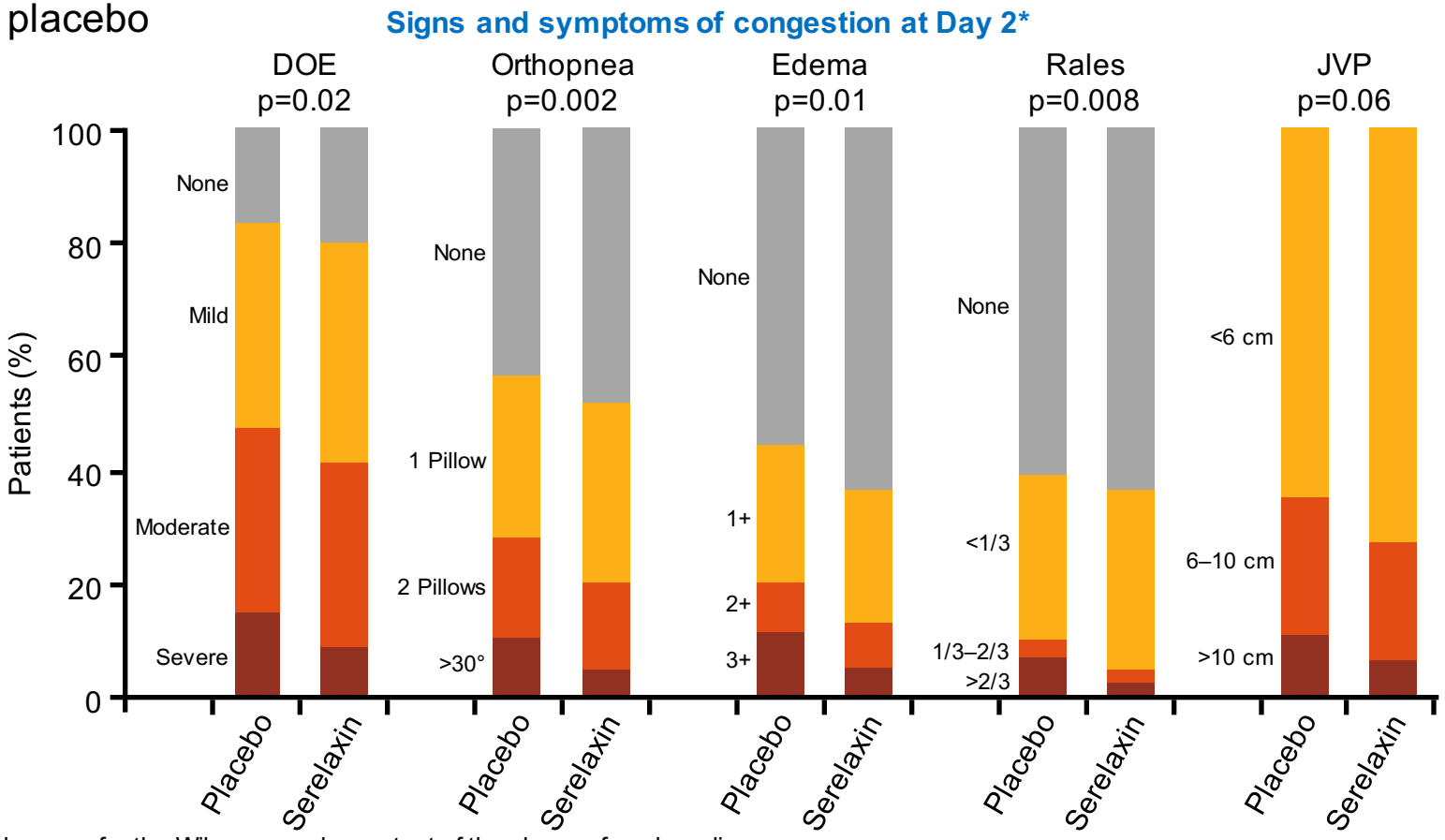


AHF=acute heart failure; AUC=area under the curve; CI=confidence interval; h=hour; RELAX-AHF=RELAXin in Acute Heart Failure; SD=standard deviation

Teerlink et al. Lancet 2013;381:29–39

RELAX-AHF: improvement in signs and symptoms of congestion with serelaxin versus placebo at Day 2 in patients with AHF

- Despite significantly lower doses of i.v. loop diuretics (161 vs 213 mg, p=0.006), serelaxin significantly improved signs and symptoms of congestion compared with placebo



*p values are for the Wilcoxon rank sum test of the change from baseline

AHF=acute heart failure; DOE=dyspnea on exertion; i.v.=intravenous; JVP=jugular venous pressure; RELAX-AHF=RELAXin in Acute Heart Failure

Teerlink et al. Lancet 2013;381:29–39

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1. Effects on signs and symptoms
2. **Effects on in-hospital measures**
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4. Effects on post-discharge events

AHF=acute heart failure

RELAX-AHF: reduction in worsening of heart failure with serelaxin despite lower doses of i.v. loop diuretics in patients with AHF

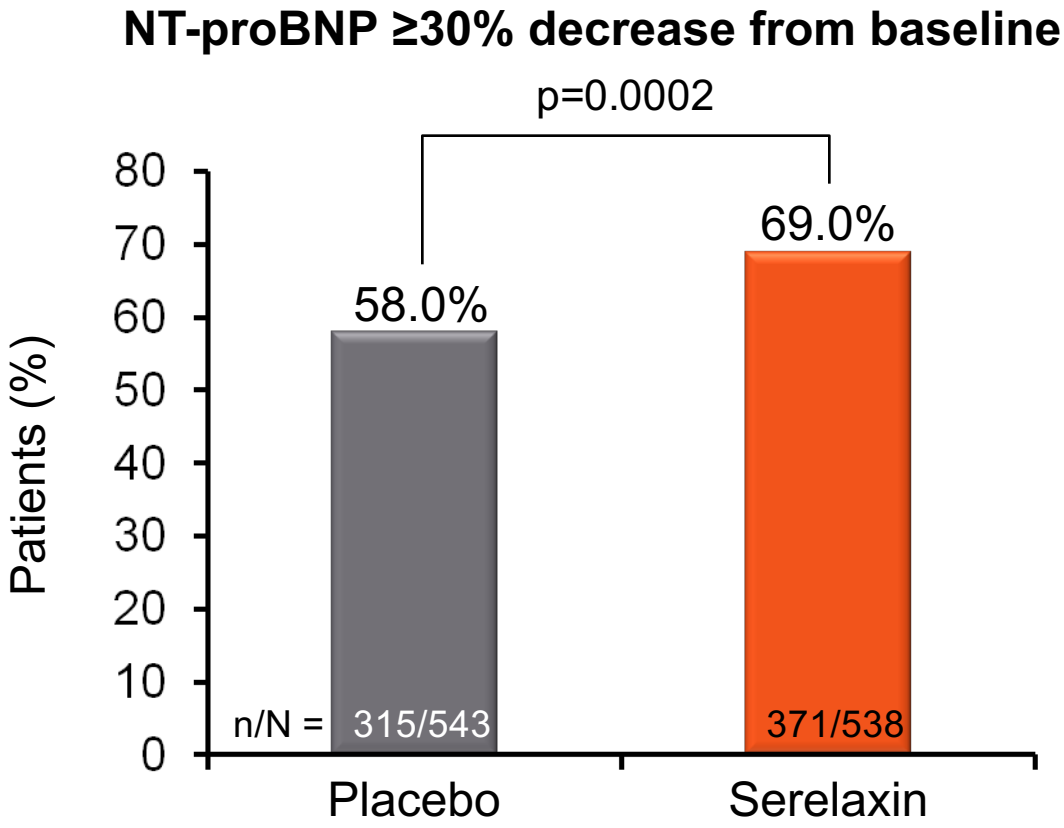
Additional efficacy outcome	Placebo	Serelaxin	Treatment effect (95% CI)	p value
Study day of WHF through Day 5[†]	5.5 (1.4)	5.8 (0.9)	0.3 (0.1, 0.4)[‡]	0.0009[¶]
WHF through 14 days, n (KM %)	91 (15.7%)	66 (11.4%)	0.70 (0.51, 0.96)*	0.024[#]
Total i.v. loop diuretic dose through Day 5, mg[##]	213 (358)	161 (265)	–52 (–88,–15)[‡]	0.006[§]
Total oral loop diuretic dose through Day 5, mg	183 (189)	193 (195)	10 (–12, 32)[‡]	0.382[§]
Change in body weight from baseline, kg				
Day 1	–1.4 (1.9)	–1.5 (2.1)	–0.1 (–0.3, 0.2)[‡]	0.540[§]
Day 2	–2.1 (2.3)	–2.0 (2.6)	0.1 (–0.2, 0.4)[‡]	0.567[§]
Day 5	–3.0 (3.3)	–2.7 (3.4)	0.3 (–0.1, 0.7)[‡]	0.167[§]
Day 14	–3.6 (4.4)	–3.0 (4.1)	0.6 (0.1, 1.1)[‡]	0.023[§]

All values mean (SD), unless otherwise noted
Treatment effect: *hazard ratio, [‡]mean difference
Statistical test: [§]two-sample t-test, [¶]Wilcoxon rank sum test, [#]log-rank test; Note, not adjusted for multiple comparisons
[†]Patients for whom the investigator did not report any WHF by Day 5 were assigned a value of Day 6
[##]Calculation of furosemide equivalents (mg) for torsemide, bumetanide and ethacrynic acid are actual dose (mg) multiplied by constant 2, 20 or 0.8, respectively

AHF=acute heart failure; CI=confidence interval; i.v.=intravenous; KM=Kaplan-Meier;
RELAX-AHF=RELAXin in Acute Heart Failure; WHF=worsening of heart failure
Teerlink et al. Lancet 2013;381:29–39

RELAX-AHF: serelaxin treatment increased the incidence of substantially decreased NT-proBNP levels in AHF patients

- At Day 2, more patients had decreases in NT-proBNP levels ≥30% from baseline with serelaxin compared with placebo



AHF=acute heart failure; NT-proBNP=N-terminal pro B-type natriuretic peptide; RELAX-AHF=RELAXin in Acute Heart Failure

Metra et al. J Am Coll Cardiol 2013;61:196–206

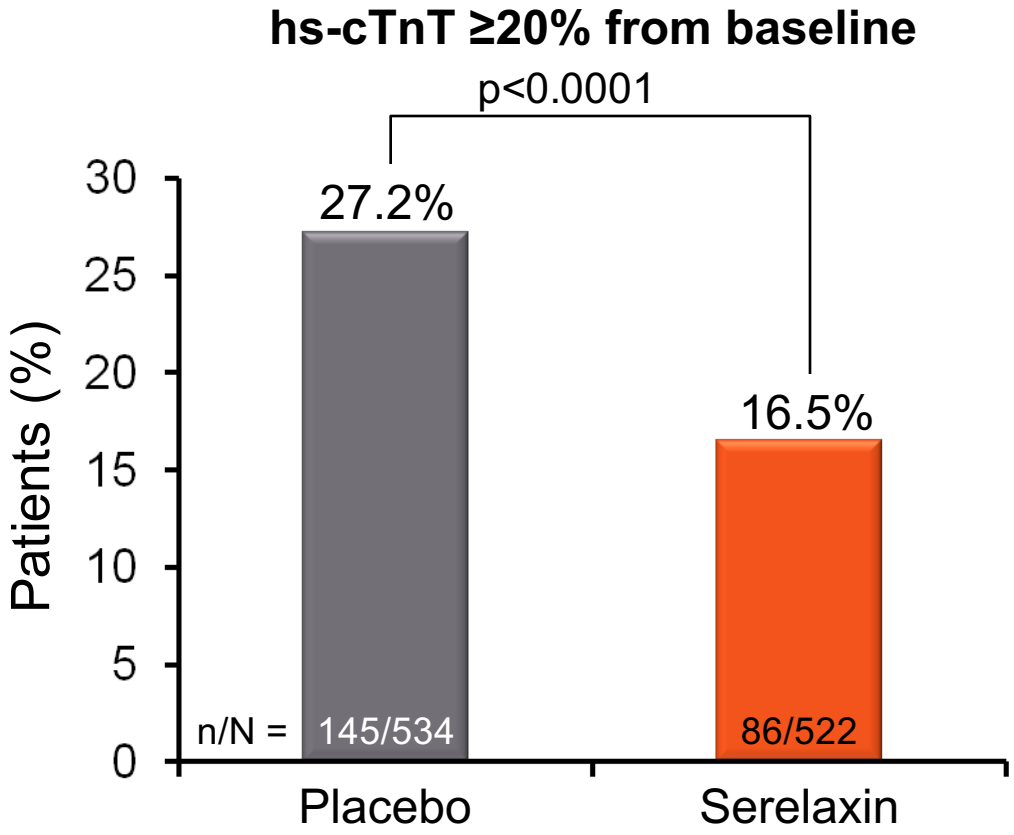
Serelaxin clinical trial program addresses the four essential endpoints for assessing AHF therapies

1. Effects on signs and symptoms
2. Effects on in-hospital measures
3. **Effects on end-organ damage**
4. Effects on post-discharge events

AHF=acute heart failure

RELAX-AHF: serelaxin treatment lowered the incidence of increased hs-cTnT levels in patients with AHF

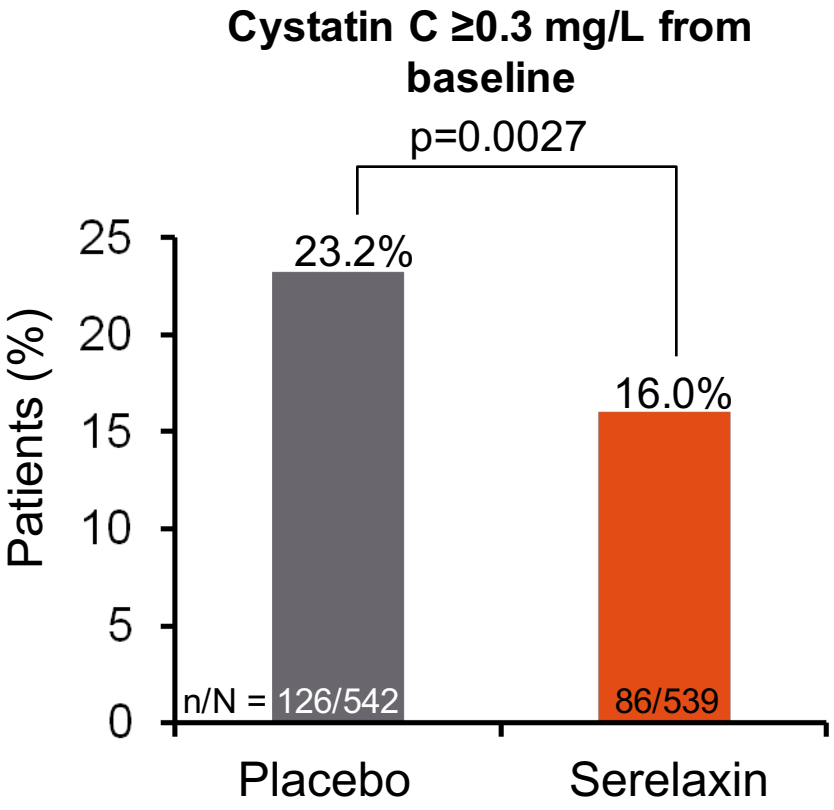
- Fewer patients had increased hs-cTnT ≥20% with serelaxin compared with placebo at Day 2

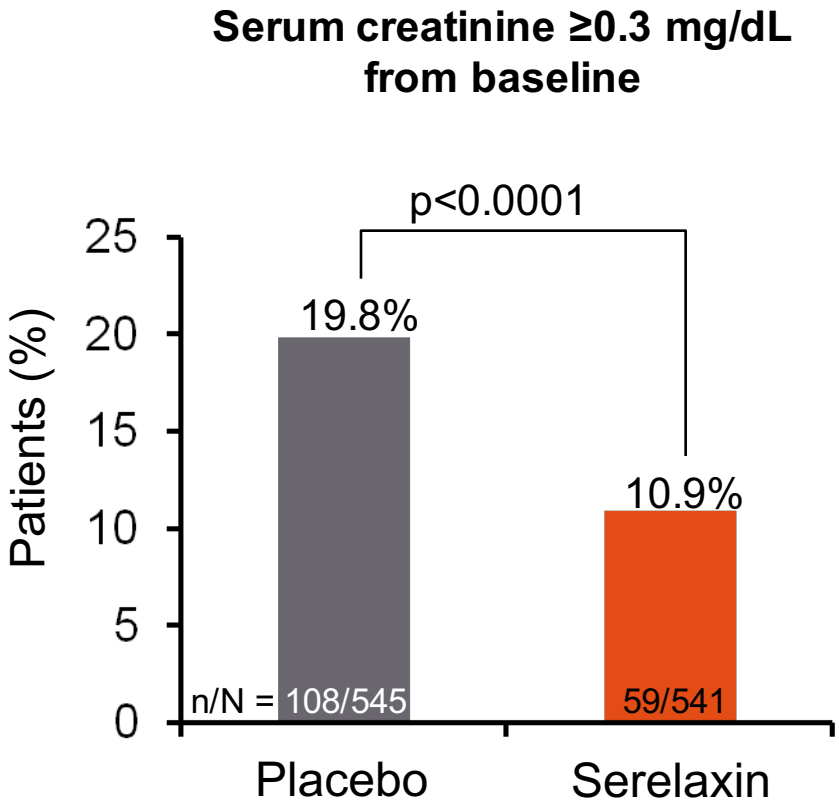


AHF=acute heart failure; hs-cTnT=high sensitivity cardiac troponin T;
RELAX-AHF=RELAXin in Acute Heart Failure
Metra et al. J Am Coll Cardiol 2013;61:196–206

RELAX-AHF: serelaxin treatment lowered the incidence of worsening renal function versus placebo in AHF patients

- Lower incidence of elevated cystatin C and serum creatinine at Day 2 with serelaxin compared with placebo





AHF=acute heart failure; RELAX-AHF=RELAXin in Acute Heart Failure
Metra et al. J Am Coll Cardiol 2013;61:196–206

Serelaxin clinical trial program addresses the four essential endpoints for assessing AHF therapies

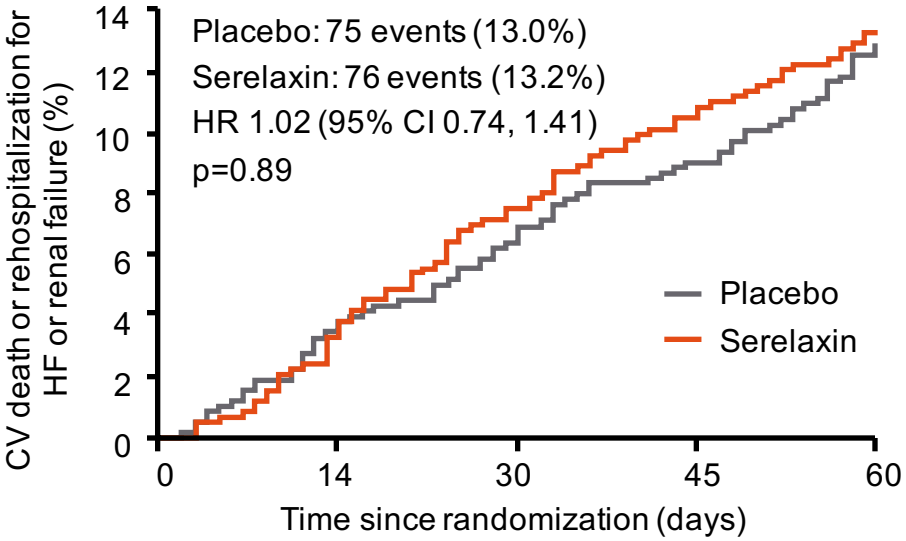
1. Effects on signs and symptoms
2. Effects on in-hospital measures
3. Effects on end-organ damage
4. **Effects on post-discharge events**

AHF=acute heart failure

RELAX-AHF: no significant effects of serelaxin versus placebo on secondary efficacy endpoints in patients with AHF

Secondary endpoints

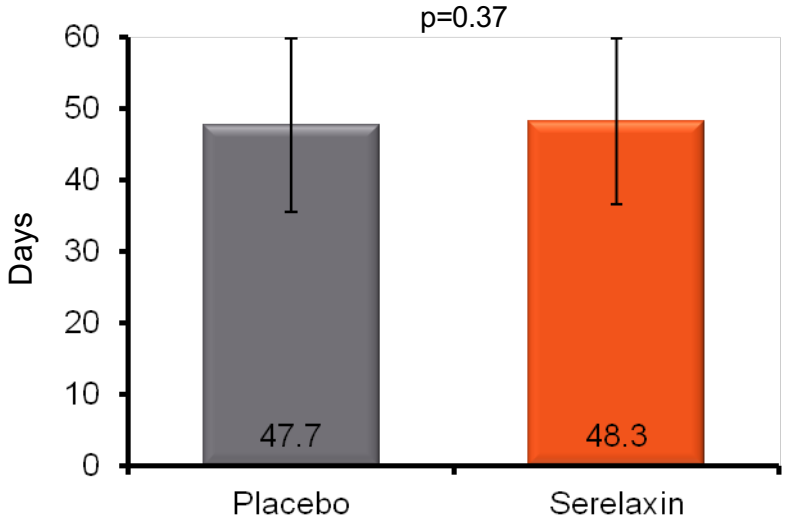
Kaplan-Meier plot of CV death or rehospitalization for HF or renal failure through Day 60



Number at risk:

Serelaxin	581	563	531	514	498
Placebo	580	559	539	522	501

Days alive and out of hospital to Day 60

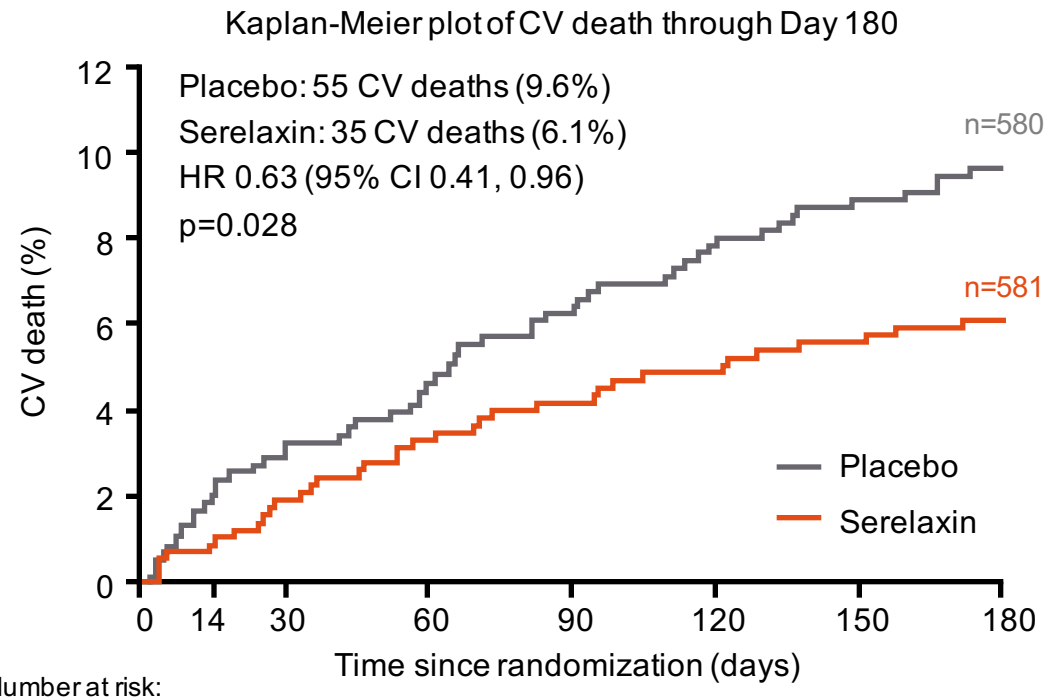


- At Day 60, there were:
  - 27 CV death events in the placebo group compared with 19 in the serelaxin group (p=ns)
  - 50 rehospitalization events in the placebo group compared with 60 in the serelaxin group (p=ns)

AHF=acute heart failure; CI=confidence interval; CV= cardiovascular; HF=heart failure; HR=hazard ratio; RELAX-AHF= RELAXin in Acute Heart Failure; Teerlink et al. Lancet 2013;381:29–39

RELAX-AHF: significant reduction in CV death through Day 180 with serelaxin in patients with AHF

- Serelaxin treatment was associated with a 37% hazard reduction in CV mortality at Day 180 (NNT=29)
- Kaplan-Meier curves for CV death separated after Day 5 and remained separated through Day 180

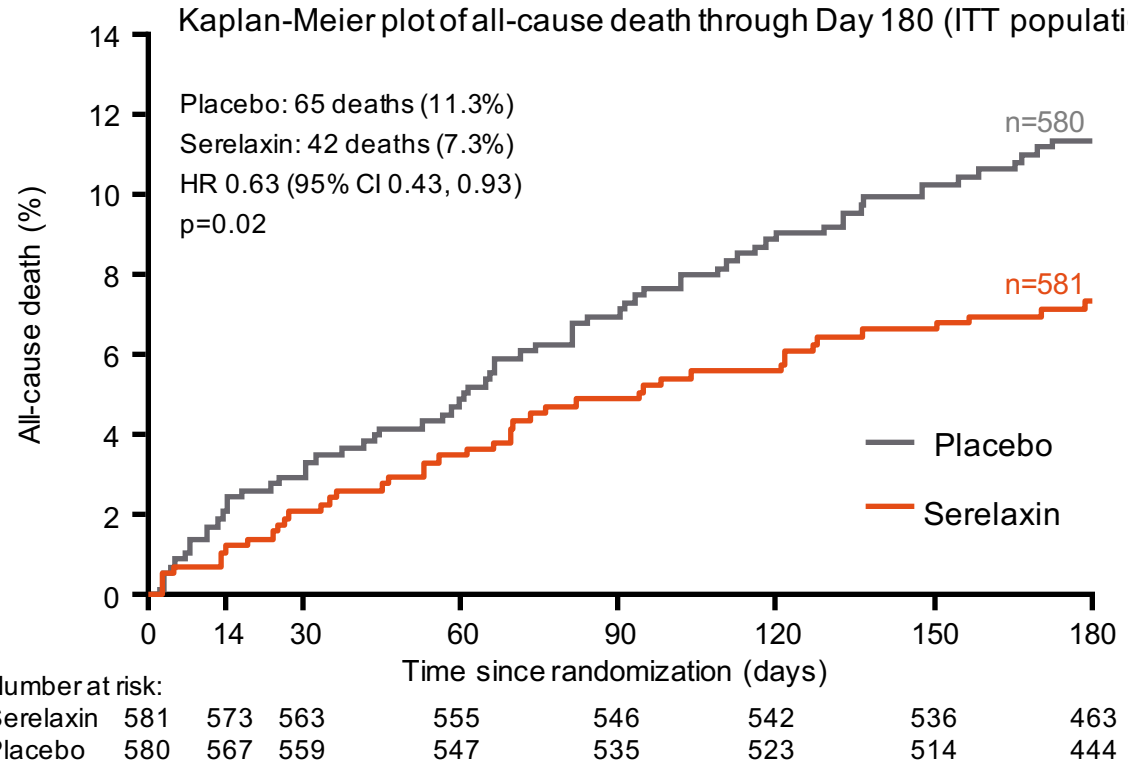


AHF=acute heart failure; CV=cardiovascular; HR=hazard ratio; NNT=number needed to treat; RELAX-AHF=RELAXin in Acute Heart Failure

Teerlink et al. Lancet 2013;381:29–39

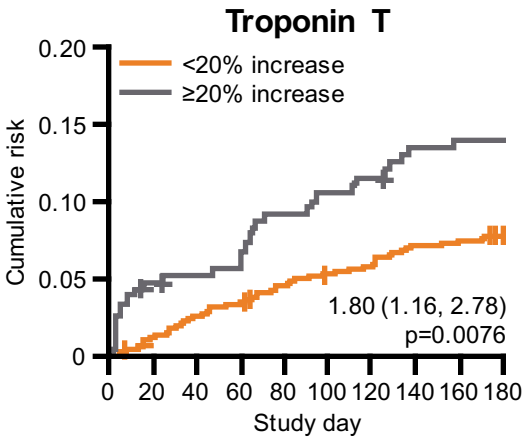
RELAX-AHF: significant reduction in all-cause mortality with serelaxin at 180 days in patients with AHF

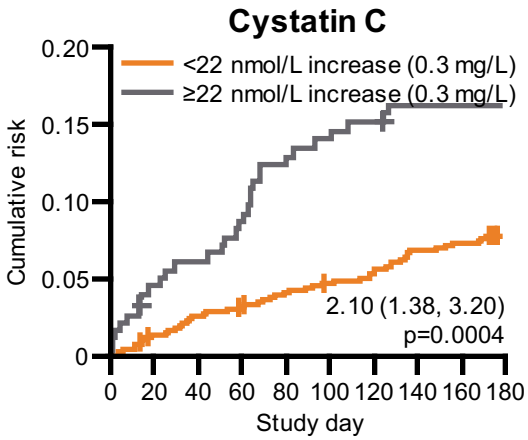
- In the prespecified safety analysis, serelaxin treatment was associated with a significant reduction in all-cause mortality at Day 180 (p=0.02; NNT=25)
- A *post-hoc* sensitivity analysis in the ITT population demonstrated a 37% hazard reduction for all-cause mortality with serelaxin compared with placebo (p=0.02)

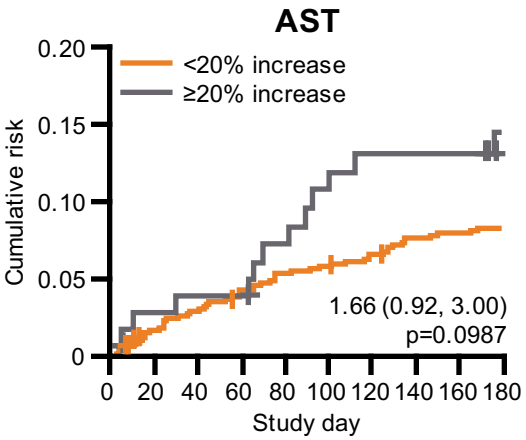


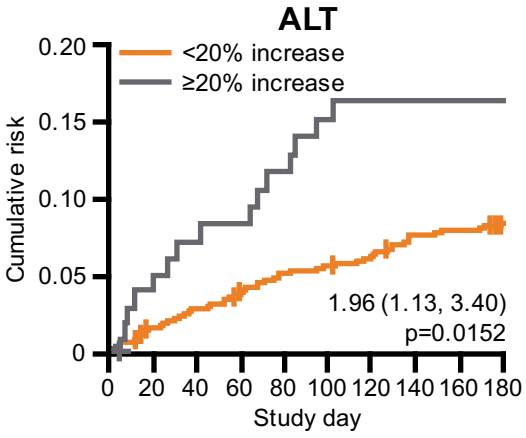
AHF=acute heart failure; CI=confidence interval; HR=hazard ratio; ITT=intention-to-treat
RELAX-AHF=RELAXin in Acute Heart Failure; NNT=number needed to treat
Teerlink et al. Lancet 2013;381:29–39

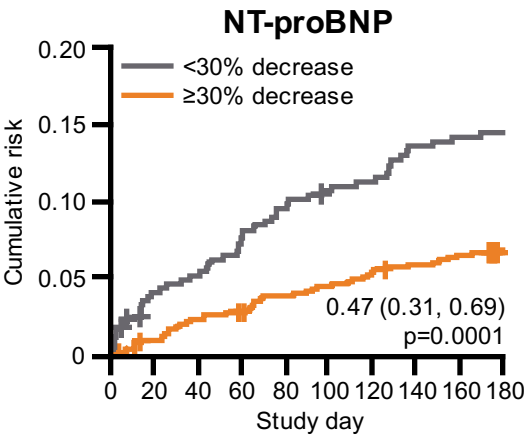
AHF: the ‘organ damage’ hypothesis

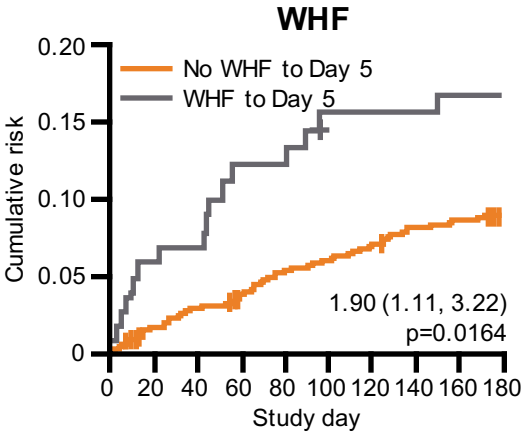












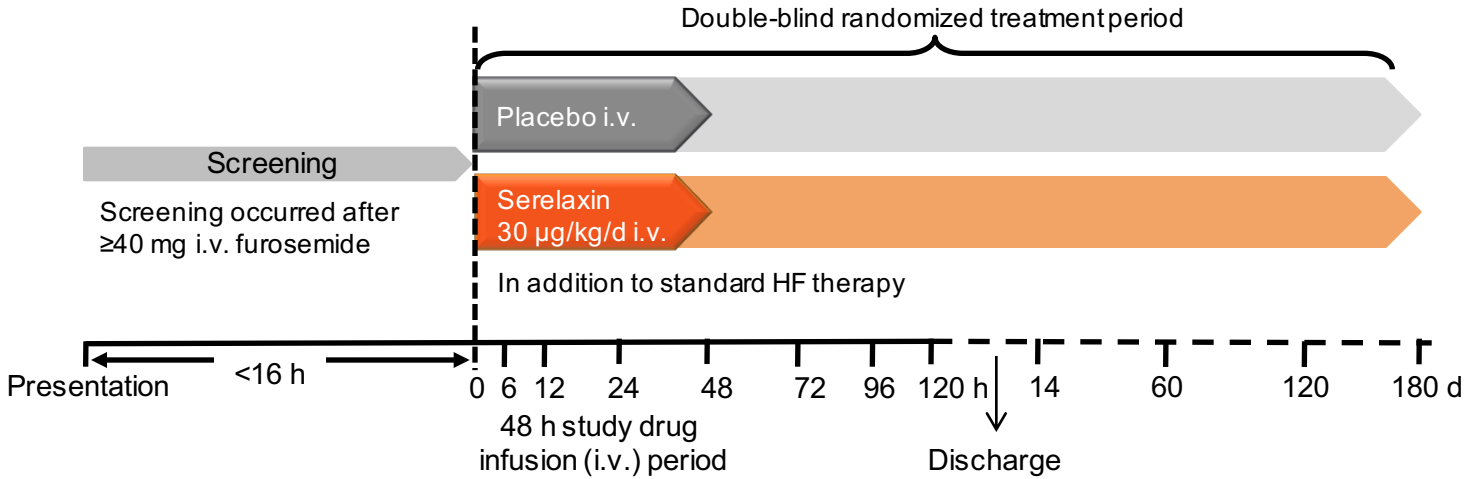
ALT=alanine aminotransferase; AST=aspartate aminotransferase; NT-proBNP=N-terminal prohormone of brain natriuretic peptide; WHF=worsening heart failure

Metra et al. J Am Coll Cardiol 2013;61:196–206

Acute Hospitalized Heart Failure

- The problem
- How to manage it
- The potential role of serelaxin in the context of this unmet need
- Ongoing studies

RELAX-AHF 2 aims to confirm the mortality benefit of serelaxin treatment



- Patients hospitalized with AHF, normal to elevated BP and mild-to-moderate renal impairment
- Primary endpoint: CV mortality at 180 days
- 32 countries
- 6,800 patients
- FPFV: September 2013
- **Results: 2017**

AHF=acute heart failure; BP=blood pressure; CV=cardiovascular; d=day; FPFV=first patient first visit; h=hour
HF=heart failure; i.v.=intravenous

Comparison of key features of Pre-RELAX-AHF, RELAX-AHF, RELAX-AHF-2, and RELAX-AHF-EU

	Pre-RELAX-AHF	RELAX-AHF	RELAX-AHF-2 (recruitment closed)	RELAX-AHF-EU (ongoing)
Overall design	Randomised, double-blind, placebo-controlled, dose-ranging	Randomised, double-blind, placebo-controlled	Randomised, double-blind, placebo-controlled	Randomised, open-label, PROBE design
Setting	Cardiology, emergency, and intensive / critical care units of large / teaching hospitals	Same as Pre-RELAX-AHF	Same as Pre-RELAX-AHF and RELAX-AHF	Same as Pre-RELAX-AHF plus internal medicine wards and regional hospitals
Size and scope	54 sites in 8 countries, N = 234	96 sites in 11 countries, N = 1,161	500 sites in 32 countries worldwide, N = 6,800	450 sites in 26 European countries, N = 2,685
Primary endpoint	All endpoints were exploratory	Change in dyspnoea (measured by Likert, VAS)	Cardiovascular death at Day 180	Time to all-cause death or in-hospital worsening of heart failure (WHF) through Day 5

RELAX-AHF: incidence of AEs/SAEs

	Placebo (N=570) n (%)	Serelaxin (N=568) n (%)
Hypotension-related AE (through Day 5)	25 (4.4)	28 (4.9)
Renal impairment-related AE (through Day 5)	49 (8.6)	26 (4.6)
Subjects with any AE (to Day 14)	**320 (56.1)**	**305 (53.7)**
Subjects with any drug-related AE	46 (8.1)	47 (8.3)
Subjects with AE leading to study drug discontinuation	22 (3.9)	26 (4.6)
Hypotension-related AE (through Day 14)	27 (4.7)	28 (4.9)
Renal impairment-related AE (through Day 14)	51 (8.9)	32 (5.6)*
Subjects with any SAE	**78 (13.7)**	**86 (15.1)**
Subjects with any drug-related SAEs	2 (0.4)	3 (0.5)
Subjects with SAE leading to drug discontinuation	3 (0.5)	5 (0.9)
Serious AE with an outcome of death	15 (2.6)	10 (1.8)

The number of subjects with any AE includes all AEs and SAEs reported through Day 14. Non-serious AEs were collected through Day 5, SAEs through Day 14

*p=0.03 vs placebo

AE=adverse event; RELAX-AHF=RELAXin in Acute Heart Failure; SAE=serious AE

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RELAX-AHF: baseline characteristics were similar between treatment groups

Baseline characteristic	Placebo (n=580)	Serelaxin (n=581)
Mean age, years (SD)	72.5 (10.8)	71.6 (11.7)
Men, n (%)	357 (62)	368 (63)
White, n (%)	552 (95)	544 (94)
Mean weight, kg (SD)	82.8 (18.7)	81.9 (18.5)
Mean body mass index, kg/m^2 (SD)	29.5 (6.1)	29.1 (5.3)
Region, n (%)*		
Eastern Europe	282 (49)	280 (48)
Western Europe	101 (17)	103 (18)
USA	55 (9)	59 (10)
Argentina	37 (6)	34 (6)
Israel	105 (18)	105 (18)
Mean SBP, mmHg (SD)	142.1 (17.0)	142.2 (16.2)
Mean diastolic blood pressure, mmHg (SD)	81.7 (13.2)	82.2 (14.2)
Mean heart rate, beats/min (SD)	80.4 (14.9)	78.9 (15.0)
Mean respiratory rate, breaths/min (SD)	22.0 (4.6)	21.8 (4.6)
Mean time from presentation to randomization, h (SD)	7.9 (4.7)	7.8 (4.6)
Mean eGFR (mL/min/1.73 m^2)‡	53.3 (12.9)	53.7 (13.1)

*Eastern Europe (Hungary, Poland, Romania), Western Europe (France, Germany, Italy, Netherlands, Spain);
‡eGFR calculated by the simplified Modification of Diet in Renal Disease formula
eGFR=estimated glomerular filtration rate; RELAX-AHF=RELAXin in Acute Heart Failure; SBP=systolic blood pressure; SD=standard deviation; USA=United States of America
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RELAX-AHF: medical histories were similar between treatment groups

Medical history, n (%)	Placebo (n=580)	Serelaxin (n=581)
Hypertension	510 (88)	496 (85)
Hyperlipidemia	313 (54)	304 (52)
Stroke or other cerebrovascular event	84 (14)	73 (13)
Cigarette smoking	81 (14)	72 (12)
Peripheral vascular disease	82 (14)	73 (13)
Mitral regurgitation	182 (31)	179 (31)
Ischemic heart disease	307 (53)	296 (51)
Pacemaker	58 (10)	63 (11)
Biventricular pacing	52 (9)	61 (10)
Implantable cardiac defibrillator	75 (13)	79 (14)
Atrial fibrillation/flutter	305 (53)	297 (51)
Atrial fibrillation at screening	246 (42)	233 (40)
Asthma, bronchitis, or COPD	88 (15)	96 (16)
Diabetes mellitus	272 (47)	279 (48)

COPD=chronic obstructive pulmonary disease; RELAX-AHF=RELAXin in Acute Heart Failure
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RELAX-AHF: baseline heart failure-related characteristics were broadly similar between treatment groups

- Baseline HF-related characteristics were similar between treatment groups except more patients in the serelaxin treatment group were hospitalized for HF in the previous year

Baseline HF characteristic	Placebo (n=580)	Serelaxin (n=581)
Concomitant HF medication at baseline, n (%)		
Angiotensin-converting enzyme inhibitors	320 (55)	313 (54)
Angiotensin receptor blockers	97 (17)	88 (15)
Beta-blocker	407 (70)	387 (67)
Aldosterone antagonist	173 (30)	193 (33)
Digoxin	108 (19)	120 (21)
Intravenous loop diuretic	580 (100)	578 (99)
Hospitalized for HF in past year, n (%)	181 (31)	216 (37)
Mean number of HF hospitalizations in past year (SD)	1.5 (1.1)	1.7 (1.5)
Mean most recent EF, % (SD)	38.6 (14.3)	38.7 (14.8)
EF <40%, n (%)	295 (55)	303 (55)
New York Heart Association class 30 days prior to admission – I/II/III/IV, n (%)	11/140/198/72 (3/33/47/17)	12/164/191/63 (3/38/44/14)
i.v. nitrates at randomization, n (%)	42 (7)	39 (7)
Geometric mean NT-proBNP, ng/L (95% CI)	5,003 (4,633, 5,404)	5,125 (4,772, 5,506)
Geometric mean troponin T, µg/L (95% CI)	0.036 (0.034, 0.039)	0.034 (0.032, 0.037)

CI=confidence interval; EF=ejection fraction; HF=heart failure; i.v. Intravenous; NT-proBNP=N-terminal pro B-type natriuretic peptide; RELAX-AHF=RELAXin in Acute Heart Failure; SD=standard deviation

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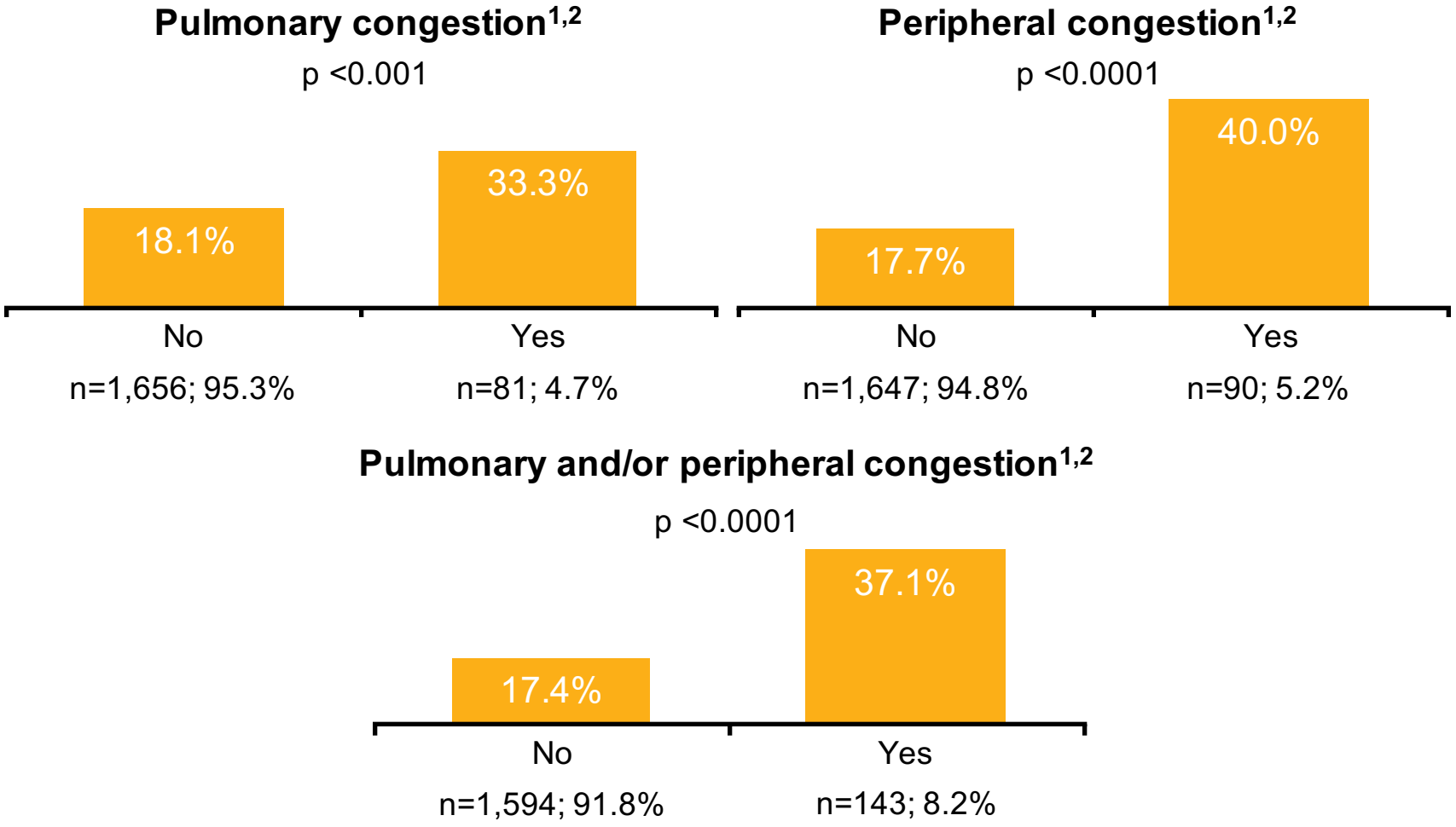
Italian Network on HF Outcome Registry: clinical status at discharge and 1-year mortality in AHF (n=1,737)

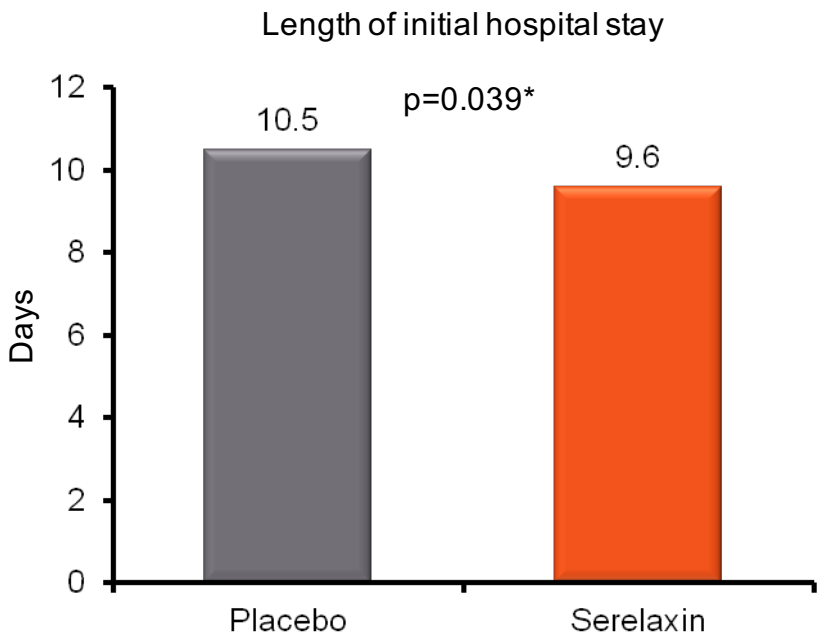


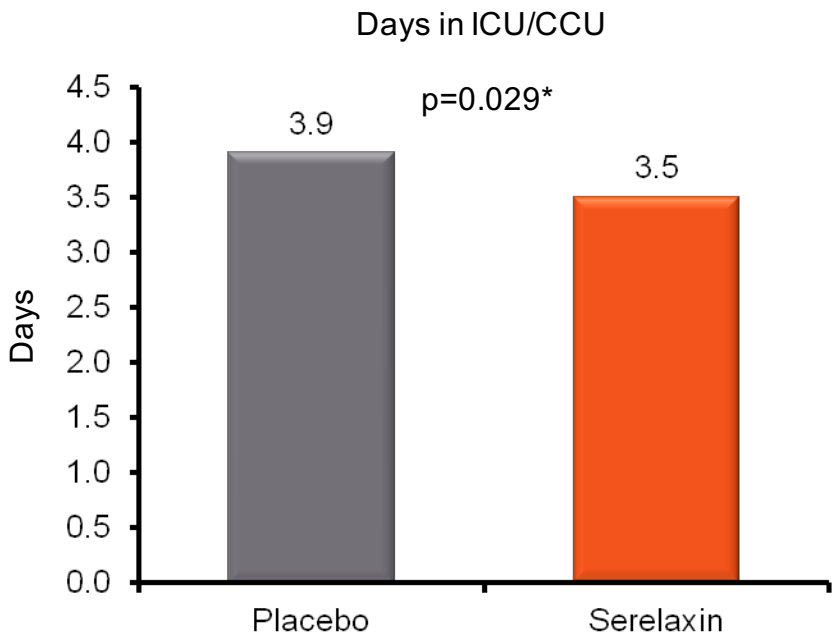
AHF=acute heart failure; HF=heart failure

1. Tavazzi et al. Circ Heart Fail 2013;6:473–81;
2. Maggioni et al. Data presented at ESC 2013, 31 Aug–04 Sep 2013, Amsterdam, Netherlands

RELAX-AHF: reduction in the hospital length of stay and duration in the ICU/CCU with serelaxin in patients with AHF

- The average length of initial hospital stay was significantly reduced by 0.9 days in serelaxin-treated patients compared with placebo (p=0.039)
- Serelaxin treatment was also associated with a significant reduction in the number of days in ICU/CCU compared with placebo (0.3 days, p=0.029)





*p values are for the Wilcoxon rank sum test

AHF=acute heart failure; CCU=coronary care unit; ICU=intensive care unit; RELAX-AHF= RELAXin in Acute Heart Failure

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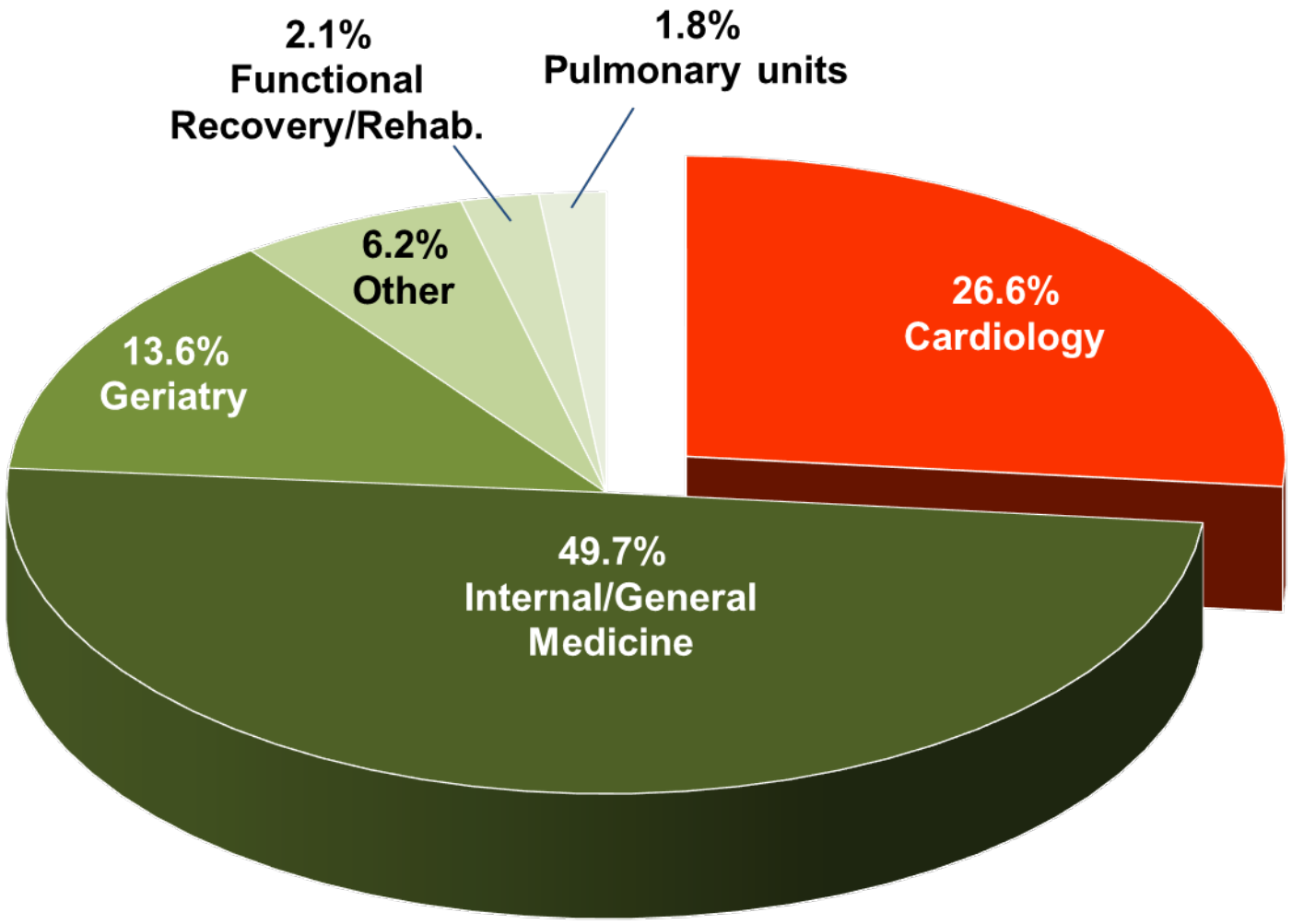
Where are the patients with AHF admitted?



Maggioni et al. European Journal of Heart Failure (2016) 18, 402–410