TRUE-AHF Trial

Short- and Long-Term Effect of Immediate Vasodilator Therapy in Acutely Decompensated Heart Failure: Results of the TRUE-AHF Trial

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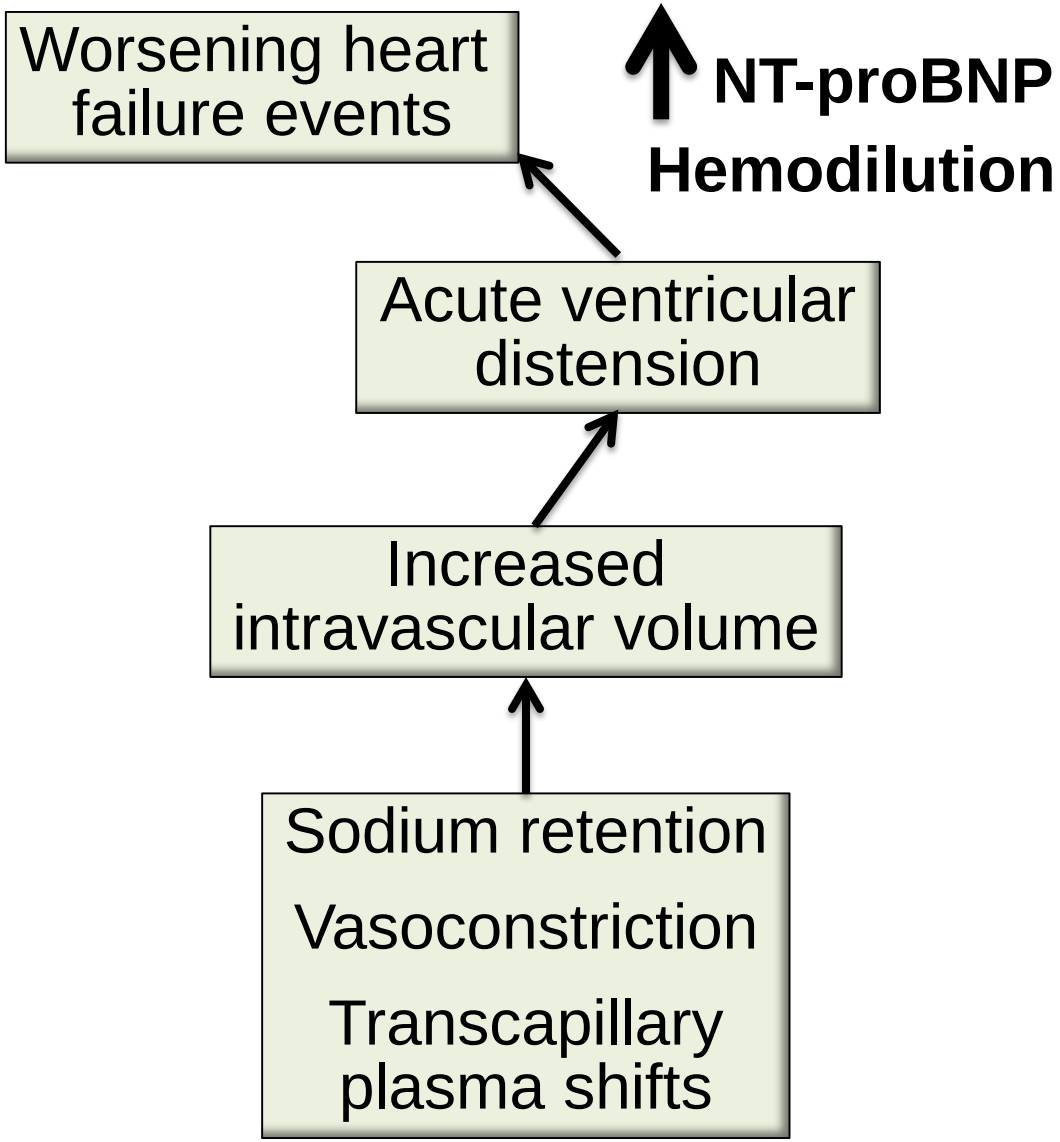
on behalf of the TRUE-AHF Executive Committee and Investigators

Disclosures

Within past 2 years:

Consultant to Admittance, Amgen, AstraZeneca, Bayer, BioControl, Boehringer Ingelheim, Boston Scientific, Celyad, Cardiorentis, Daiichi Sankyo, GlaxoSmithKline, Novartis, NovoNordisk, Relypsa, Takeda, ZS Pharma

Potential Mechanisms in Acute Heart Failure



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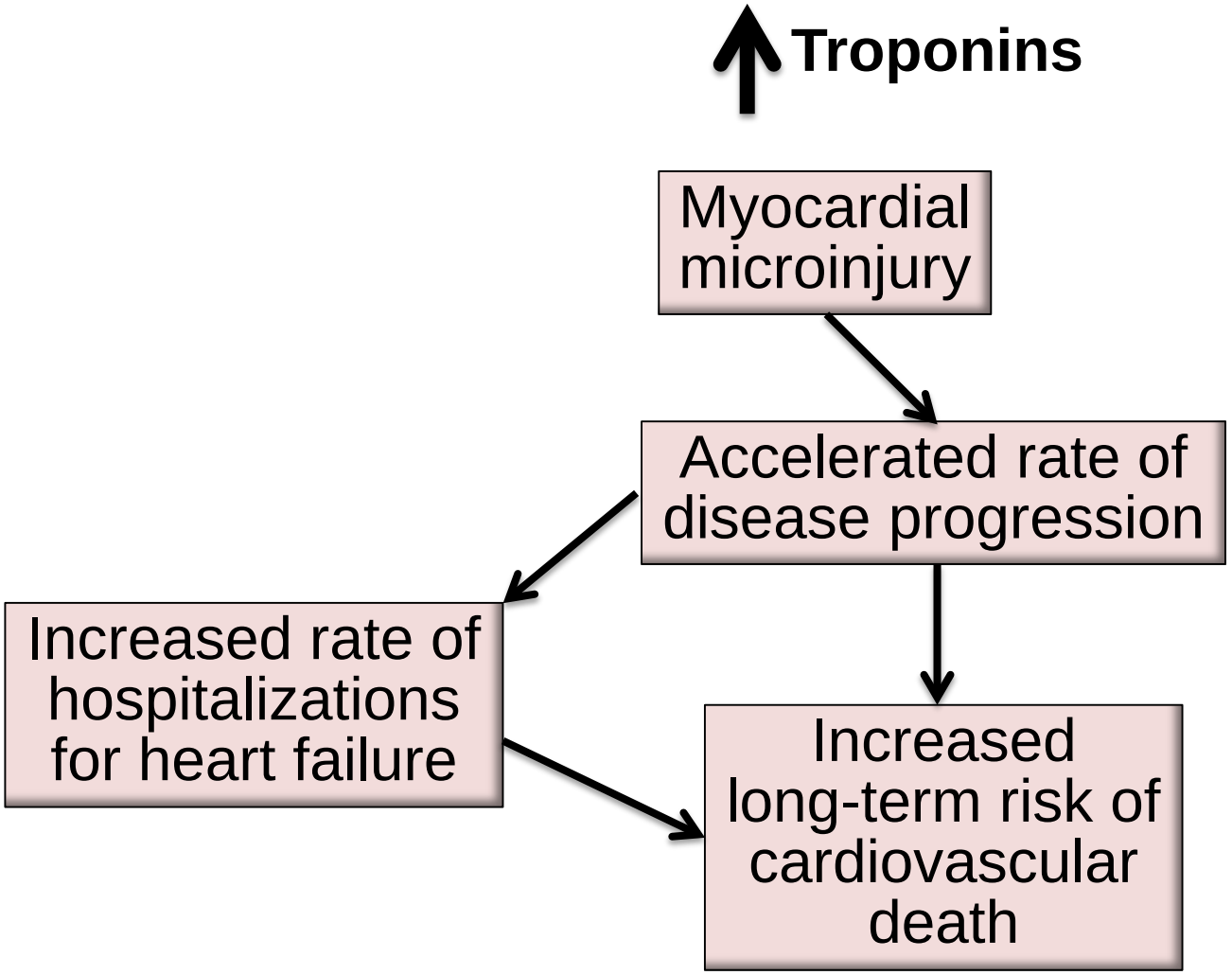
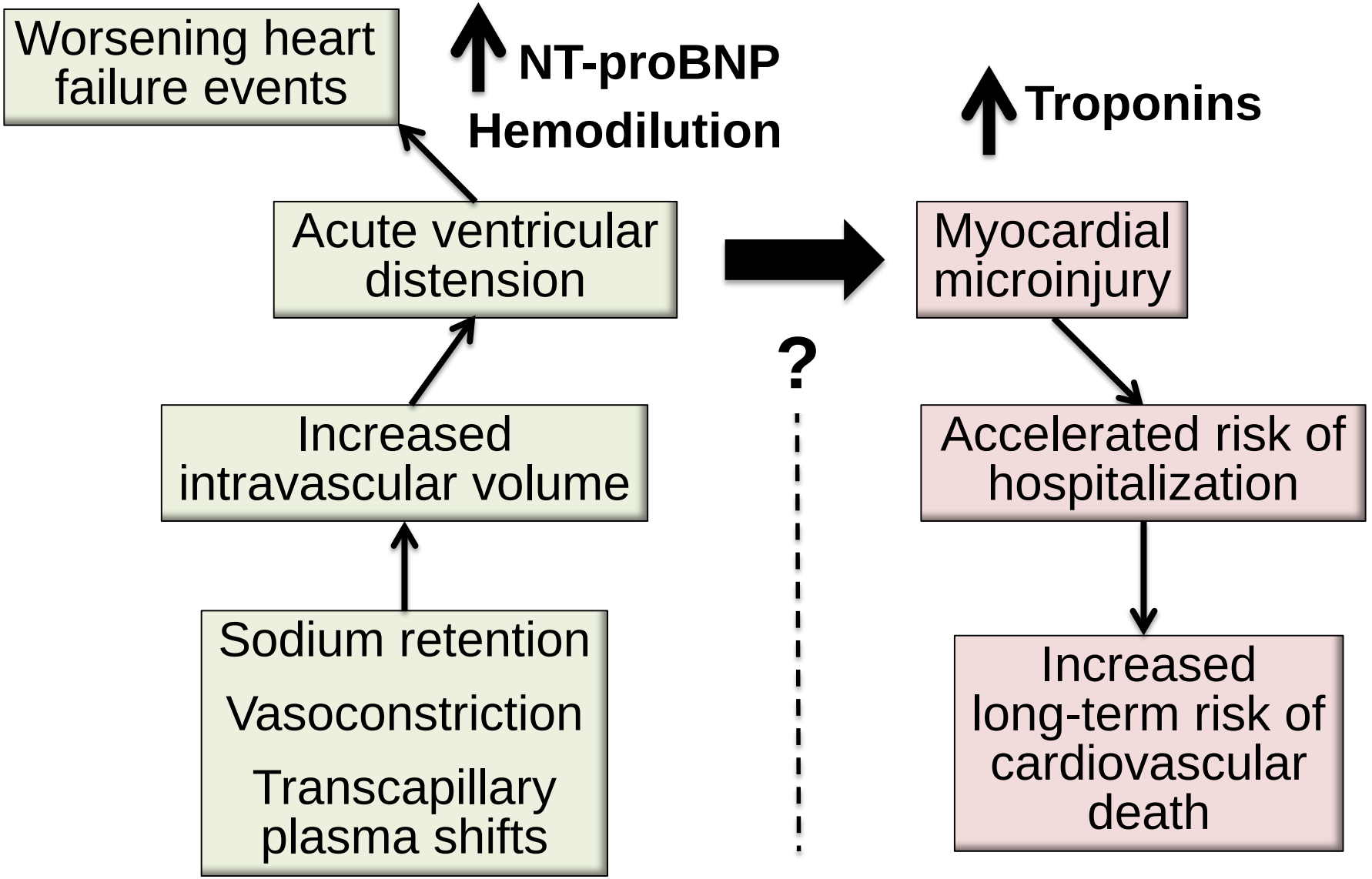


Are These Two Pathways Causally Related?



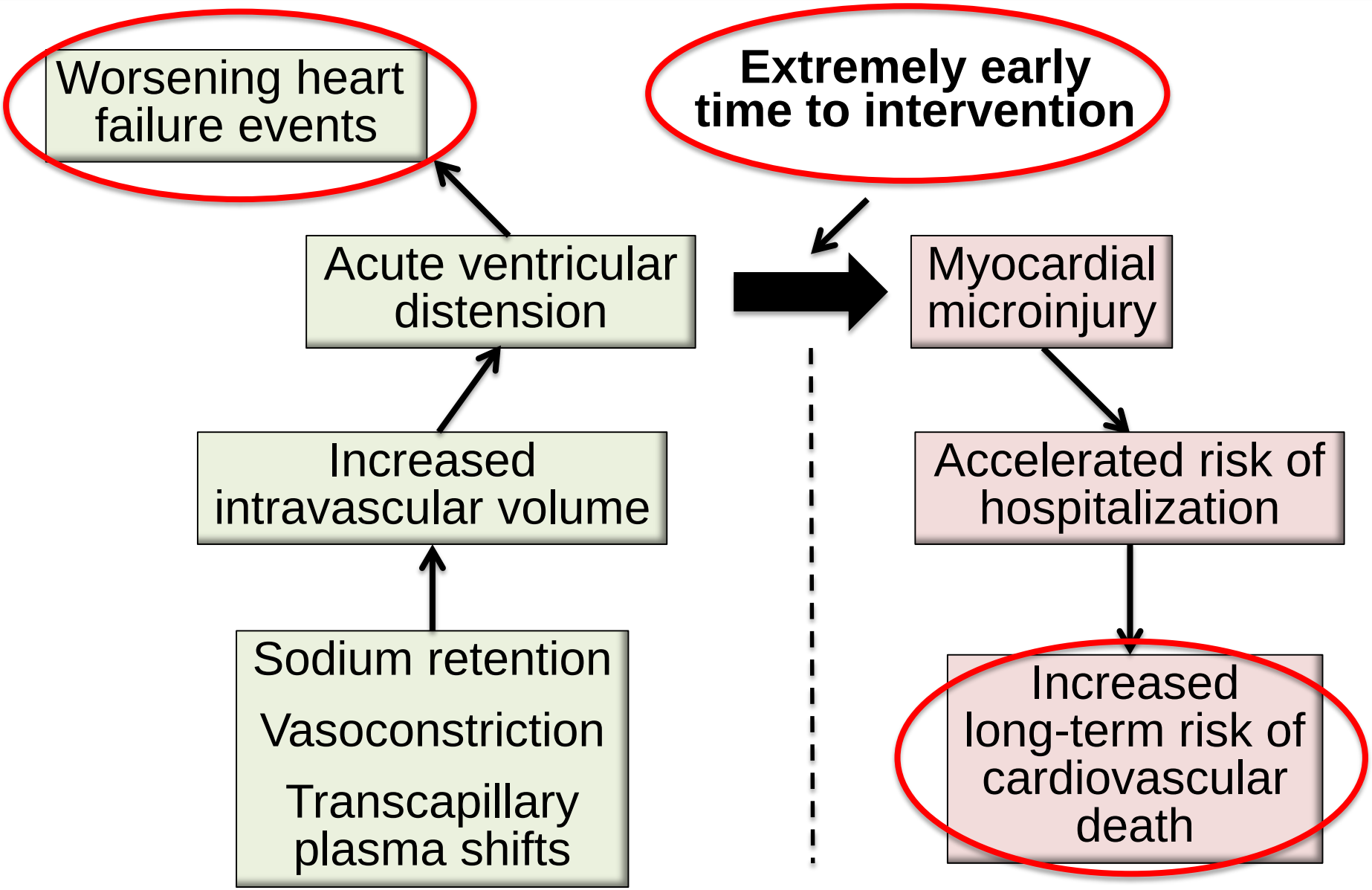
Timing of Onset of Treatment in Trials of Acutely Decompensated Heart Failure

	Planned Time From Admission to Start of Study Drug	Actual Time From Admission to Start of Study Drug	Did the Trial Report a Drug Effect?
ASCEND	≤ 48 hours	15.5 hours	No effect
EVEREST	≤ 48 hours	----	Transient effect
VERITAS	≤ 24 hours	11 hours	No effect
PROTECT	≤ 24 hours	----	No effect
RELAX-HF	≤ 16 hours	7 hours	Yes

Primary Goal of the TRUE-AHF Trial

The TRUE-AHF trial determined if, in patients with acute heart failure, the urgent administration of the natriuretic peptide ularitide, in doses sufficient to provide meaningful decongestion and reduce cardiac wall stress, would reduce the long-term risk of cardiovascular death.

Unique Aspects of the TRUE-AHF Trial



Intravenous Ularitide in Acutely Decompensated Heart Failure

- Ularitide is synthetic analogue of urodilatin, which causes systemic and renal vasodilation, diuresis and natriuresis, and inhibition of the renin-angiotensin system.

- Hemodynamic and symptomatic benefits in two randomized placebo-controlled heart failure trials (SIRIUS I and SIRIUS II).

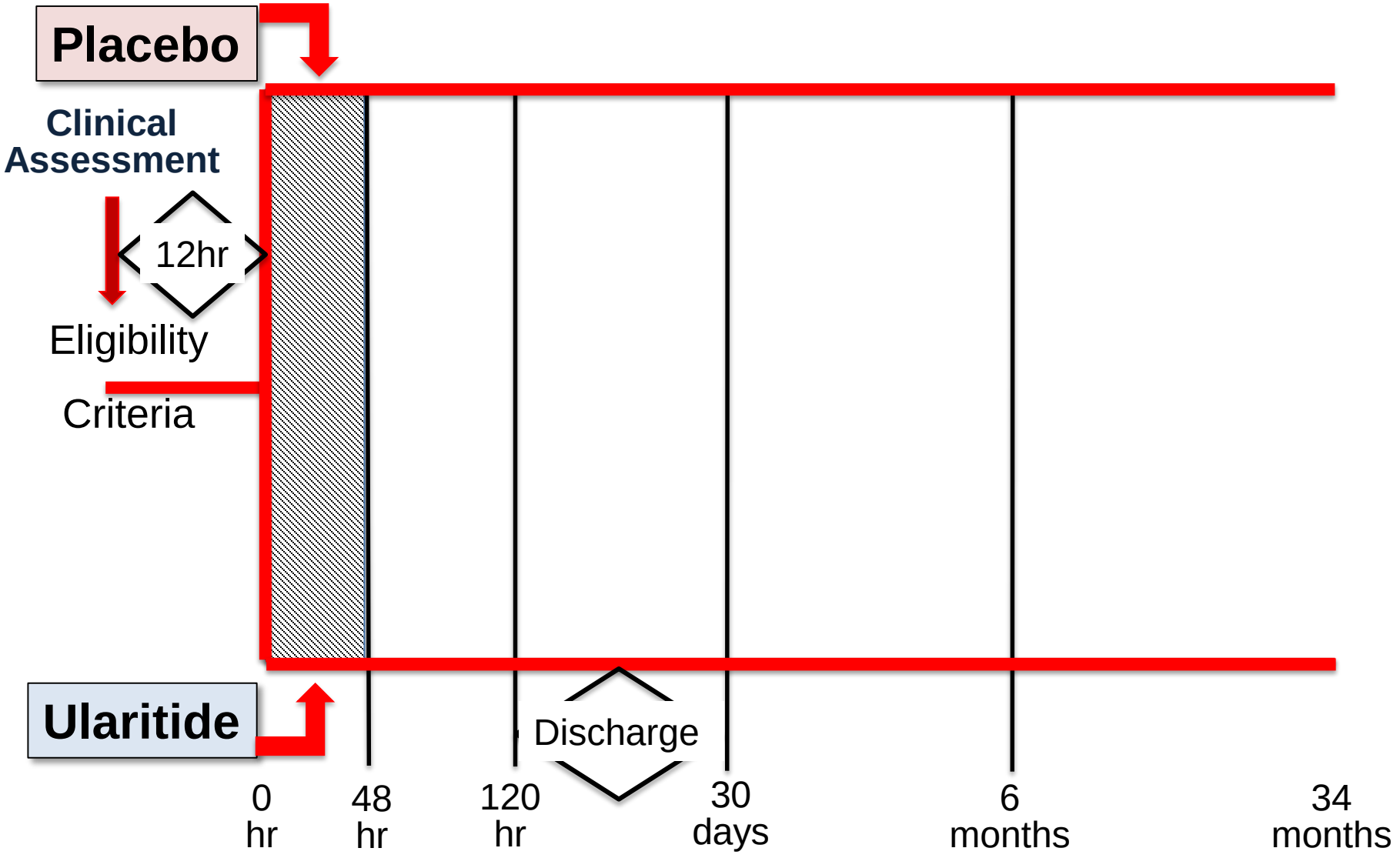
  — 15 ng/kg/min and 30 ng/kg/min produced similar improvement in dyspnea and global clinical status, but 30 ng/kg/min led to more frequent hypotension

  — Mortality at 30 days was 13.2% in the placebo group and 3.0% in the ularitide groups (total: 12 events)

TRUE-AHF: Entry Criteria

- Men or women, aged 18 to 85 years
- Unplanned hospitalization or ED visit for acutely decompensated heart failure
- Dyspnea at rest, worsened within the past week
- Evidence of heart failure on chest X-ray
- BNP > 500 pg/mL or NT-pro BNP > 2000 pg/mL
- Persistence of dyspnea at rest despite ≥ 40 mg of IV furosemide (or equivalent)
- Systolic BP ≥ 116 mmHg and ≤ 180 mmHg
- Start of study drug infusion within 12 hours after initial clinical assessment

TRUE-AHF Design: Eur J Heart Fail (Today)



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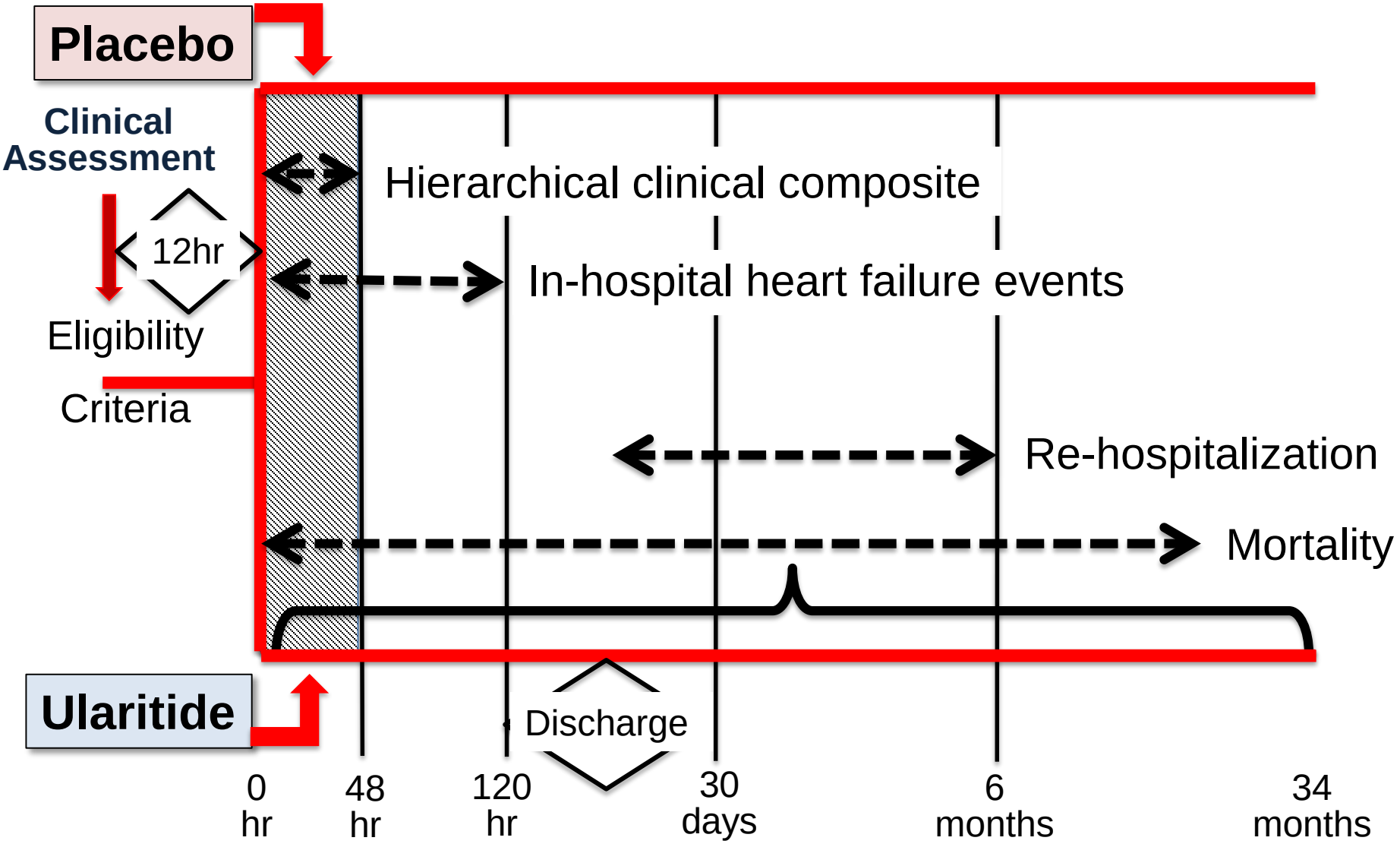


Primary Endpoints (Short- and Long-Term)

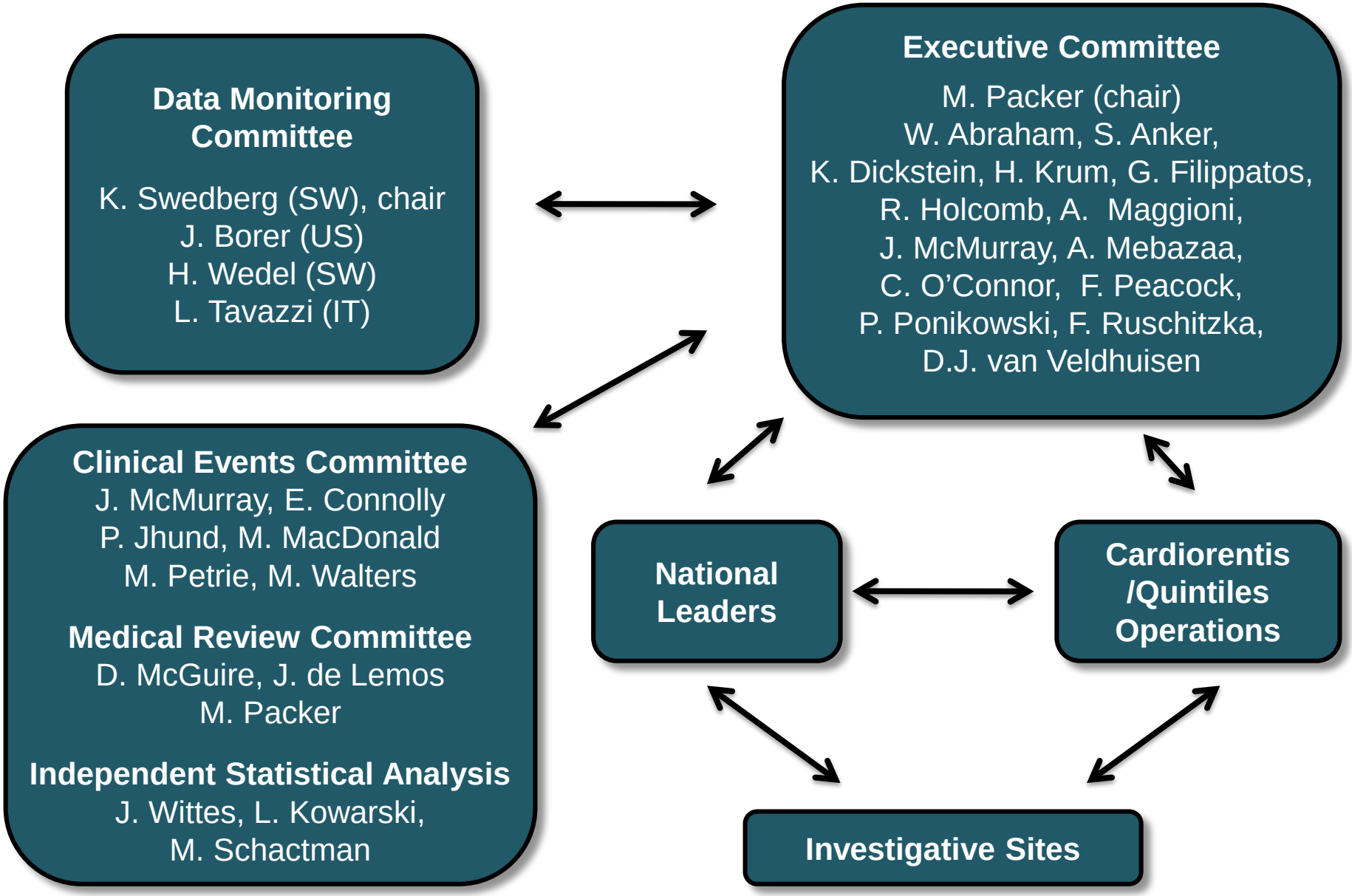
Cardiovascular Mortality ($\alpha = 0.04$)
No cardiovascular death
Cardiovascular death (time-to-event)

Hierarchical Clinical Composite at 48 Hours ($\alpha = 0.01$)
Moderate or marked improvement in symptoms at 6, 24 and 48 hours without in-hospital worsening heart failure or death
Modest improvement or unchanged symptoms
Worsening of symptoms at 6, 24 or 48 hours
Persistent or worsening heart failure (in-hospital) requiring IV or mechanical interventions during first 48 hours
Death during first 48 hours

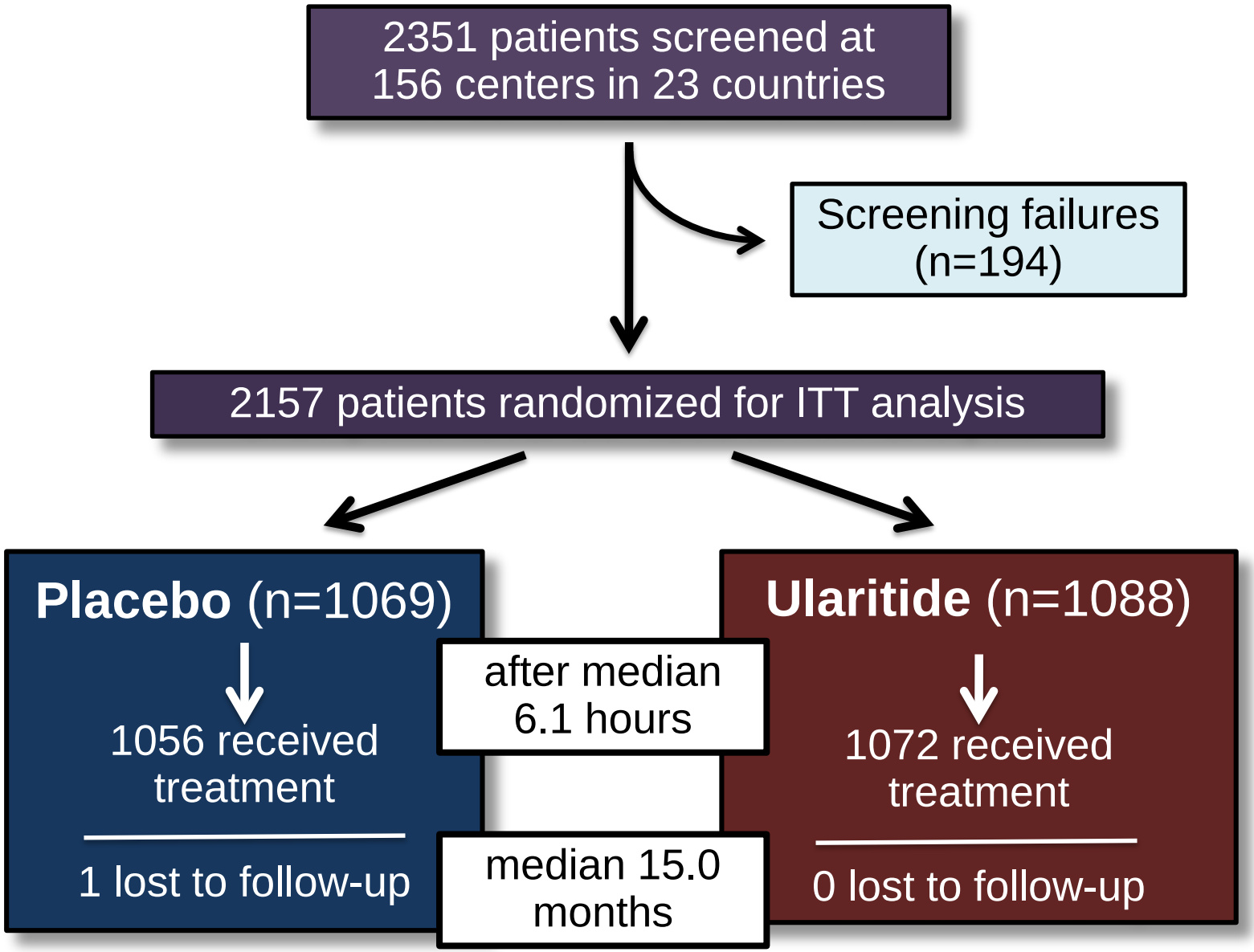
Secondary Endpoints (Short- and Long-Term)

- Length of stay of index hospitalization
- Length of stay in intensive care during the first 120 hours
- Number of episodes of persistent or worsening heart failure requiring an intervention during first 120 hours
- Proportion of patients with persistent or worsening heart failure requiring an intervention during the first 120 hours
- Change of N-terminal pro-BNP after 48 hours
- Time to completion of last dose of intravenous treatment for heart failure
- Change in serum creatinine during first 72 hours
- Risk of ***rehospitalization*** for heart failure within 30 days after initial hospital discharge
- Risk of death for any reason or ***rehospitalization*** for a cardiovascular reason during first 180 days

TRUE-AHF: Study Organization



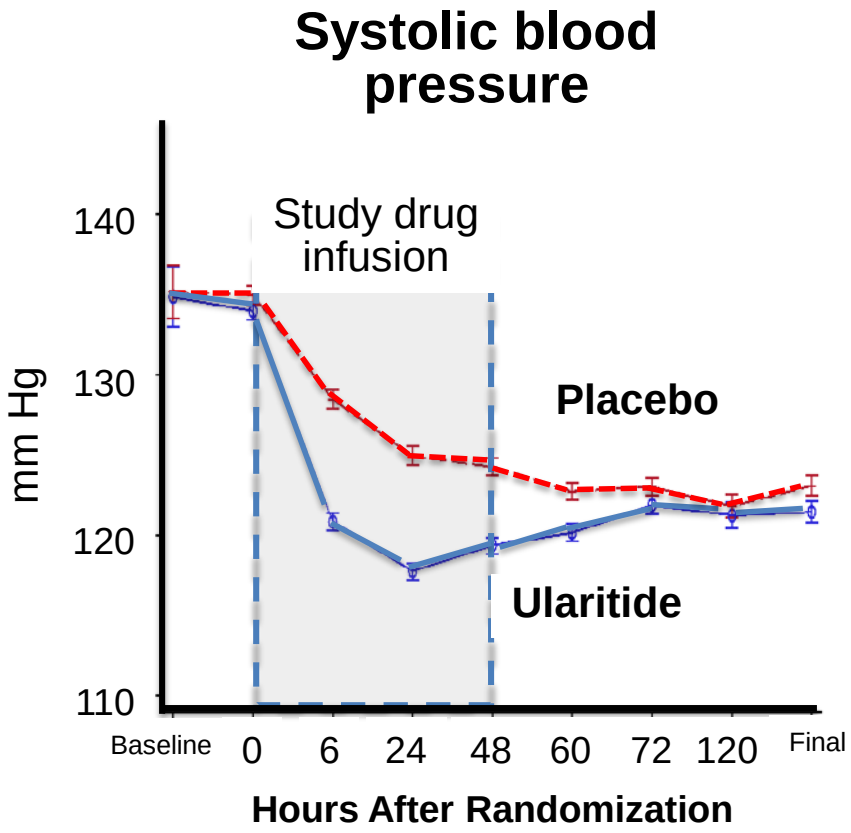
TRUE-AHF: Patient Disposition

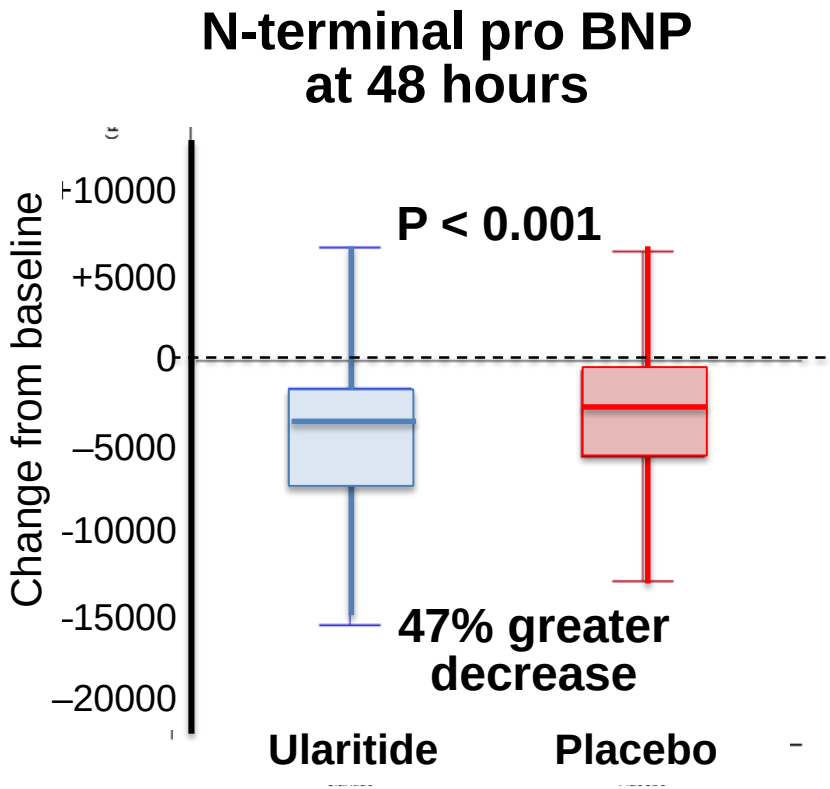


TRUE-AHF: Baseline Characteristics

	Placebo (n=1069)	Ularitide (n=1088)
Age (years)	68.3 ± 11.3	68.7 ± 11.4
Men/women	706/363	714/374
Non-black, n (%)	973 (91.0%)	989 (90.9%)
LV ejection fraction < 40%, n (%)	449 (65.9%)	445 (64.5%)
Time to treatment ≤ 6 hours, n (%)	528 (49.4%)	533 (49.0%)
Coronary artery disease, n (%)	549 (51.4%)	556 (51.1%)
Diabetes, n (%)	429 (40.1%)	414 (38.1%)
Prior heart failure (n,%)	806 (75.6%)	825 (75.9%)
Systolic blood pressure	135.1_± 17.9	134.2 ± 17.8
Heart rate (beats/min)	85.6 ± 19.1	85.4 ± 18.8
N-terminal proBNP (pg/mL), median (25,75 percentiles)	7121 (3974,12599)	7156 (4230,13238)
Cardiac troponin T (pg/ml), median, (25,75 percentiles)	33 (21, 54)	34 (22, 54)
Intravenous nitrates at baseline	110 (10.3%)	101 (9.3%)

Ularitide Exerted Expected Effects on Cardiac Distension and Intravascular Congestion





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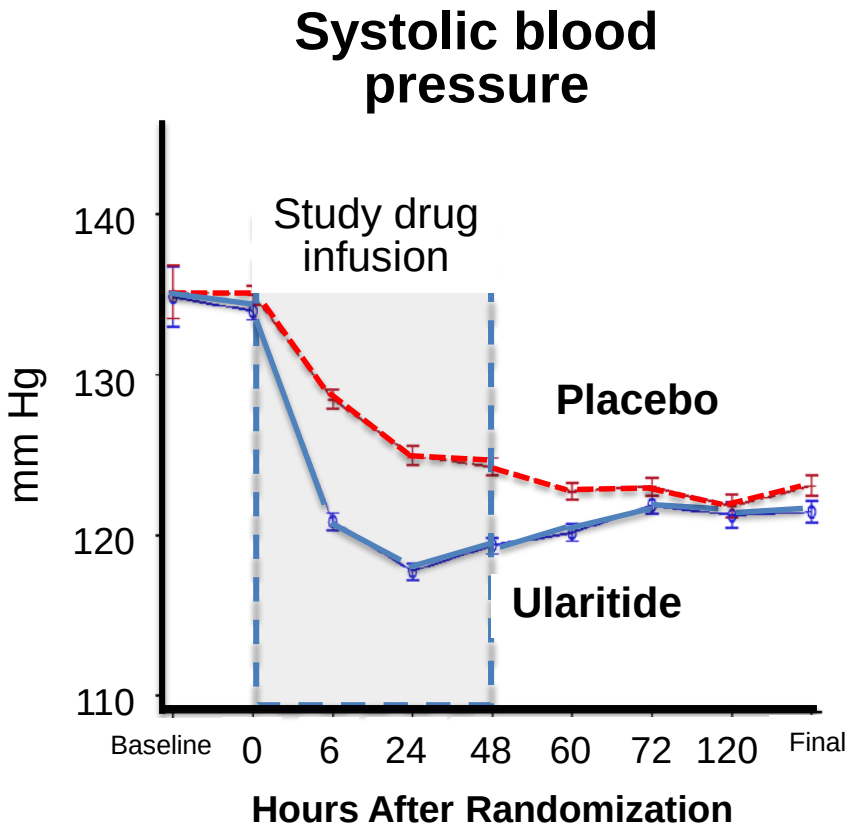
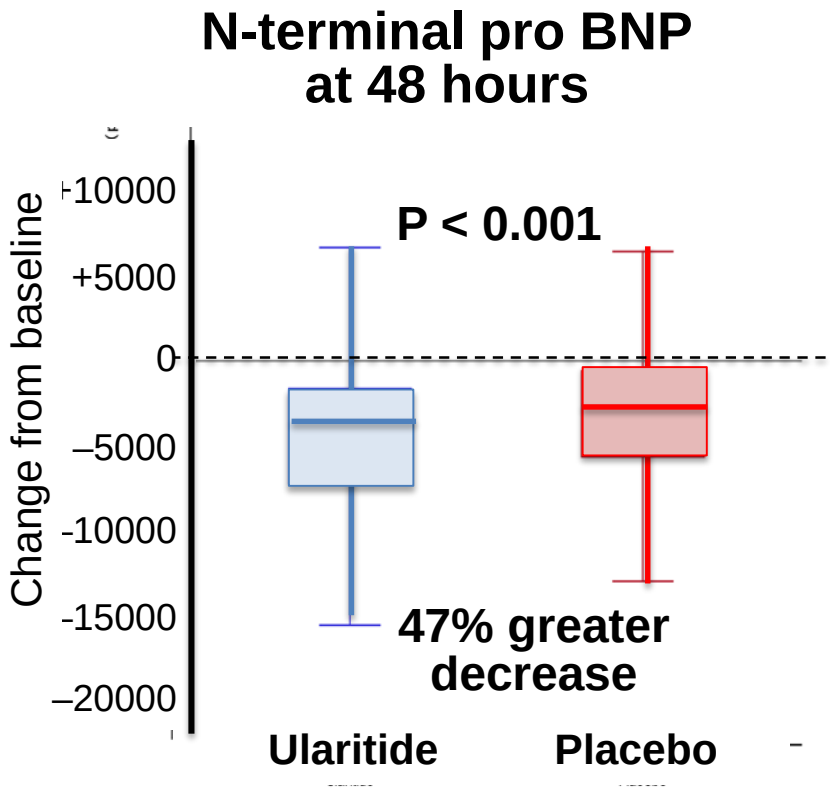
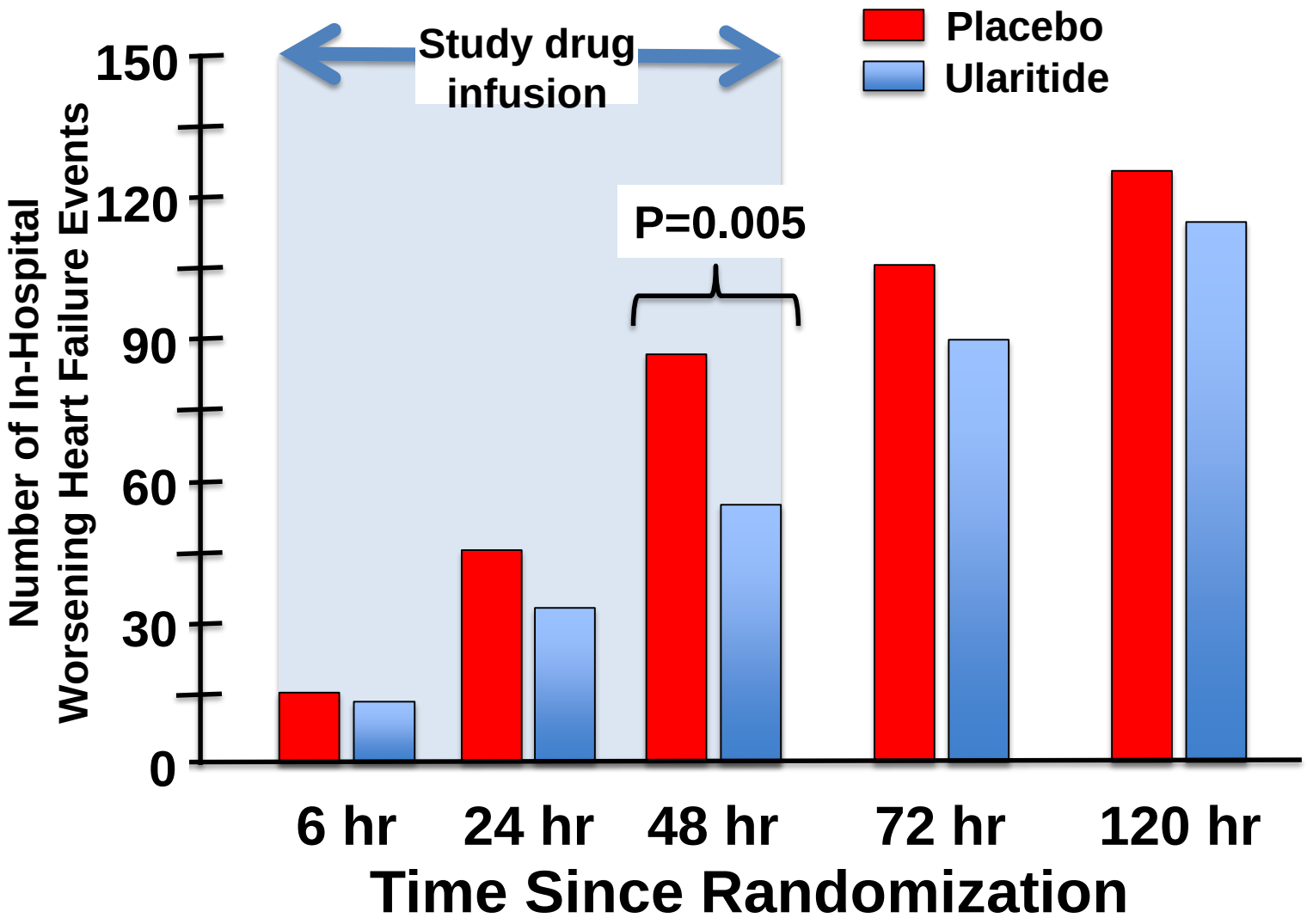




As compared with placebo, at 48 hours, ularitide led to significant increases in hemoglobin (P<0.001) and serum creatinine (P=0.005) and decreases in hepatic transaminases (P<0.001), indicative of ***intravascular decongestion***

Effect of Ularitide on In-Hospital Heart Failure Events During First 120 Hours



TRUE-AHF: Treatment of Persistent or Worsening Events During First 48 Hours

	Placebo	Ularitide
Low-intensity interventions Events requiring IV diuretics only (with or without low-dose dopamine)	50	35
Medium-intensity interventions Events requiring IV vasodilators (including morphine) and/or noninvasive ventilatory support; low-level interventions may be used	20	12
High-intensityinterventions Events requiring IV positive inotropic agents or pressors and/or invasive ventilation, volume filtration and/or surgery; low- and medium-level interventions may also be used	17	8
Total number of events	87	55

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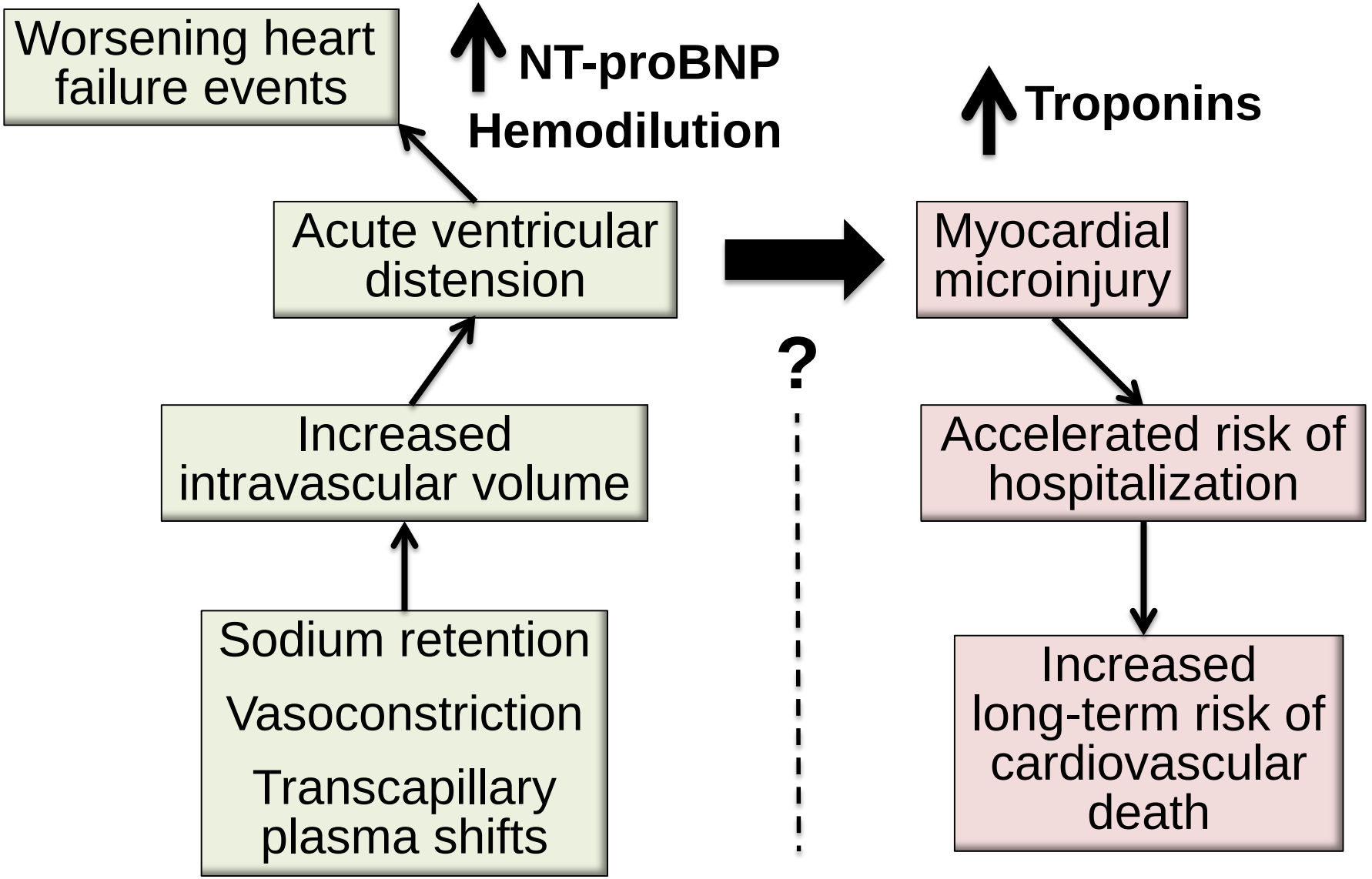
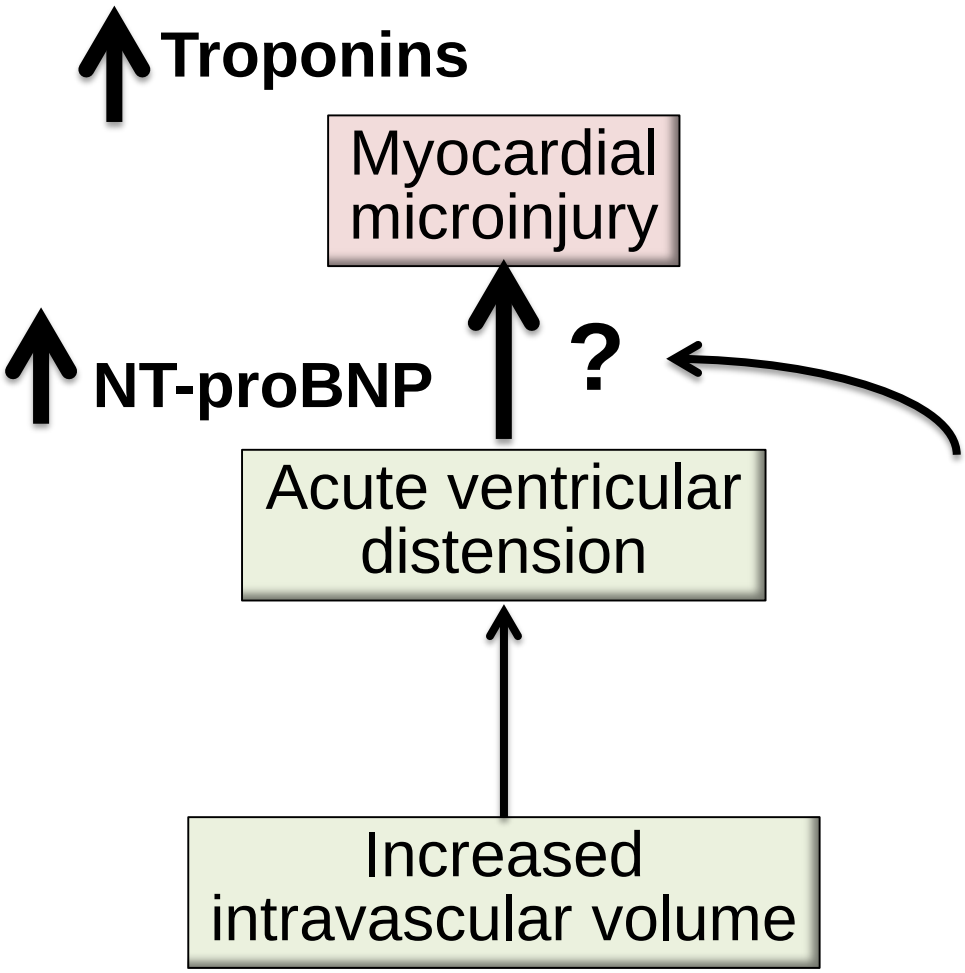
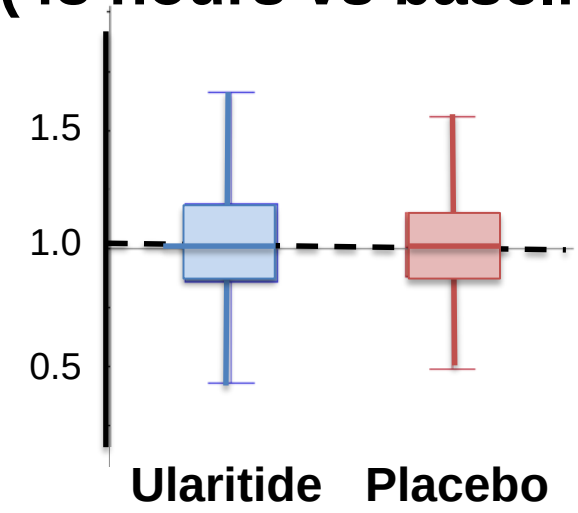


Will Rapid Reduction of Cardiac Distension Prevent Cardiac Microinjury?

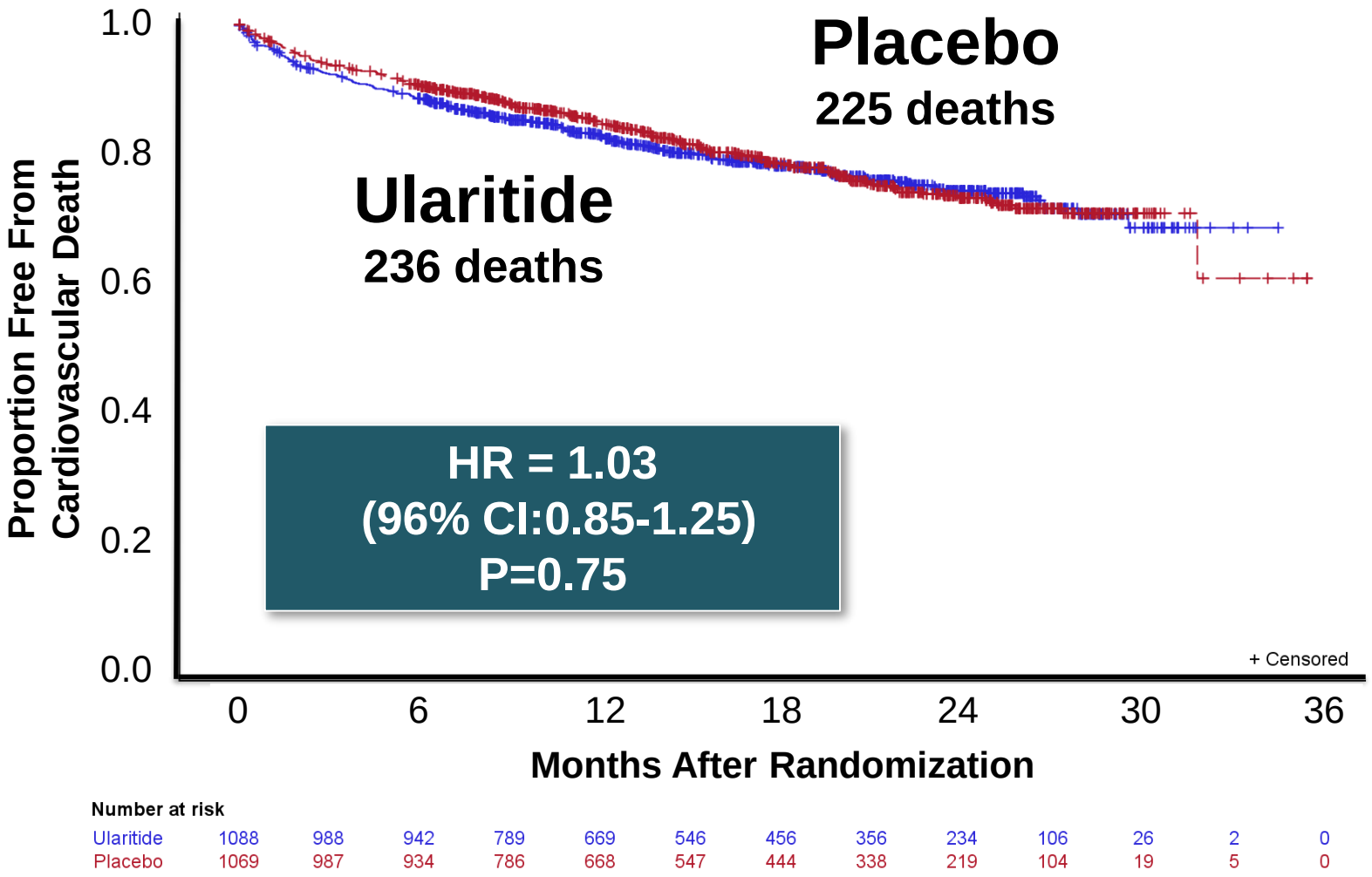


Ratio of high sensitivity cardiac troponin T (48 hours vs baseline)

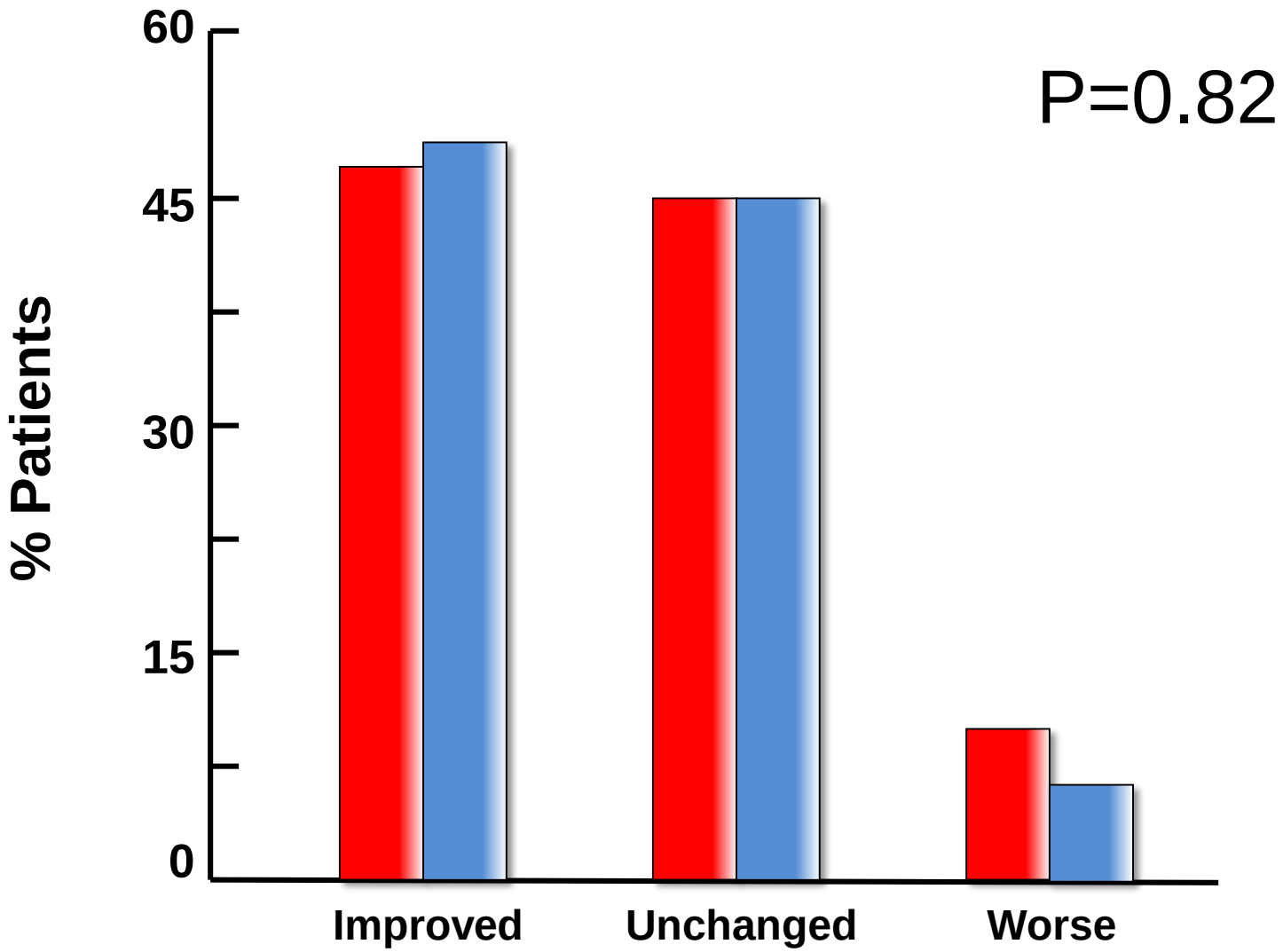


P=0.70

TRUE-AHF: Cardiovascular Mortality



TRUE-AHF: Clinical Composite



TRUE-AHF: Secondary Endpoints

	Placebo (n=1069)	Ularitide (n=1088)	P Value
Length of stay (hr) in intensive care during first 120 hours,	69.8 (50.3, 94.3)	68.0 (49.3, 93.6)	0.24
Length of stay (hr) in the hospital during first 30 days,	148.2 (94.0, 216.8)	160.8 (96.0, 228.9)	0.16
Episodes of in-hospital worsening HF during first 120 hr	126	115	0.63
Proportion with in-hospital worsening HF during first 120 hr	94 (8.8%)	90 (8.3%)	0.70
Rehospitalization for HF within 30 days of hospital discharge	74 (7.0%)	75 (7.1%)	1.00
Duration (hours) of IV therapy for HF during index admission,	68.9 (44.6, 115.5)	70.5 (42.7, 115.4)	0.53
All-cause mortality or CV hospitalization at 6 months	398 (37.2%)	443 (40.7%)	0.10

TRUE-AHF: Safety

Most Common Adverse Events

	Placebo (n=1056)	Ularitide (n=1072)
Hypotension	107 (10.1%)	240 (22.4%)

Renal Events

	Placebo (n=1056)	Ularitide (n=1072)
Renal failure	23 (2.2%)	24 (2.2%)
Acute kidney injury	24 (2.3%)	15 (1.4%)
Renal impairment	18 (1.7%)	19 (1.8%)
Chronic kidney disease	7 (0.7%)	13 (1.2%)
Serum creatinine at 30 days	1.3 ± 0.5	1.3 ± 0.5

TRUE-AHF: Conclusions

- It has been hypothesized that ventricular distension during acute heart failure leads to myocardial injury, explaining why such episodes are followed by acceleration of the downhill course of these patients.
- Our findings indicate that early vasodilator therapy can produce meaningful decongestion and ameliorate cardiac wall stress as well as reduce the risk and number of in-hospital heart failure events.
- However, this benefit does not reduce myocardial injury or change the natural history of these patients, including the long-term risk of cardiovascular death.