Medical Management in Acute Heart Failure

פרופ' עידו י. בירתי

מנהל המערך הקרדיווסקולרי

ע"ש לידיה וקרול קיטנר, לאה ובנימין דוידאי

מרכז רפואי פדה-פוריה

ראש החוג לקרדיולוגיה, אוניברסיטת בר-אילן

Disclosures

AstraZaneca	Speaker Honoria
BI	Speaker Honoria
Novo Nordisk	Speaker Honoria
CTS	Speaker Honoria
American Regent	Research support paid to the University of Pennsylvania
Medtronic	Research support paid to the University of Pennsylvania

Outline

- What is acute heart failure ?
  - Definition of cardiogenic shock

- Medical therapy in acute heart failure:
  - Diuretics
  - Vasodilators
  - Inotropes
  - SGLT2 inhibitors

Definition of Acute Heart Failure

- AHF refers to **rapid or gradual** onset of symptoms and/or signs of HF, severe enough for the patient to seek urgent medical attention, leading to an unplanned hospital admission or an emergency department visit

- Acute heart failure:
  - Leading cause of hospitalizations in subjects aged >65 years
  - Associated with high mortality and re-hospitalization rates
  - In-hospital mortality ranges from 4% to 10%.
  - Post-discharge 1-year mortality can be 25-30%

Eur Heart J 2006;27:27252736.
Eur J Heart Fail 2017;19:12421254.
Eur J Heart Fail 2019;21:13381352.

Classification and Clinical Presentation of Acute Heart Failure

- **De-novo** (new onset) heart failure
  - Symptoms occur in patients without previous history of HF
  - Requires a more extensive diagnostic process

- **Acute decompensated heart failure** (ADHF)
  - Symptoms progression in patients with previously diagnosed chronic HF

- As HF is a chronic and progressive disease, the **majority** of hospitalizations are related to **ADHF** rather than de novo AHF

- **Clinical presentation of acute heart failure**
  - Characterized **mostly** by symptoms and signs related to systemic **congestion**
  - Only a **minority** of patients with AHF present with **cardiogenic shock**

Definition of Cardiogenic Shock

- **SBP < 90 mmHg for ≥30 min or need for vasopressors to maintain SBP ≥ 90 mmHg**

And

- **End-organ hypo-perfusion**
  - Urine output <30 ml/hr
  - Cool extremities
  - Altered mental status
  - Lactate >2.0

And

- **Hemodynamic Criteria**
  - CI ≤2.2 l/min/m2

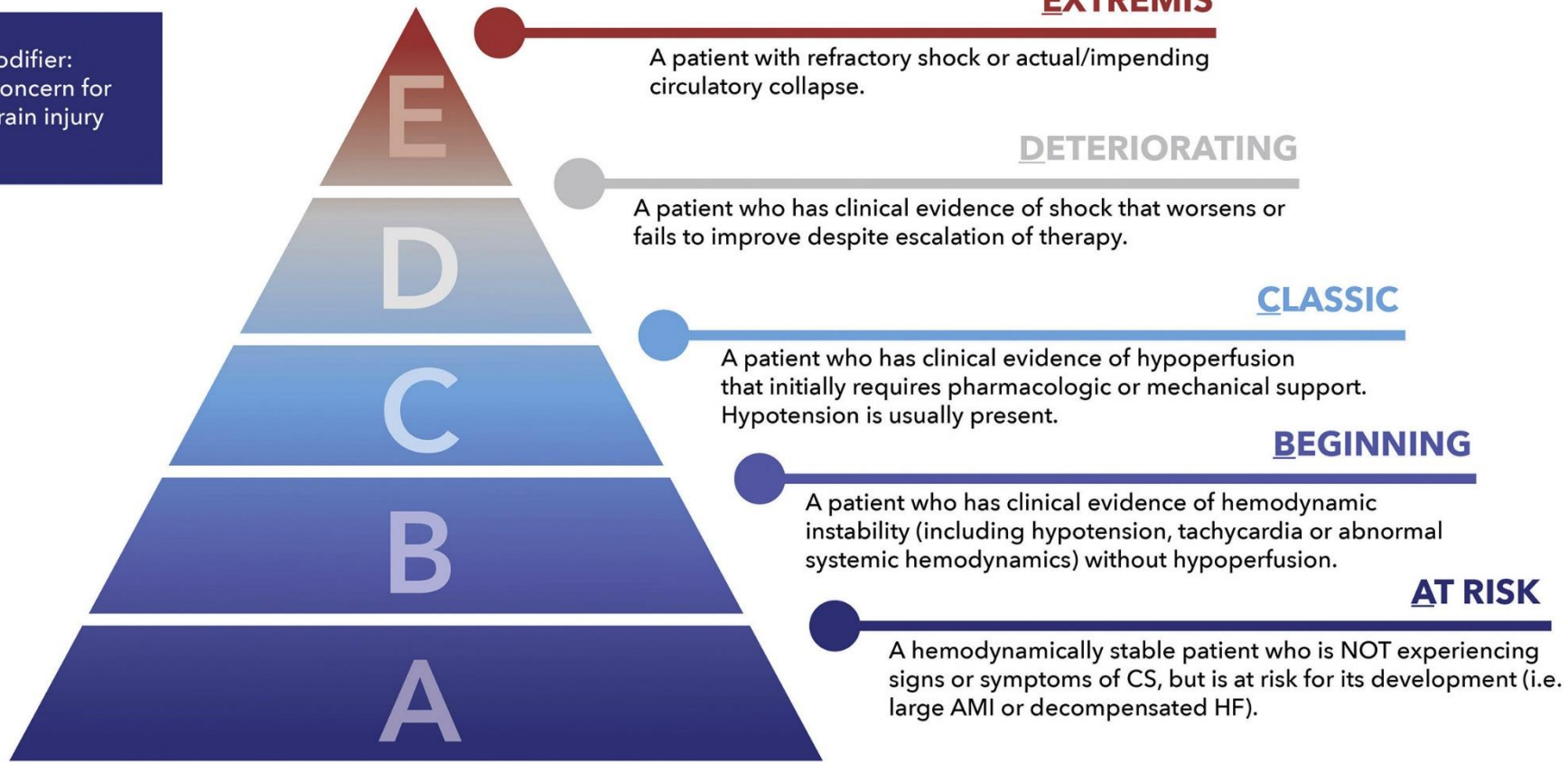
  and

  - PCWP >15 mm Hg

Tehrani et al. J Am Coll Cardiol HF 2020;8:879–91

SCAI stages

(A) Modifier:
CA with concern for anoxic brain injury



ESC
European Society of Cardiology

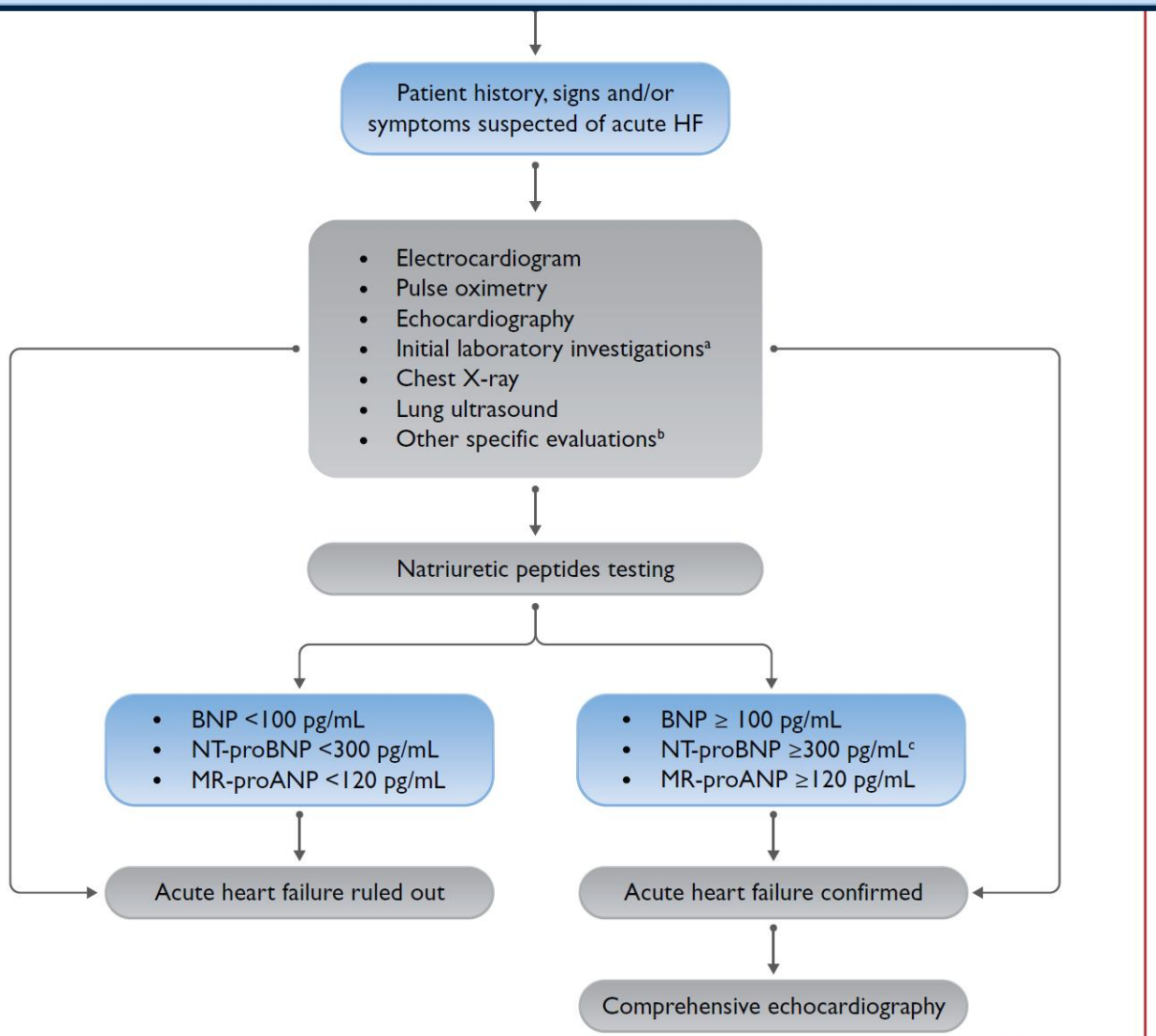
European Heart Journal (2021) **00**, 1–128
doi:10.1093/eurheartj/ehab368

ESC GUIDELINES

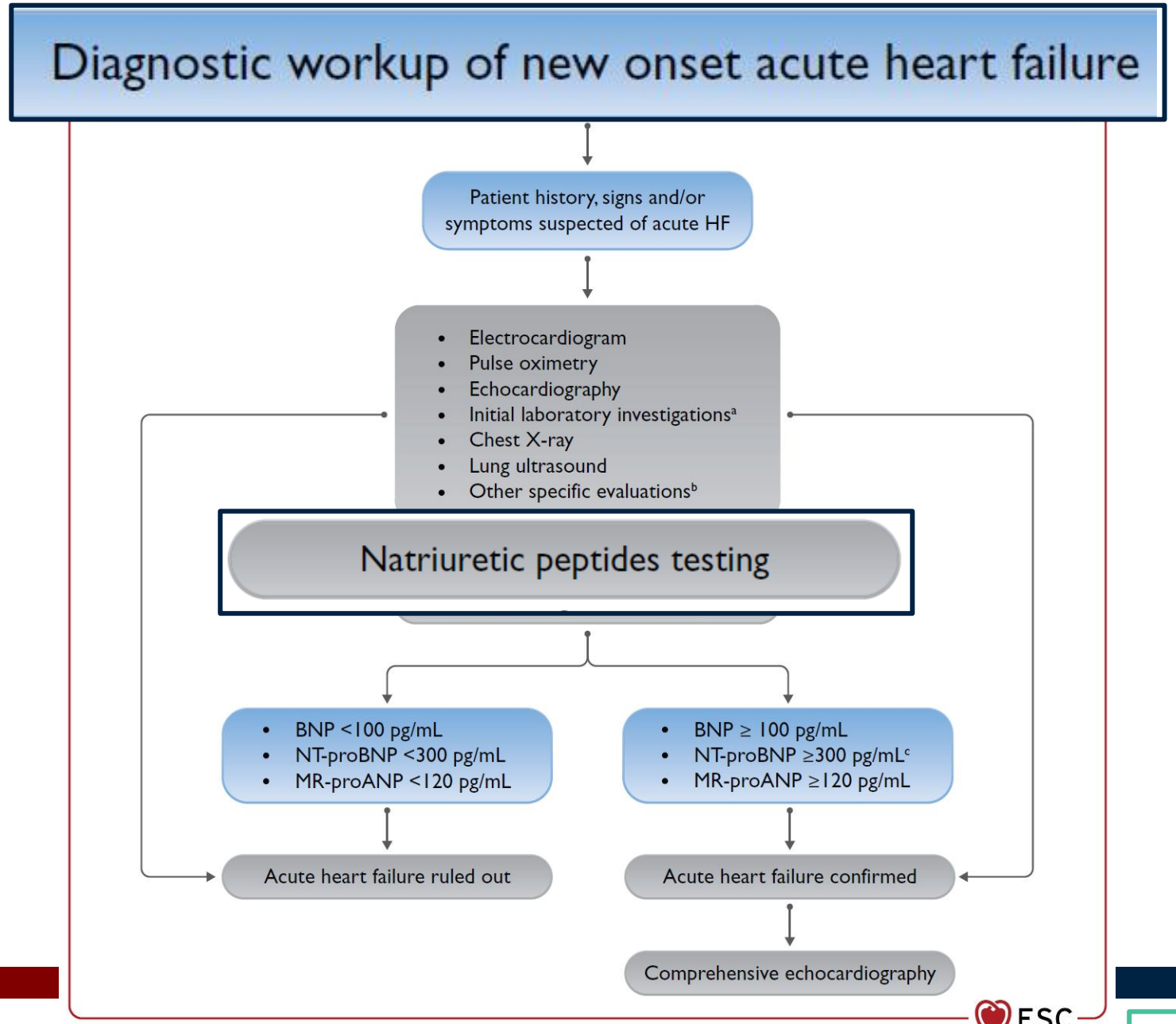
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

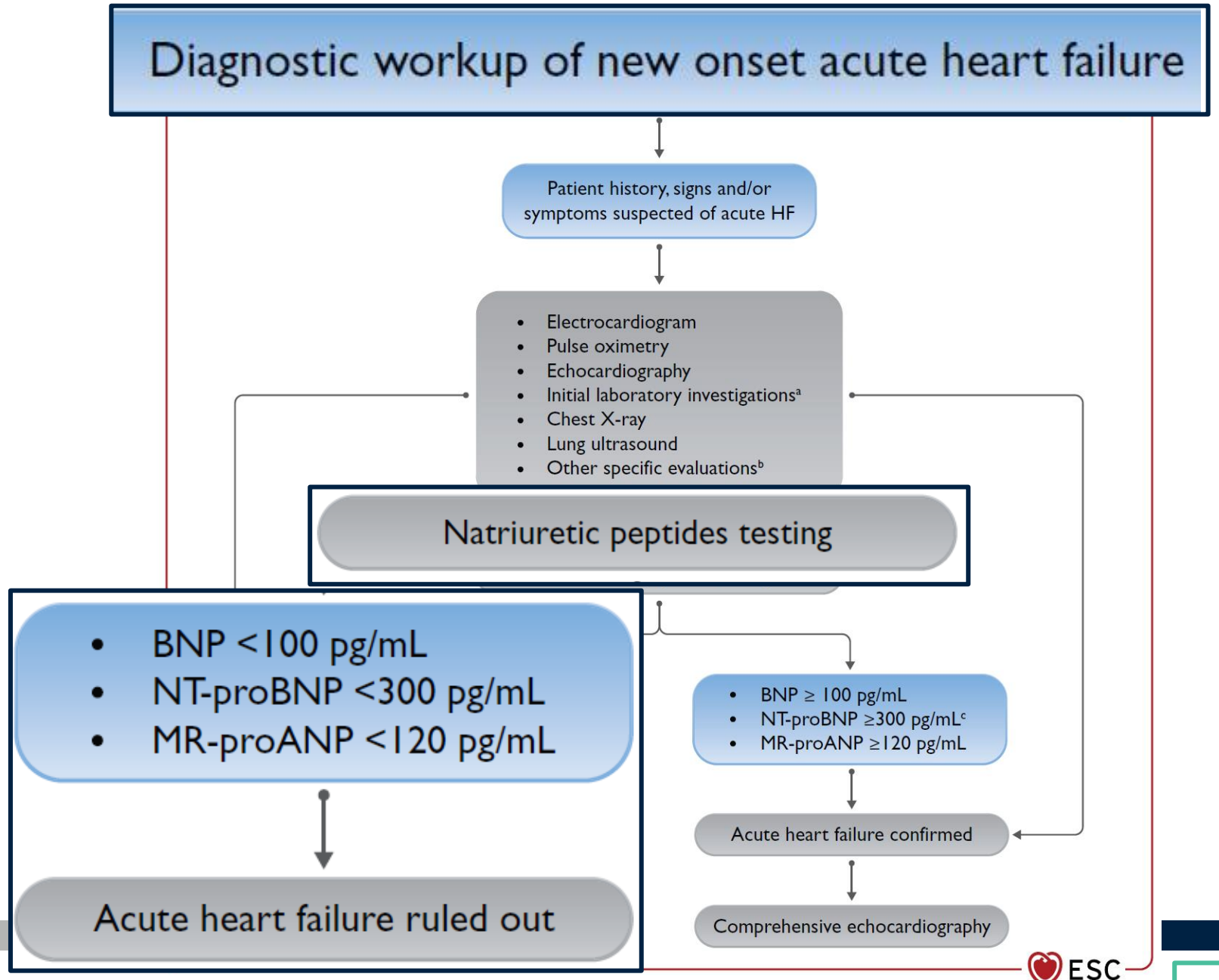
Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

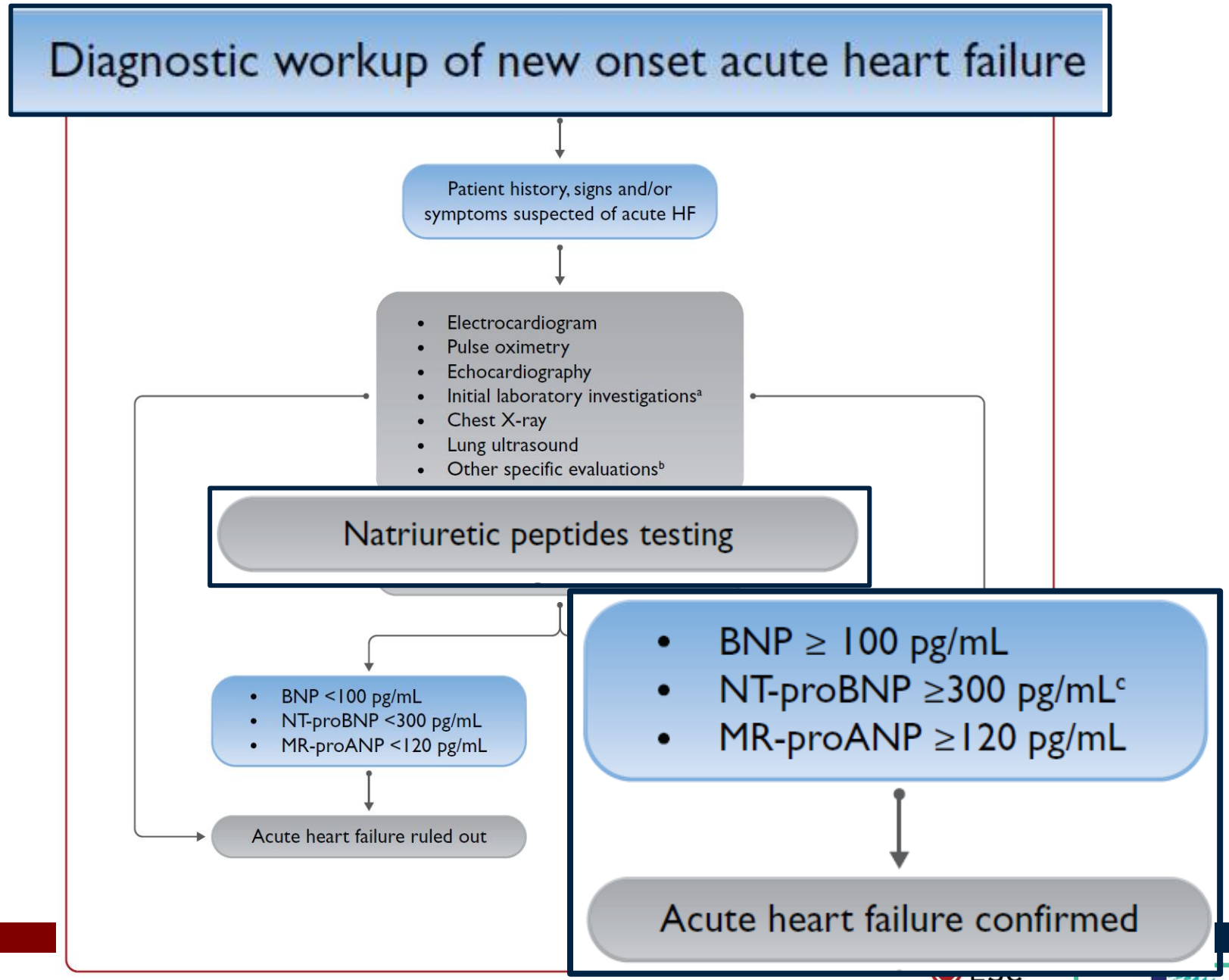
Diagnostic workup of new onset acute heart failure

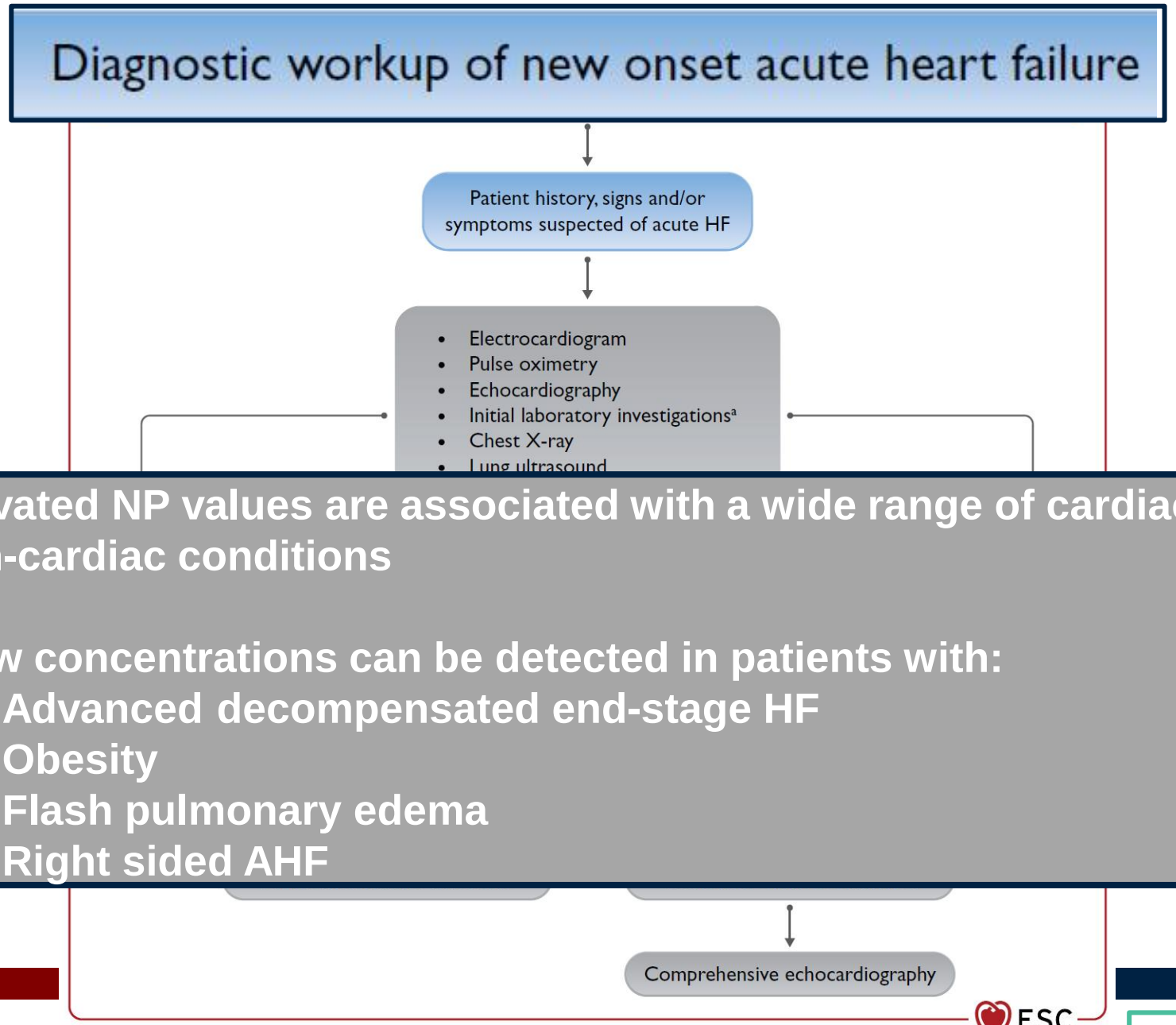


ESC


Diagnostic workup of new onset acute heart failure
Patient history, signs and/or symptoms suspected of acute HF
Electrocardiogram
Pulse oximetry
Echocardiography
Initial laboratory investigations[a]
Chest X-ray
Lung ultrasound
Other specific evaluations[b]
Natriuretic peptides testing
BNP <100 pg/mL
NT-proBNP <300 pg/mL
MR-proANP <120 pg/mL
BNP ≥ 100 pg/mL
NT-proBNP ≥300 pg/mL[c]
MR-proANP ≥120 pg/mL
Acute heart failure ruled out
Acute heart failure confirmed
Comprehensive echocardiography
ESC


Diagnostic workup of new onset acute heart failure
Patient history, signs and/or symptoms suspected of acute HF
Electrocardiogram
Pulse oximetry
Echocardiography
Initial laboratory investigations[a]
Chest X-ray
Lung ultrasound
Other specific evaluations[b]
Natriuretic peptides testing
BNP <100 pg/mL
NT-proBNP <300 pg/mL
MR-proANP <120 pg/mL
Acute heart failure ruled out
BNP ≥ 100 pg/mL
NT-proBNP ≥300 pg/mL[c]
MR-proANP ≥120 pg/mL
Acute heart failure confirmed
Comprehensive echocardiography
ESC

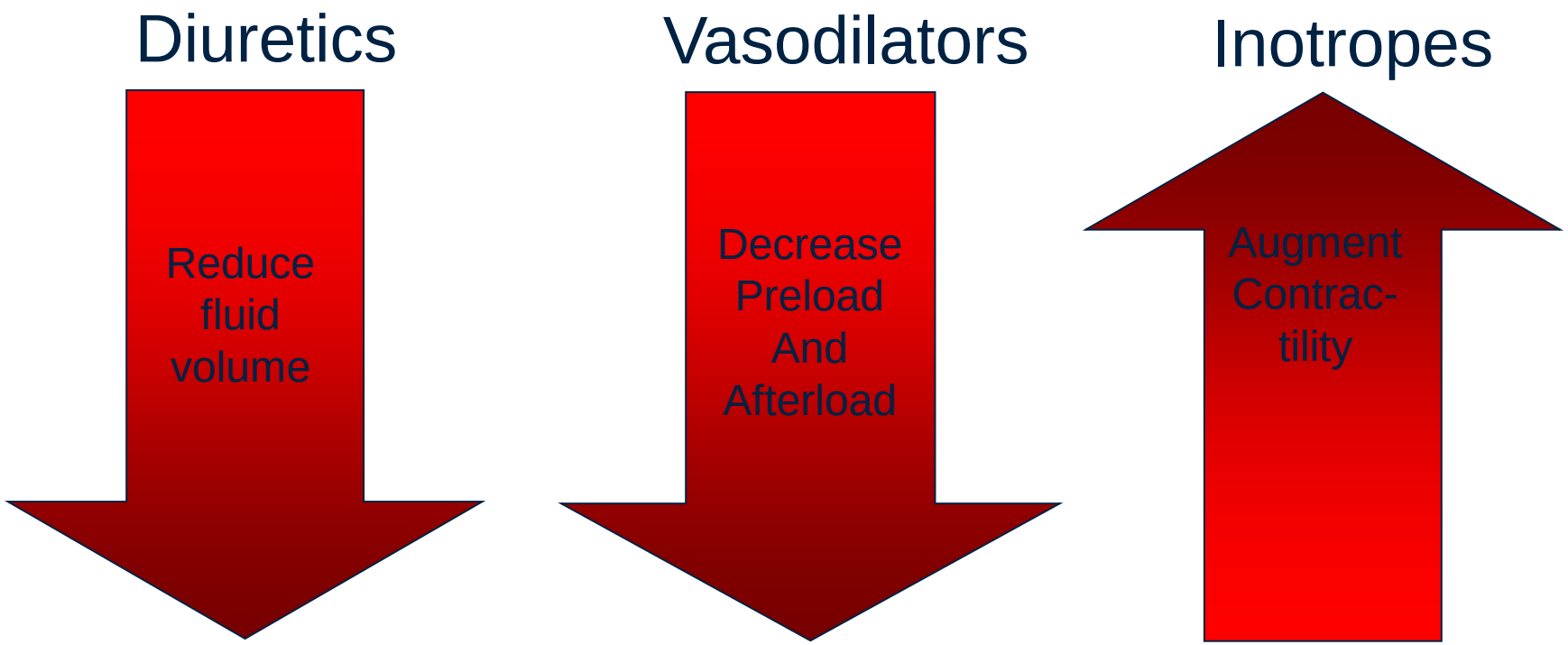

Diagnostic workup of new onset acute heart failure
Patient history, signs and/or symptoms suspected of acute HF
Electrocardiogram
Pulse oximetry
Echocardiography
Initial laboratory investigations[a]
Chest X-ray
Lung ultrasound
Other specific evaluations[b]
Natriuretic peptides testing
BNP <100 pg/mL
NT-proBNP <300 pg/mL
MR-proANP <120 pg/mL
Acute heart failure ruled out
BNP ≥ 100 pg/mL
NT-proBNP ≥300 pg/mL[c]
MR-proANP ≥120 pg/mL
Acute heart failure confirmed



- **Elevated NP values are associated with a wide range of cardiac and non-cardiac conditions**

- **Low concentrations can be detected in patients with:**
  - **Advanced decompensated end-stage HF**
  - **Obesity**
  - **Flash pulmonary edema**
  - **Right sided AHF**

Current Medical Therapy of Acute Heart Failure

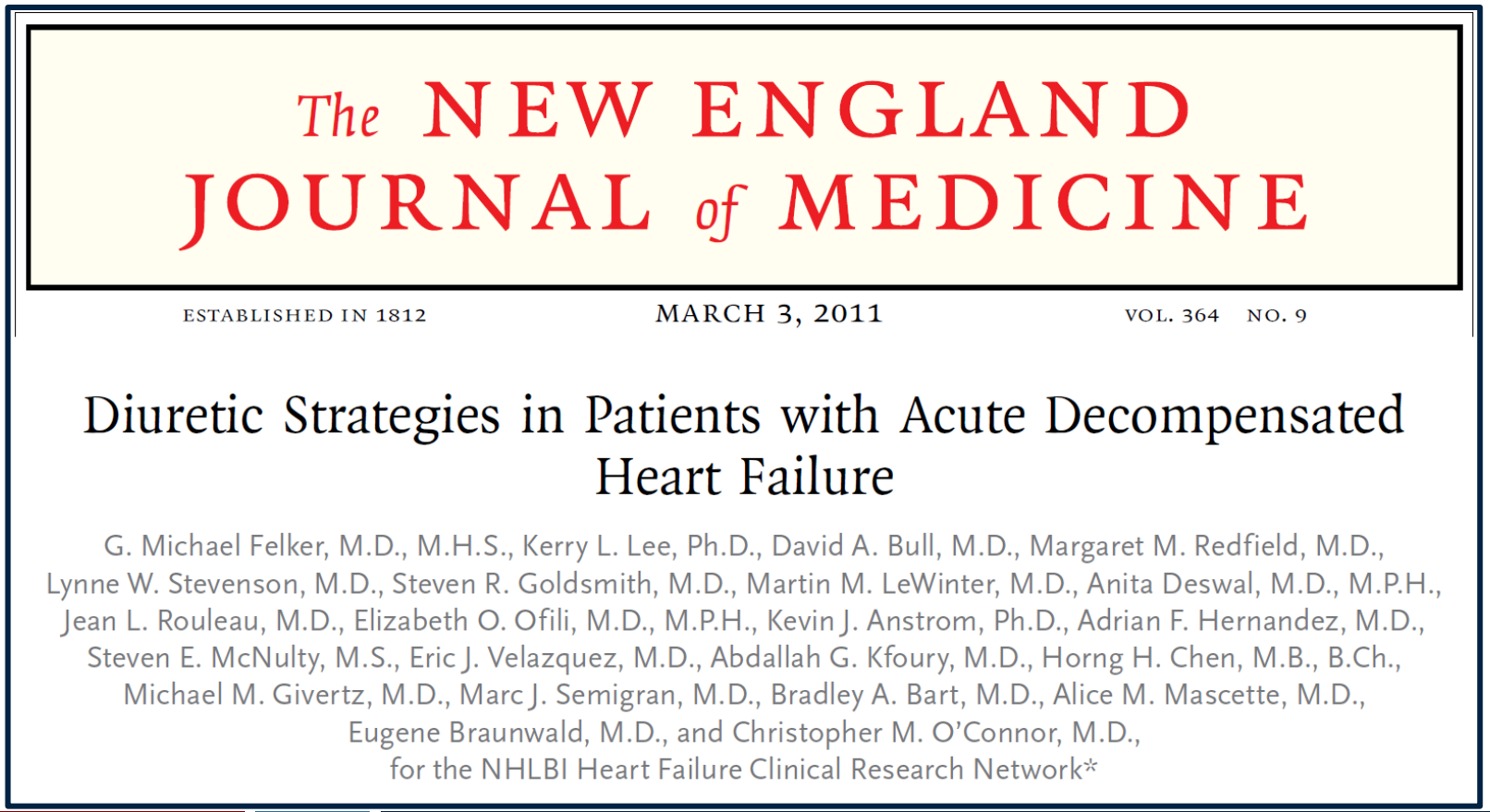


Diuretics

- The cornerstone of the management strategy

Diuretics

- The cornerstone of the management strategy



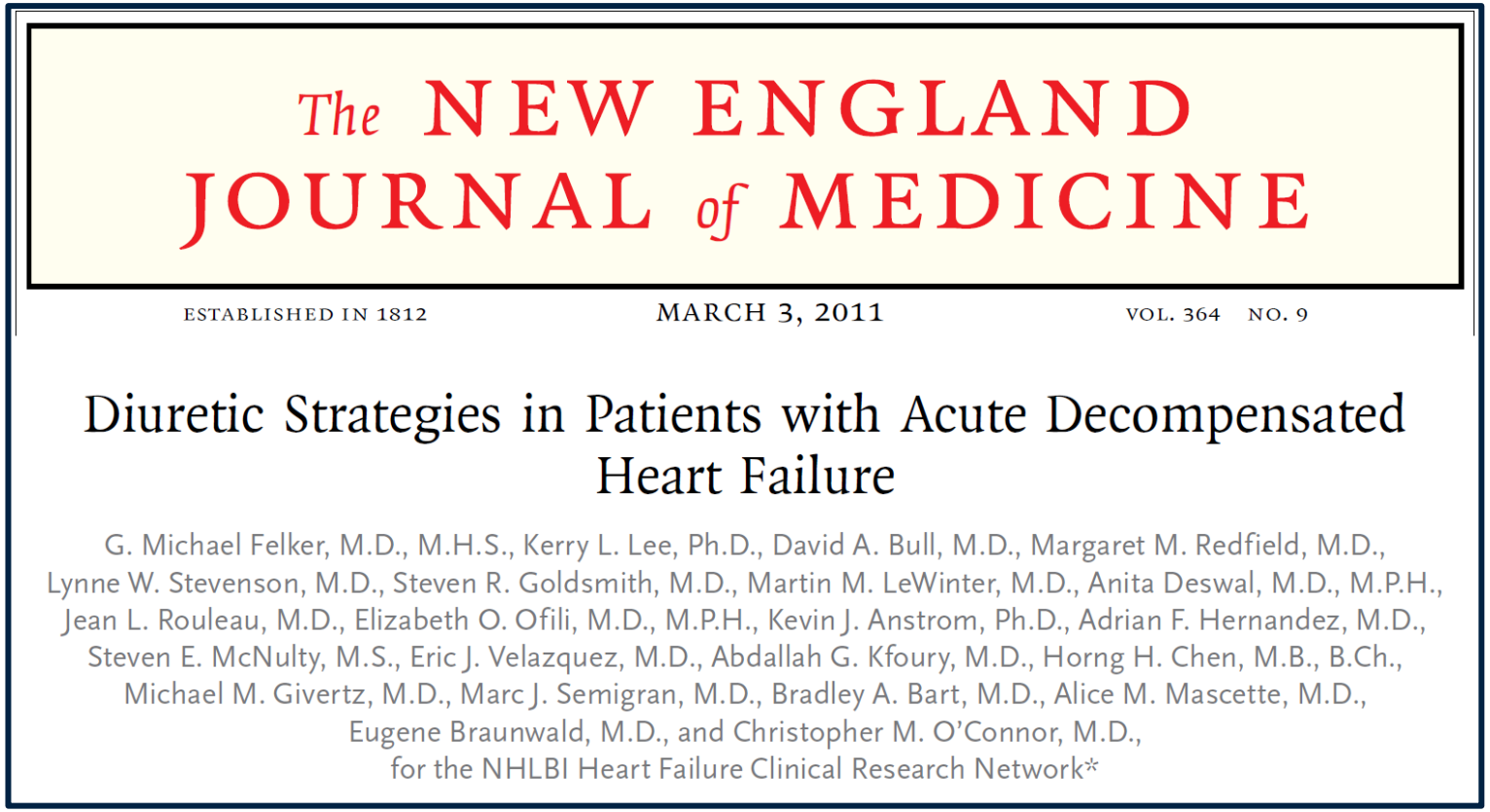
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 3, 2011 VOL. 364 NO. 9

Diuretic Strategies in Patients with Acute Decompensated Heart Failure

G. Michael Felker, M.D., M.H.S., Kerry L. Lee, Ph.D., David A. Bull, M.D., Margaret M. Redfield, M.D., Lynne W. Stevenson, M.D., Steven R. Goldsmith, M.D., Martin M. LeWinter, M.D., Anita Deswal, M.D., M.P.H., Jean L. Rouleau, M.D., Elizabeth O. Ofili, M.D., M.P.H., Kevin J. Anstrom, Ph.D., Adrian F. Hernandez, M.D., Steven E. McNulty, M.S., Eric J. Velazquez, M.D., Abdallah G. Kfoury, M.D., Horng H. Chen, M.B., B.Ch., Michael M. Givertz, M.D., Marc J. Semigran, M.D., Bradley A. Bart, M.D., Alice M. Mascette, M.D., Eugene Braunwald, M.D., and Christopher M. O'Connor, M.D., for the NHLBI Heart Failure Clinical Research Network*

N Engl J Med 364;9



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 3, 2011 VOL. 364 NO. 9

Diuretic Strategies in Patients with Acute Decompensated Heart Failure

G. Michael Felker, M.D., M.H.S., Kerry L. Lee, Ph.D., David A. Bull, M.D., Margaret M. Redfield, M.D., Lynne W. Stevenson, M.D., Steven R. Goldsmith, M.D., Martin M. LeWinter, M.D., Anita Deswal, M.D., M.P.H., Jean L. Rouleau, M.D., Elizabeth O. Ofili, M.D., M.P.H., Kevin J. Anstrom, Ph.D., Adrian F. Hernandez, M.D., Steven E. McNulty, M.S., Eric J. Velazquez, M.D., Abdallah G. Kfoury, M.D., Horng H. Chen, M.B., B.Ch., Michael M. Givertz, M.D., Marc J. Semigran, M.D., Bradley A. Bart, M.D., Alice M. Mascette, M.D., Eugene Braunwald, M.D., and Christopher M. O'Connor, M.D., for the NHLBI Heart Failure Clinical Research Network*

- **Heart Failure Clinical Research Network**
- **Inclusion criteria:**
  - **Patients presented within the previous 24 hours with acute decompensated heart failure**
  - **History of chronic heart failure and receipt of an oral loop diuretic** for at least 1 month before hospitalization, at a dose between 80 mg and 240 mg daily in the case of furosemide and an equivalent dose in the case of a different loop diuretic

N Engl J Med 364;9

Dose study

- Randomly assigned, in a 2-by-2 factorial design to:
  - **A low-dose strategy** - total IV furosemide dose equal to their total daily oral loop diuretic dose in furosemide equivalents
  - **A high-dose strategy** - total daily IV furosemide dose 2.5 times their total daily oral loop diuretic dose in furosemide equivalents
  - Administration of furosemide either by **IV bolus** every 12 hours
  - Administration of furosemide by **continuous IV infusion**

N Engl J Med 364;9

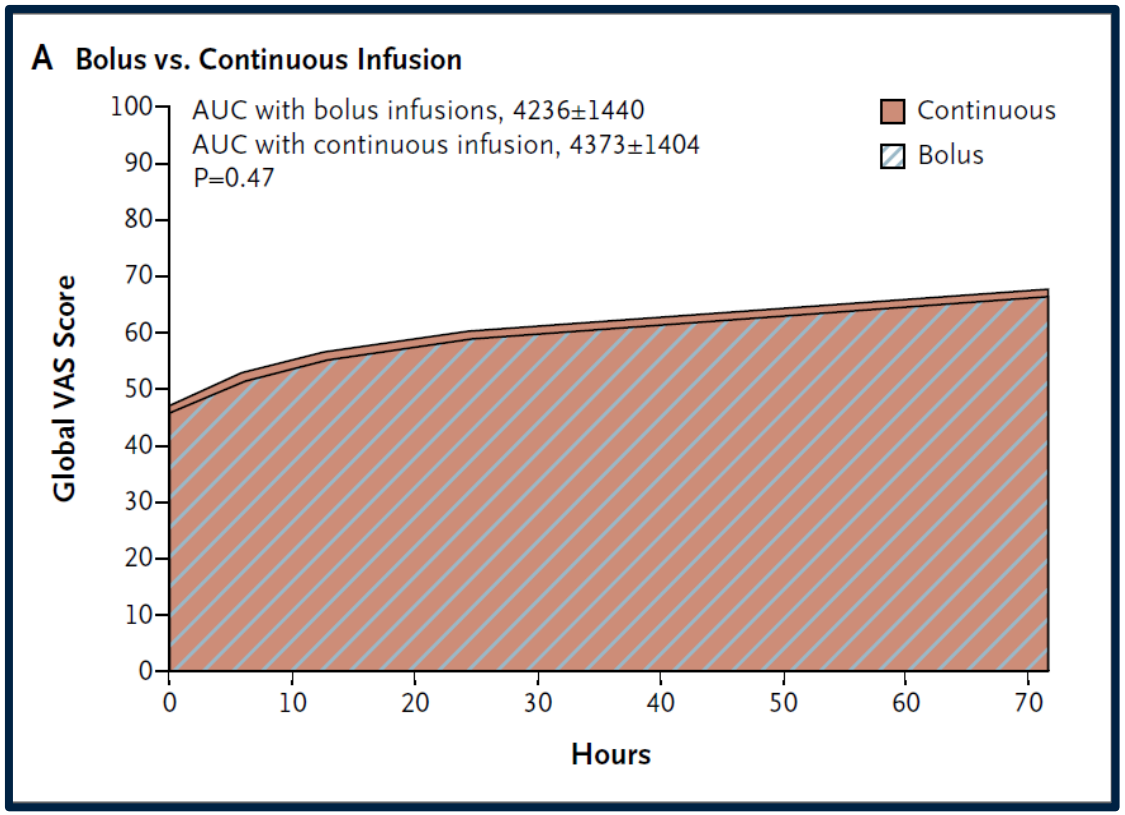
Dose study

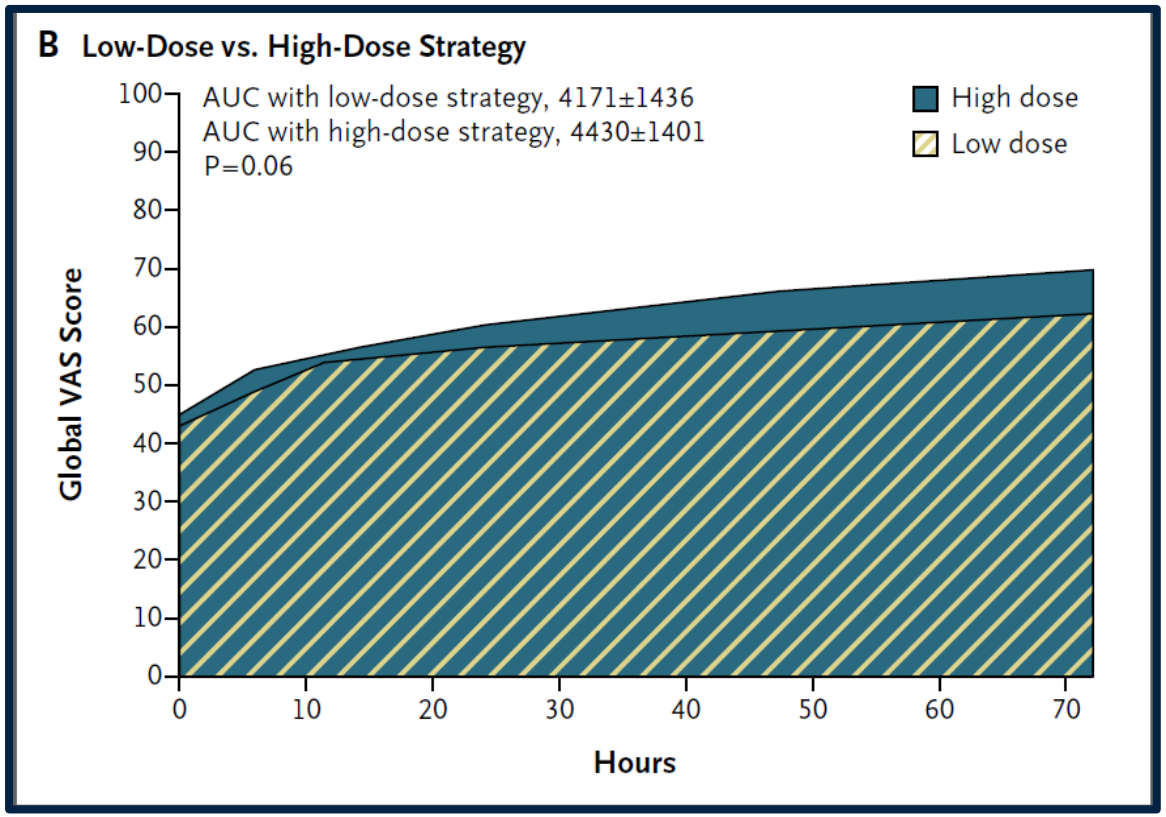
- Randomly assigned, in a 2-by-2 factorial design to:
  - **A low-dose strategy** - total IV furosemide dose equal to their total daily oral loop diuretic dose in furosemide equivalents
  - **A high-dose strategy** - total daily IV furosemide dose 2.5 times their total daily oral loop diuretic dose in furosemide equivalents
  - Administration of furosemide either by **IV bolus** every 12 hours
  - Administration of furosemide by **continuous IV infusion**

- **The primary efficacy end point** was the **patient's global assessment of symptoms**, measured with the use of a visual-analogue scale and quantified as the area under the curve (**AUC**) of serial assessments from baseline to 72 hours
- **The primary safety end point** was the **change in the serum creatinine** level from baseline to 72 hours

N Engl J Med 364;9

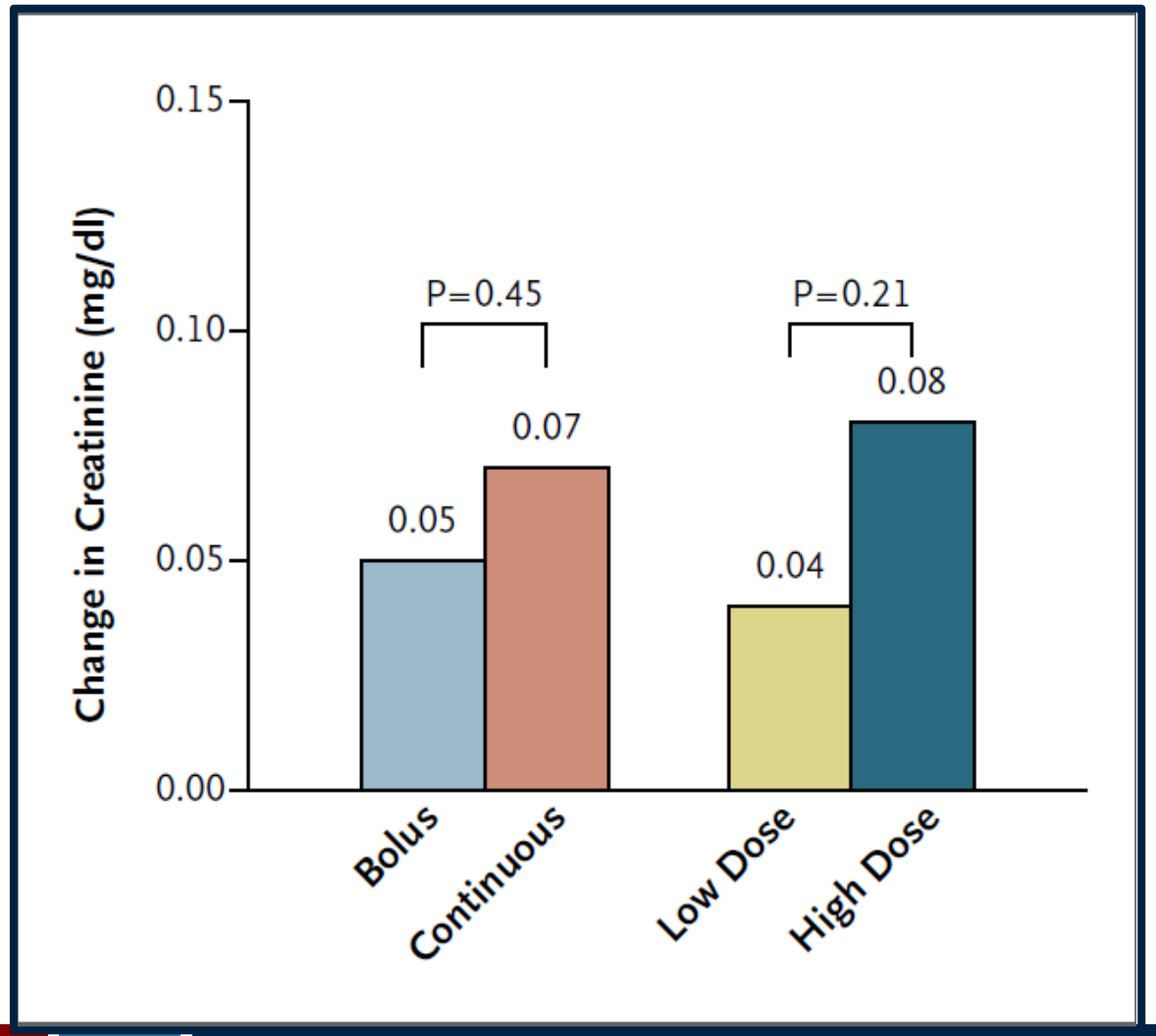
Patients' Global Assessment of Symptoms during the 72-Hour Study-Treatment Period





N Engl J Med 364;9

Mean change in creatinine



N Engl J Med 364;9

Secondary Endpoints

End Point	Bolus Every 12 Hr (N=156)	Continuous Infusion (N=152)	Value	Low Dose (N=151)	High Dose (N=157)	lue
AUC for dyspnea at 72 hr	4456±1468	4699±1573	0.36	4478±1550	4668±1496	0.04
Freedom from congestion at 72 hr — no./total no. (%)	22/153 (14)	22/144 (15)	0.78	16/143 (11)	28/154 (18)	0.09
Change in weight at 72 hr — lb	−6.8±7.8	−8.1±10.3	0.20	−6.1±9.5	−8.7±8.5	0.01
Net fluid loss at 72 hr — ml	4237±3208	4249±3104	0.89	3575±2635	4899±3479	0.001
Change in NT-proBNP at 72 hr — pg/ml	−1316±4364	−1773±3828	0.44	−1194±4094	−1882±4105	0.06
Worsening or persistent heart failure — no./total no. (%)	38/154 (25)	34/145 (23)	0.78	38/145 (26)	34/154 (22)	0.40
Treatment failure — no./total no. (%)†	59/155 (38)	57/147 (39)	0.88	54/147 (37)	62/155 (40)	0.56
Increase in creatinine of >0.3 mg/dl within 72 hr — no./total no. (%)	27/155 (17)	28/146 (19)	0.64	20/147 (14)	35/154 (23)	0.04
Length of stay in hospital — days			0.97			0.55
Median	5	5		6	5	
Interquartile range	3–9	3–8		4–9	3–8	
Alive and out of hospital — days			0.36			0.42
Median	51	51		50	52	
Interquartile range	42–55	38–55		39–54	42–56	

N Engl J Med 364;9

Secondary Endpoints

End Point	Bolus Every 12 Hr (N=156)	Continuous Infusion (N=152)	P Value	Low Dose (N=151)	High Dose (N=157)	P Value
AUC for dyspnea at 72 hr	4456±1468	4699±1573	0.36	4478±1550	4668±1496	0.04
Freedom from congestion at 72 hr — no./total no. (%)	22/153 (14)	22/144 (15)		16/143 (11)	28/154 (18)	0.09
Change in weight at 72 hr — lb	−6.8±7.8	−8.1±10.3	0.78	−6.1±9.5	−8.7±8.5	0.01
Net fluid loss at 72 hr — ml	4237±3208	4249±3104		3575±2635	4899±3479	0.001
Change in NT-proBNP at 72 hr — pg/ml	−1316±4364	−1773±3828		−1194±4094	−1882±4105	0.06
Worsening or persistent heart failure — no./total no. (%)	38/154 (25)	34/145 (23)	0.20	38/145 (26)	34/154 (22)	0.40
Treatment failure — no./total no. (%)†	59/155 (38)	57/147 (39)	0.89	54/147 (37)	62/155 (40)	0.56
Increase in creatinine of >0.3 mg/dl within 72 hr — no./total no. (%)	27/155 (17)	28/146 (19)		20/147 (14)	35/154 (23)	0.04
Length of stay in hospital — days			0.44			0.55
Median	5	5		6	5	
Interquartile range	3–9	3–8		4–9	3–8	
Alive and out of hospital — days			0.36			0.42
Median	51	51		50	52	
Interquartile range	42–55	38–55		39–54	42–56	

N Engl J Med 364;9

Secondary Endpoints

End Point	Bolus Every 12 Hr (N=156)	Continuous Infusion (N=152)	P Value	Low Dose (N=151)	High Dose (N=157)	lue
AUC for dyspnea at 72 hr	4456±1468	4699±1573	0.36	4478±1550	4668±1496	0.04
no./total no. (%)	22/153 (14)	22/144 (15)	0.78	16/143 (11)	28/154 (18)	0.09
Change in weight at 72 hr — lb	−6.8±7.8	−8.1±10.3	0.20	−6.1±9.5	−8.7±8.5	0.01
Net fluid loss at 72 hr — ml	4237±3208	4249±3104	0.89	3575±2635	4899±3479	0.001
Change in NT-proBNP at 72 hr — pg/ml	−1316±4364	−1773±3828	0.44	−1194±4094	−1882±4105	0.06
Worsening or persistent heart failure — no./total no. (%)	38/154 (25)	34/145 (23)	0.78	38/145 (26)	34/154 (22)	0.40
Treatment failure — no./total no. (%)†	59/155 (38)	57/147 (39)	0.88	54/147 (37)	62/155 (40)	0.56
Increase in creatinine of >0.3 mg/dl within 72 hr — no./total no. (%)	27/155 (17)	28/146 (19)	0.64	20/147 (14)	35/154 (23)	0.04
Length of stay in hospital — days			0.97			0.55
Median	5	5		6	5	
Interquartile range	3–9	3–8		4–9	3–8	
Alive and out of hospital — days			0.36			0.42
Median	51	51		50	52	
Interquartile range	42–55	38–55		39–54	42–56	

N Engl J Med 364;9

Secondary Endpoints

End Point	Bolus Every 12 Hr (N=156)	Continuous Infusion (N=152)	P Value	Low Dose (N=151)	High Dose (N=157)	P Value
AUC for dyspnea at 72 hr	4456±1468	4699±1573	0.36	4478±1550	4668±1496	0.04
Freedom from congestion at 72 hr — no./total no. (%)	22/153 (14)	22/144 (15)	0.78	16/143 (11)	28/154 (18)	0.09
Change in weight at 72 hr — lb		−8.1±10.3	0.20	−6.1±9.5	−8.7±8.5	0.01
	8	4249±3104	0.89	3575±2635	4899±3479	
Net fluid loss at 72 hr — ml	4	−1773±3828	0.44	−1194±4094	−1882±4105	0.001
Worsening or persistent heart failure — no./total no. (%)	38/154 (25)	34/145 (23)	0.78	38/145 (26)	34/154 (22)	0.40
Treatment failure — no./total no. (%)†	59/155 (38)	57/147 (39)	0.88	54/147 (37)	62/155 (40)	0.56
Increase in creatinine of >0.3 mg/dl within 72 hr — no./total no. (%)	27/155 (17)	28/146 (19)	0.64	20/147 (14)	35/154 (23)	0.04
Length of stay in hospital — days			0.97			0.55
Median	5	5		6	5	
Interquartile range	3–9	3–8		4–9	3–8	
Alive and out of hospital — days			0.36			0.42
Median	51	51		50	52	
Interquartile range	42–55	38–55		39–54	42–56	

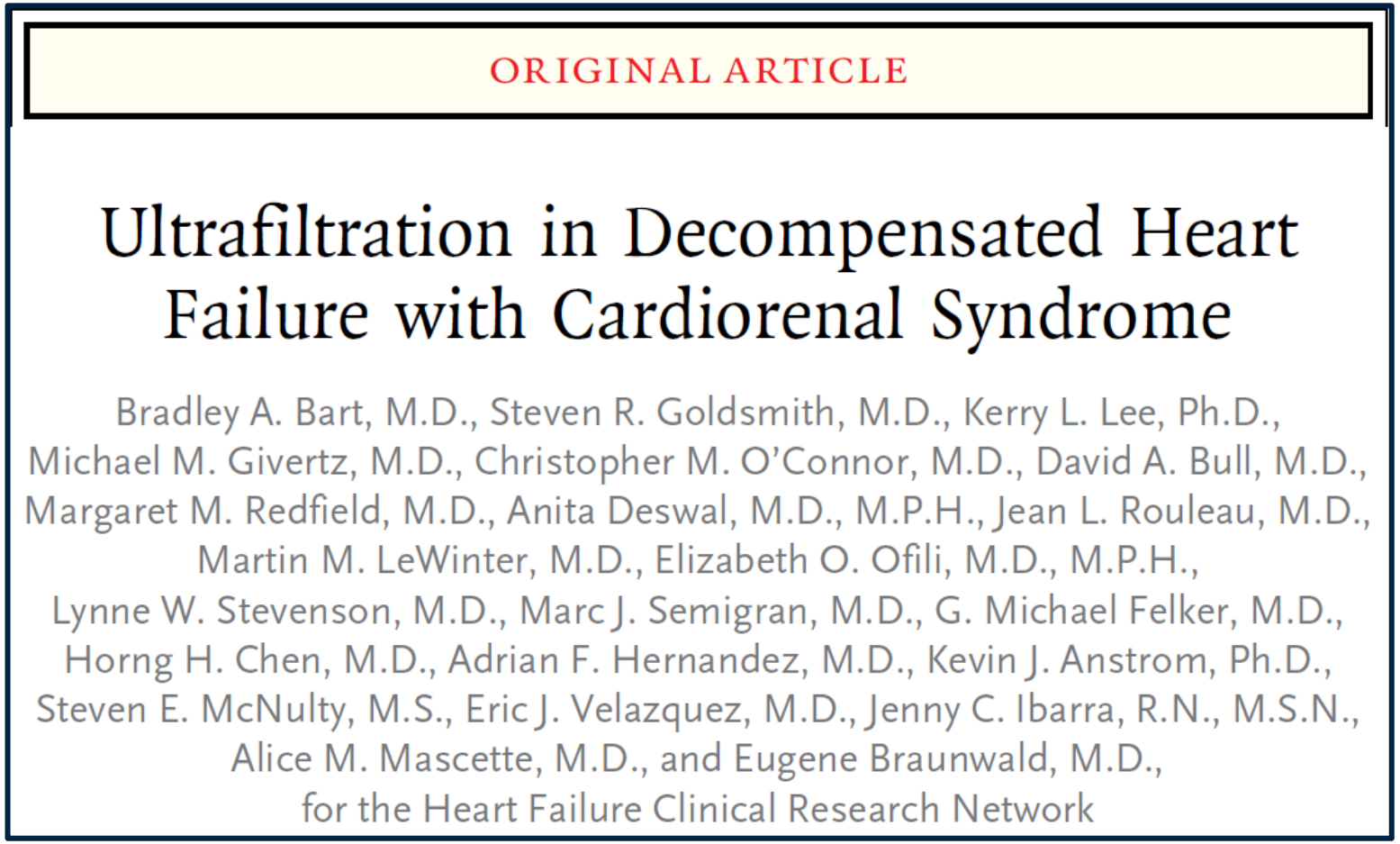
N Engl J Med 364;9

Secondary Endpoints

End Point	Bolus Every 12 Hr (N=156)	Continuous Infusion (N=152)	P Value	Low Dose (N=151)	High Dose (N=157)	lue
AUC for dyspnea at 72 hr	4456±1468	4699±1573	0.36	4478±1550	4668±1496	0.04
Freedom from congestion at 72 hr — no./total no. (%)	22/153 (14)	22/144 (15)	0.78	16/143 (11)	28/154 (18)	0.09
Change in weight at 72 hr — lb	−6.8±7.8	−8.1±10.3	0.20	−6.1±9.5	−8.7±8.5	0.01
Net fluid loss at 72 hr — ml	4237±3208	4249±3104	0.89	3575±2635	4899±3479	0.001
Change in NT-proBNP at 72 hr — pg/ml	−1316±4364	−1773±3828	0.44	−1194±4094	−1882±4105	0.06
Worsening or persistent heart failure — no./total no. (%)	38/154 (25)	34/145 (23)	0.78	38/145 (26)	34/154 (22)	0.40
Treatment failure — no./total no. (%)†	59/155 (38)	57/147 (39)	0.88	54/147 (37)	62/155 (40)	0.56
Increase in creatinine of >0.3 mg/dl within 72 hr — no./total no. (%)	27/155 (17)	28/146 (19)	0.64	20/147 (14)	35/154 (23)	0.04
Length of stay in hospital — days			0.97			0.55
Interquartile range	3–9	3–8		4–9	3–8	
Alive and out of hospital — days			0.36			0.42
Median	51	51		50	52	
Interquartile range	42–55	38–55		39–54	42–56	

Increase in creatinine of >0.3 mg/dl within 72 hr — no./total no. (%) 27/155 (17) 28/146 (19) 0.64 20/147 (14) 35/154 (23) 0.04

N Engl J Med 364;9


ORIGINAL ARTICLE

Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome

Bradley A. Bart, M.D., Steven R. Goldsmith, M.D., Kerry L. Lee, Ph.D., Michael M. Givertz, M.D., Christopher M. O'Connor, M.D., David A. Bull, M.D., Margaret M. Redfield, M.D., Anita Deswal, M.D., M.P.H., Jean L. Rouleau, M.D., Martin M. LeWinter, M.D., Elizabeth O. Ofili, M.D., M.P.H., Lynne W. Stevenson, M.D., Marc J. Semigran, M.D., G. Michael Felker, M.D., Horng H. Chen, M.D., Adrian F. Hernandez, M.D., Kevin J. Anstrom, Ph.D., Steven E. McNulty, M.S., Eric J. Velazquez, M.D., Jenny C. Ibarra, R.N., M.S.N., Alice M. Mascette, M.D., and Eugene Braunwald, M.D., for the Heart Failure Clinical Research Network

CARRESS-HF

- A randomized trial that compared ultrafiltration with a strategy of diuretic-based stepped pharmacologic therapy

N Engl J Med 367;24

CARRESS-HF

- **Inclusion criteria**:
  - Patients **admitted with acute decompensated heart failure** as the primary diagnosis were eligible for enrollment
  - Had **worsened renal function** defined as an increase in the serum creatinine level of at least 0.3 mg/dl within 12 weeks before or 10 days after the index admission for heart failure
  - Evidence of **volume overload** on physical exam

N Engl J Med 367;24

CARRESS-HF

- **Inclusion criteria**:
  - Patients **admitted with acute decompensated heart failure** as the primary diagnosis were eligible for enrollment
  - Had **worsened renal function** defined as an increase in the serum creatinine level of at least 0.3 mg/dl within 12 weeks before or 10 days after the index admission for heart failure
  - Evidence of **volume overload** on physical exam

- Randomly assigned, in a 1:1 ratio, to either **ultrafiltration therapy** or **stepped pharmacologic therapy**
  - **Ultrafiltration therapy**
    - Loop **diuretics** were to be **discontinued** for the duration of the ultrafiltration intervention
    - Ultrafiltration was performed at a fluid-removal rate of **200 ml/hour**

  - **Stepped pharmacologic therapy**
    - Investigators were encouraged to decrease doses, increase doses, or continue current doses of diuretics as necessary **to maintain a urine output of 3 to 5 liters per day**

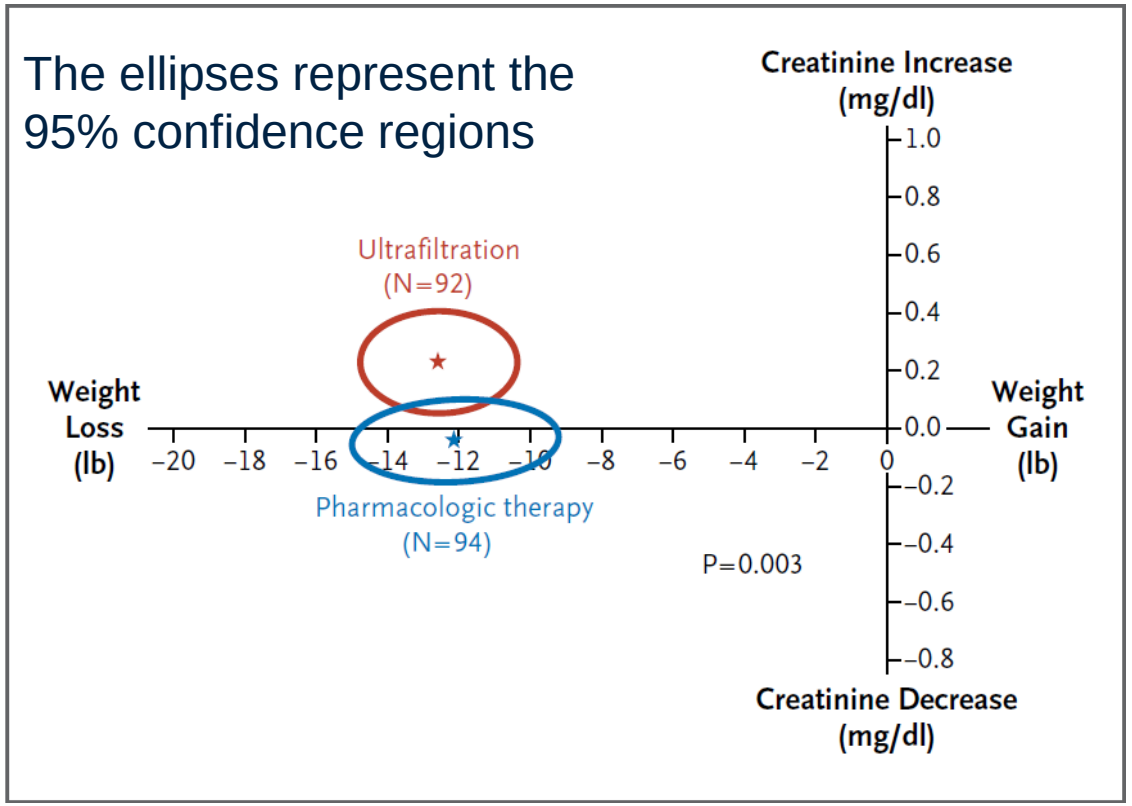
N Engl J Med 367;24

CARRESS-HF

- **Primary end point**
  - **Change in the serum creatinine level** and the **change in weight**, considered as a bivariate response, between the time of randomization and 96 hours after randomization

CARRESS-HF

- **Primary end point**
  - **Change in the serum creatinine level** and the **change in weight**, considered as a bivariate response, between the time of randomization and 96 hours after randomization



There was a **significant difference** between the treatment groups in the **bivariate end point** of change in weight and change in serum creatinine level 96 hours after enrollment **(P = 0.003)**

- This difference was **due** primarily to an **increase** in the serum **creatinine** level in the ultrafiltration group
- No significant difference between pharmacologic therapy and ultrafiltration with respect to the mean weight loss

Original Article

Loop Diuretic Efficiency

A Metric of Diuretic Responsiveness With Prognostic Importance in Acute Decompensated Heart Failure

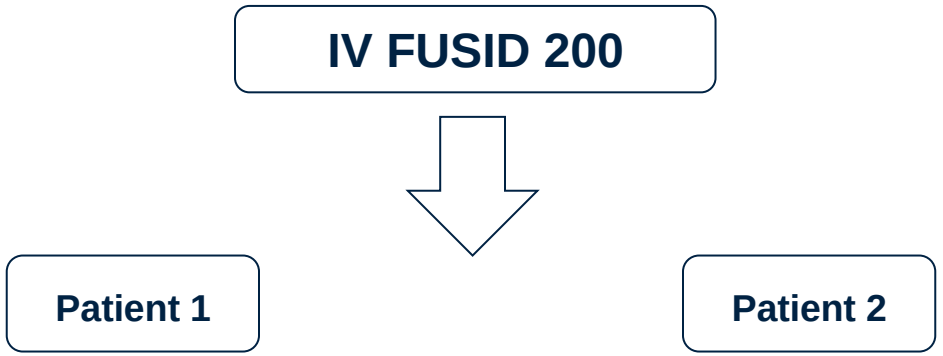
Jeffrey M. Testani, MD, MTR; Meredith A. Brisco, MD, MSCE; Jeffrey M. Turner, MD; Erica S. Spatz, MD, MHS; Lavanya Bellumkonda, MD; Chirag R. Parikh, MD, PhD; W.H. Wilson Tang, MD

Circ Heart Fail. 2014;7:261-270

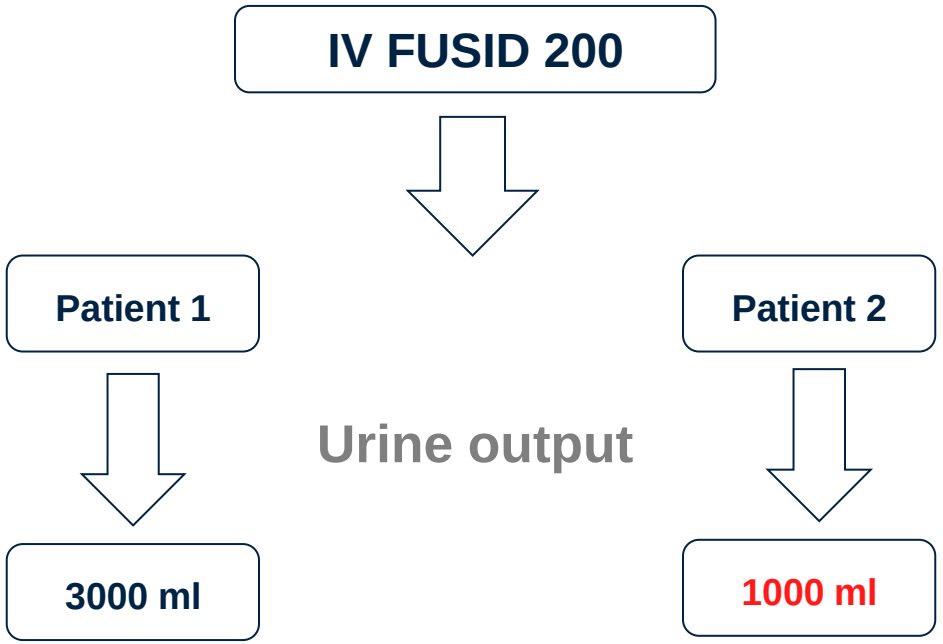
- **Resistance to loop diuretics is an adverse prognostic indicator**

Circ Heart Fail. 2014;7:261-270.

Loop diuretic efficiency

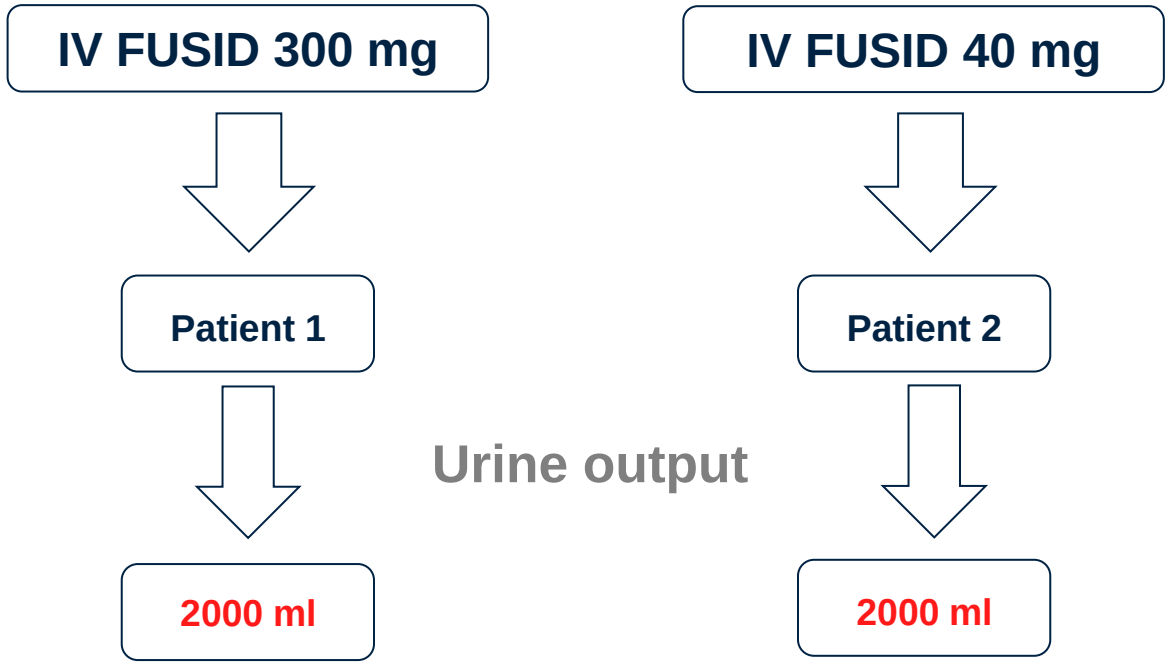


Loop diuretic efficiency

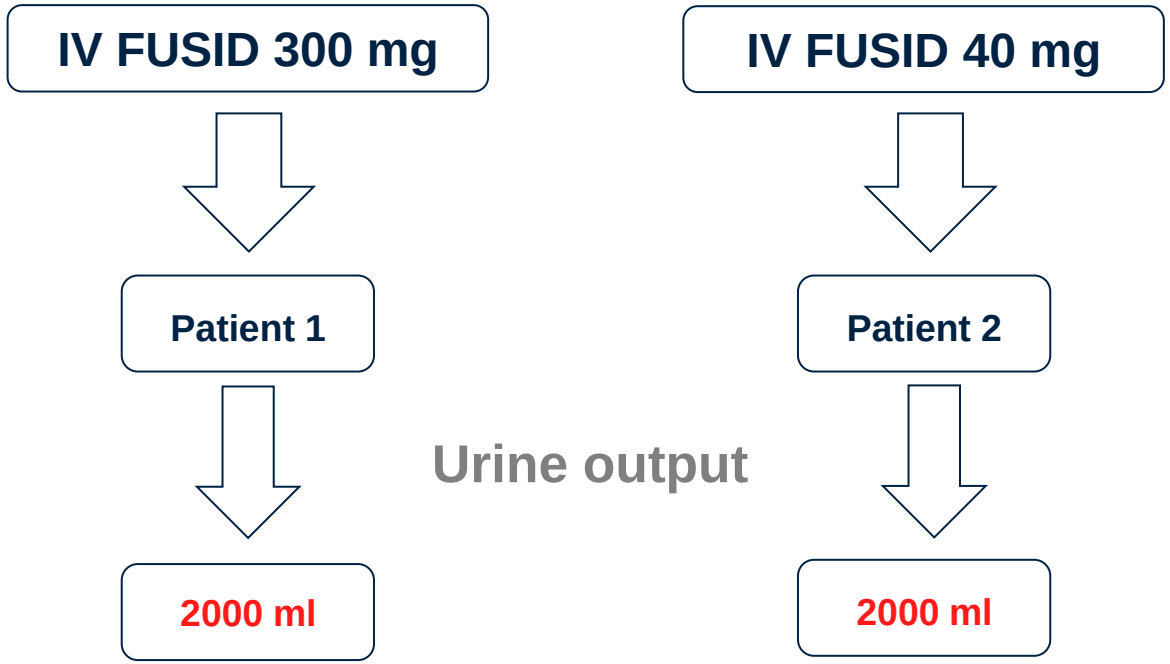


Loop diuretic efficiency

Loop diuretic efficiency



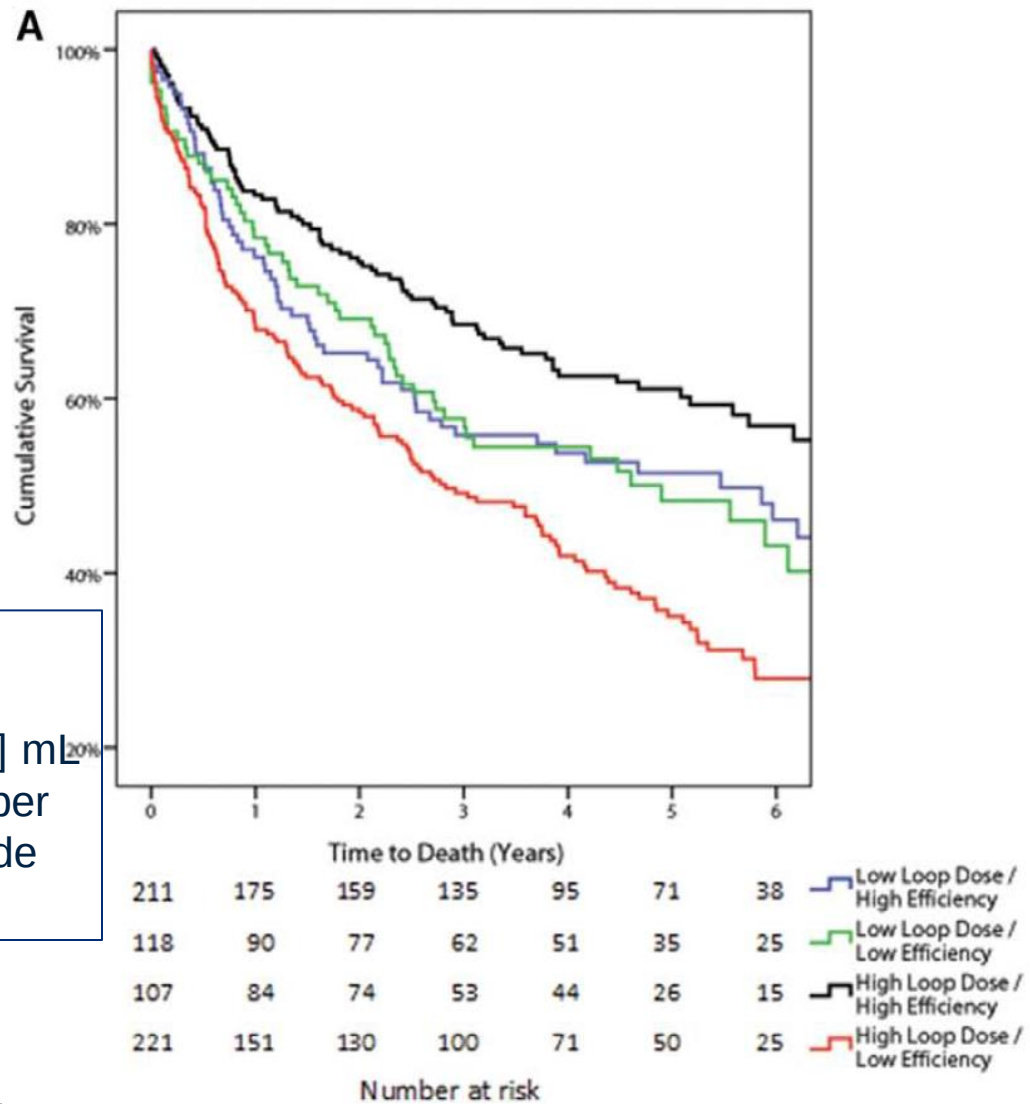
Loop diuretic efficiency

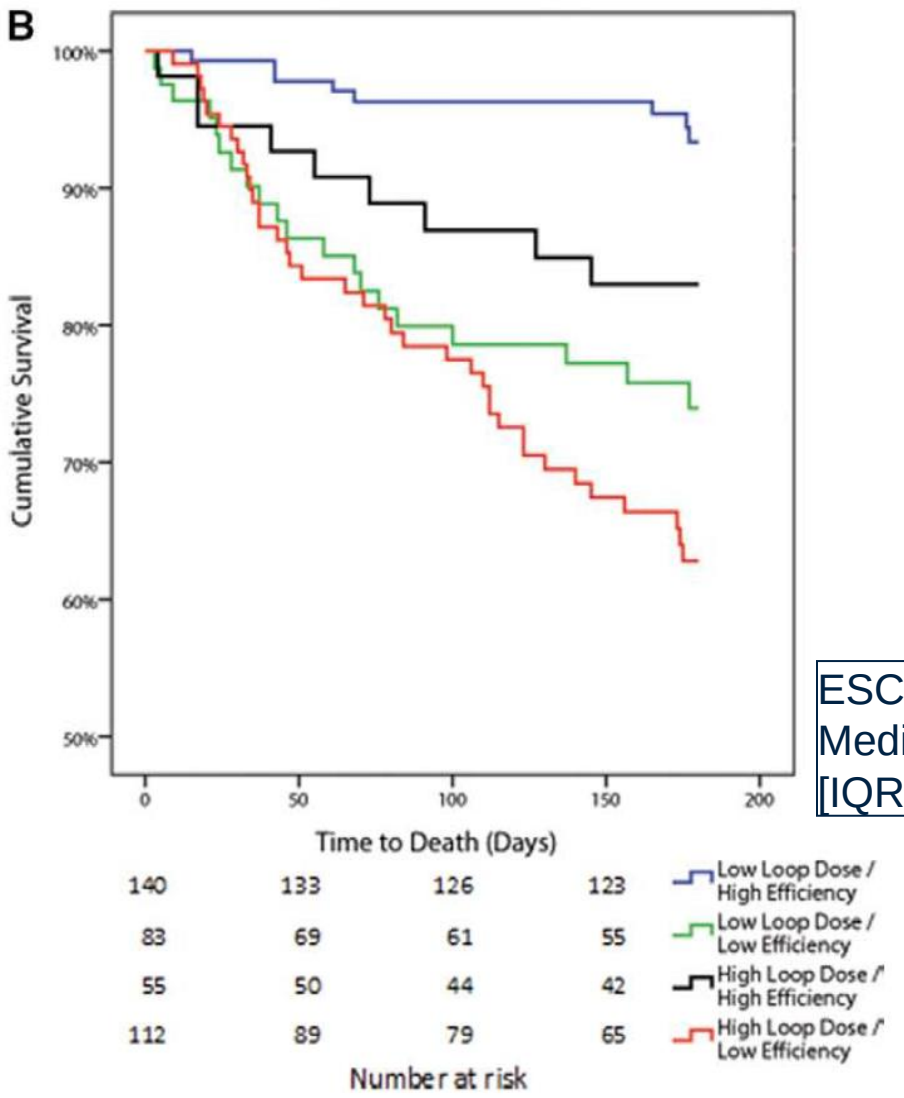


- Defined **diuretic efficiency** (DE) as the **net fluid lost per milligram of loop diuretic** during an ADHF hospitalization
  - **Relative DE** in each patient was determined as fluid output per milligram of loop diuretic received (expressed as **milliliters of net fluid output per 40 mg of furosemide** equivalents)
  - **Peak DE** was calculated using the average daily fluid output divided by the peak intravenous loop diuretic

DE and Survival

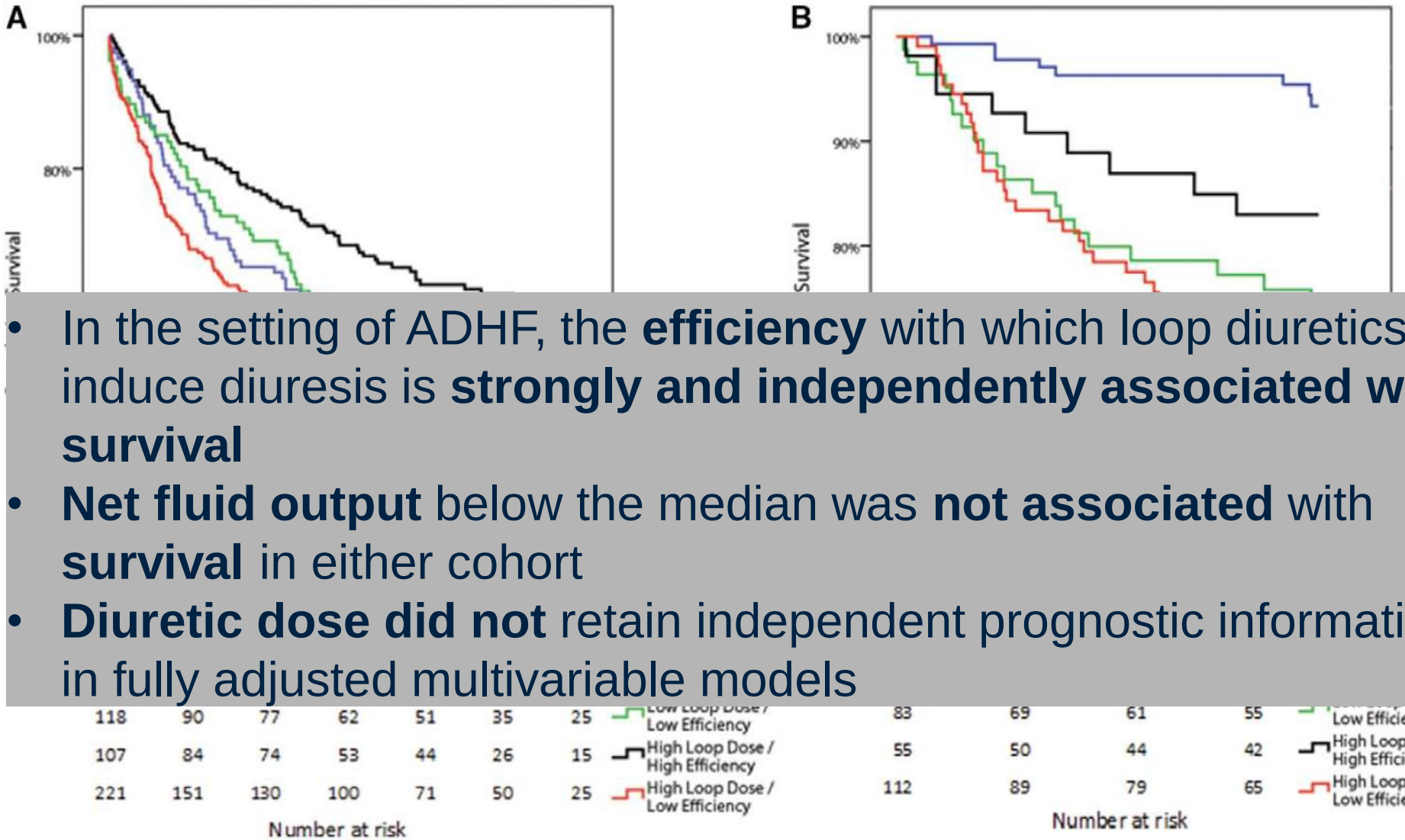
Penn cohort:
Median DE 480 [IQR, 195–1024] mL net fluid output per 40 mg furosemide equivalents;





ESCAPE cohort:
Median 148 [IQR, 61–283]

DE and Survival



- In the setting of ADHF, the **efficiency** with which loop diuretics induce diuresis is **strongly and independently associated with survival**
- **Net fluid output** below the median was **not associated** with **survival** in either cohort
- **Diuretic dose did not** retain independent prognostic information in fully adjusted multivariable models

Low-Dose Dopamine or Low-Dose Nesiritide in Acute Heart Failure With Renal Dysfunction
The ROSE Acute Heart Failure Randomized Trial

Horng H. Chen, MBBCh; Kevin J. Anstrom, PhD; Michael M. Givertz, MD; Lynne W. Stevenson, MD; Marc J. Semigran, MD; Steven R. Goldsmith, MD; Bradley A. Bart, MD; David A. Bull, MD; Josef Stehlik, MD; Martin M. LeWinter, MD; Marvin A. Konstam, MD; Gordon S. Huggins, MD; Jean L. Rouleau, MD; Eileen O'Meara, MD; W. H. Wilson Tang, MD; Randall C. Starling, MD, MPH; Javed Butler, MD, MPH; Anita Deswal, MD; G. Michael Felker, MD; Christopher M. O'Connor, MD; Raphael E. Bonita, MD, ScM; Kenneth B. Margulies, MD; Thomas P. Cappola, MD, ScM; Elizabeth O. Ofili, MD; Douglas L. Mann, MD; Víctor G. Dávila-Román, MD; Steven E. McNulty, MS; Barry A. Borlaug, MD; Eric J. Velazquez, MD; Kerry L. Lee, PhD; Monica R. Shah, MD, MHS, MSJ; Adrian F. Hernandez, MD, MHS; Eugene Braunwald, MD; Margaret M. Redfield, MD; for the NHLBI Heart Failure Clinical Research Network

THE ROSE Study

JAMA. 2013;310(23):2533-2543.

ROSE study

- **Dopamine** is an endogenous catecholamine that, at **low doses** (≤3 µg/kg/min), may selectively activate dopamine receptors and **promote renal vasodilatation**
- Previous studies have suggested that the addition of **low-dose dopamine** to diuretic therapy enhances **decongestion** and preserves renal function during diuretic therapy in acute heart failure

- **Nesiritide** is human recombinant B-type natriuretic peptide and is approved for management of acute heart failure
- Small studies using low-dose nesiritide (0.005 µg/kg/min without bolus) in acute heart failure and cardiac surgery patients have demonstrated favorable effects on urine output and renal function

ROSE study

- **Dopamine** is an endogenous catecholamine that, at low doses (≤3 μg/kg/min), may selectively activate dopamine receptors and promote renal vasodilatation
- Previous studies have suggested that the addition of low-dose dopamine to diuretic therapy enhances decongestion and preserves renal function during diuretic therapy in acute heart failure

- **Nesiritide** is human **recombinant B-type natriuretic peptide** and is approved for management of acute heart failure
- Small studies using low-dose nesiritide (0.005 μg/kg/min without bolus) in acute heart failure and cardiac surgery patients have demonstrated **favorable effects on urine output and renal function**

ROSE study

- **Dopamine** is an endogenous catecholamine that, at low doses (≤3 μg/kg/min), may selectively activate dopamine receptors and promote renal vasodilatation
- Previous studies have suggested that the addition of low-dose dopamine to diuretic therapy enhances decongestion and preserves renal function during diuretic therapy in acute heart failure

- **Nesiritide** is human recombinant B-type natriuretic peptide and is approved for management of acute heart failure
- Small studies using low-dose nesiritide (0.005 μg/kg/min without bolus) in acute heart failure and cardiac surgery patients have demonstrated favorable effects on urine output and renal function

Hypothesis: Compared with placebo, the addition of low-dose dopamine (2 μg/kg/min) or low-dose nesiritide (0.005 μg/kg/min without bolus) **will enhance decongestion and preserve renal function** in patients with **acute heart failure and renal dysfunction**

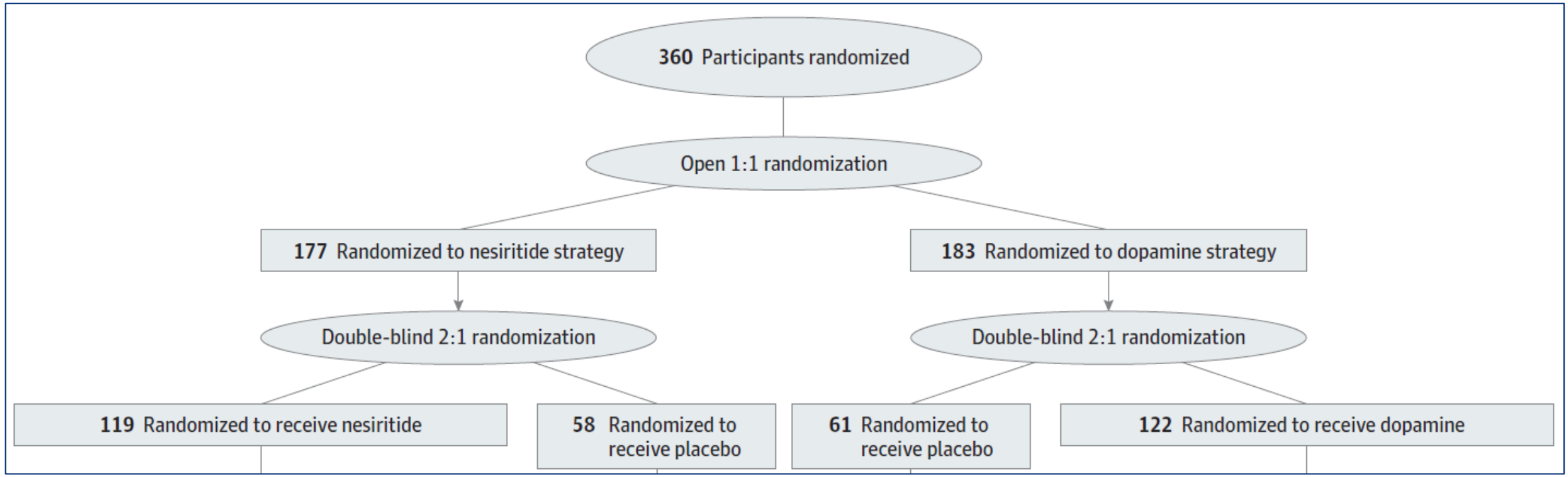
ROSE study

- Patients hospitalized for **acute heart failure who had renal dysfunction** (glomerular filtration rate of 15-60 mL/min/1.73 m2) at admission were enrolled within 24 hours of admission
- **All** patients received open-label, **intravenous loop diuretic** treatment with a recommended total daily dose equal to 2.5 times the total daily oral outpatient

JAMA. 2013;310(23):2533-2543.

ROSE study

- Patients hospitalized for acute heart failure who had renal dysfunction (glomerular filtration rate of 15-60 mL/min/1.73 m2) at admission were enrolled within 24 hours of admission
- All patients received open-label, intravenous loop diuretic treatment with a recommended total daily dose equal to 2.5 times the total daily oral outpatient

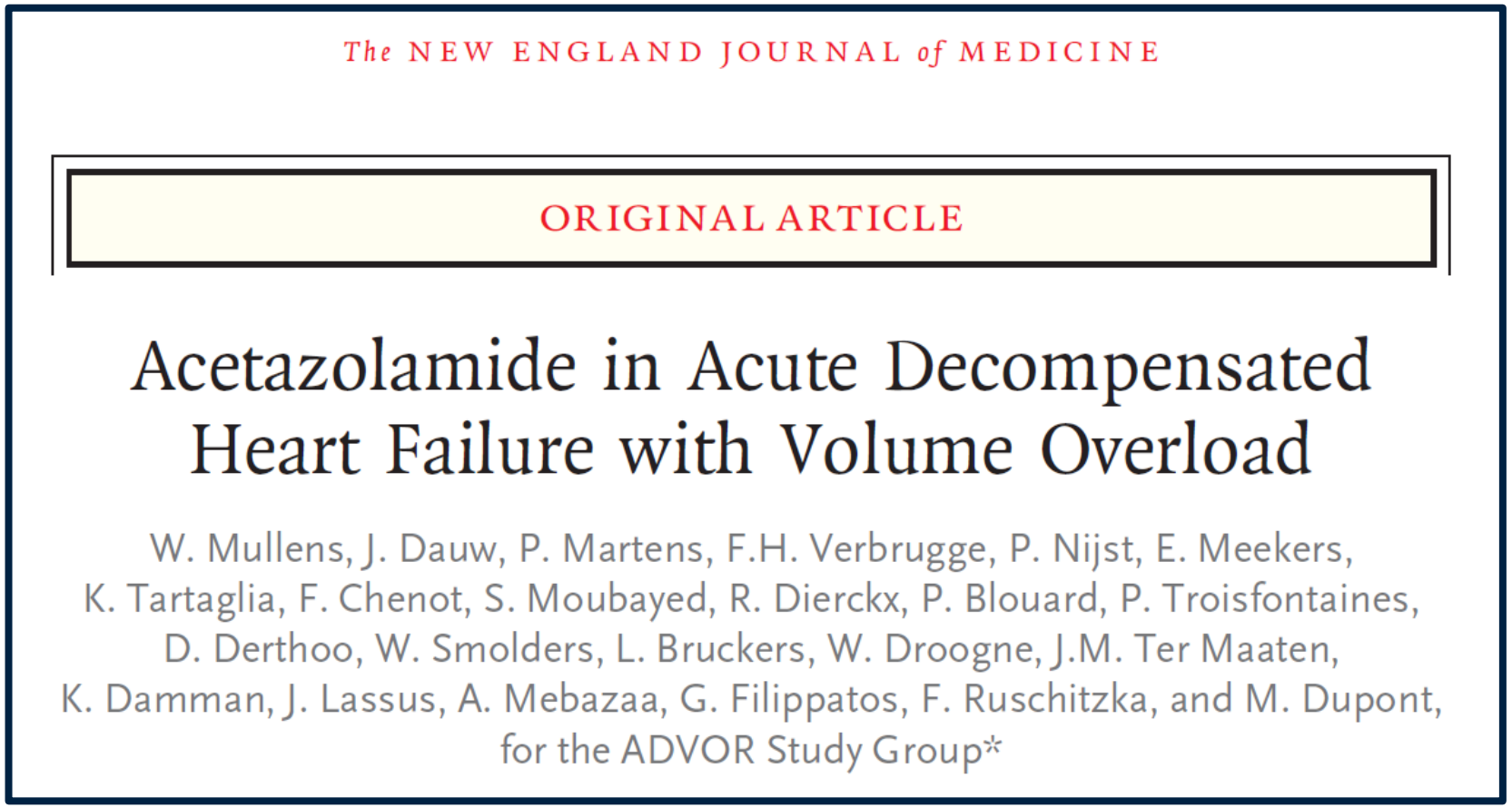


JAMA. 2013;310(23):2533-2543.

ROSE study – Primary End Point

	Mean (95% CI)			
	Placebo	Drug	Treatment Difference	*P* Value
Dopamine strategy	Placebo (n = 119)	Dopamine (n = 122)		
Cumulative urine volume from randomization to 72 h, mL	8296 (7762 to 8830)	8524 (7917 to 9131)	229 (−714 to 1171)	.59
Change in cystatin C level from randomization to 72 h, mg/L	0.11 (0.06 to 0.16)	0.12 (0.06 to 0.18)	0.01 (−0.08 to 0.10)	.72
Nesiritide strategy	Placebo (n = 119)	Nesiritide (n = 119)		
Cumulative urine volume from randomization to 72 h, mL	8296 (7762 to 8830)	8574 (8014 to 9134)	279 (−618 to 1176)	.49
Change in cystatin C level from randomization to 72 h, mg/L	0.11 (0.06 to 0.16)	0.07 (0.01 to 0.13)	−0.04 (−0.13 to 0.05)	.36

Compared with placebo, neither low-dose dopamine nor low-dose nesiritide enhanced decongestion or favorably affected renal function



- **Acetazolamide** is a carbonic anhydrase inhibitor that **reduces proximal tubular sodium reabsorption** and may improve diuretic efficiency when added to loop diuretics

- **Study question** - Whether the addition of acetazolamide to standardized intravenous loop-diuretic therapy would improve the incidence of successful decongestion among patients with acute decompensated heart failure

N Engl J Med. 2022 Aug 27

ADVOR trial

- Multicenter, randomized, parallel-group, double-blind, placebo-controlled, **investigator-initiated**, academic, clinical trial **without industry involvement**

- **Inclusion criteria:**
  - **Patients hospitalized with acute decompensated heart failure**
    - Clinical signs of volume overload (edema, pleural effusion, ascites)
    - NT-proBNP >1000 pg/mL or BNP >250 pg/Ml
    - Oral maintenance therapy with 40 mg of furosemide, 20 mg of torsemide, 1 mg of bumetanide or more for ≥1 month prior to randomization

- **Exclusion criteria:**
  - Receipt of acetazolamide maintenance therapy
  - **Treatment with SGLT2i**
  - Systolic blood pressure <90 mm Hg
  - Estimated glomerular filtration rate <20 mL/min/1.73 m^2
  - Treatment with dose >80 mg IV furosemide equivalent during index hospitalization

N Engl J Med. 2022 Aug 27

ADVOR trial

- **Primary end point**
  - **Successful decongestion** - Defined as the **absence of signs of volume overload** (i.e., no more than trace edema, no residual pleural effusion, and no residual ascites) **within 3 days** after randomization without an indication for escalation of decongestive therapy

N Engl J Med. 2022 Aug 27

ADVOR trial – Results

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N = 260)	Acetazolamide (N = 259)	Total (N = 519)
Age — yr	78.5±8.8	77.9 ±9.0	78.2±8.9

N Engl J Med. 2022 Aug 27

ADVOR trial – Results

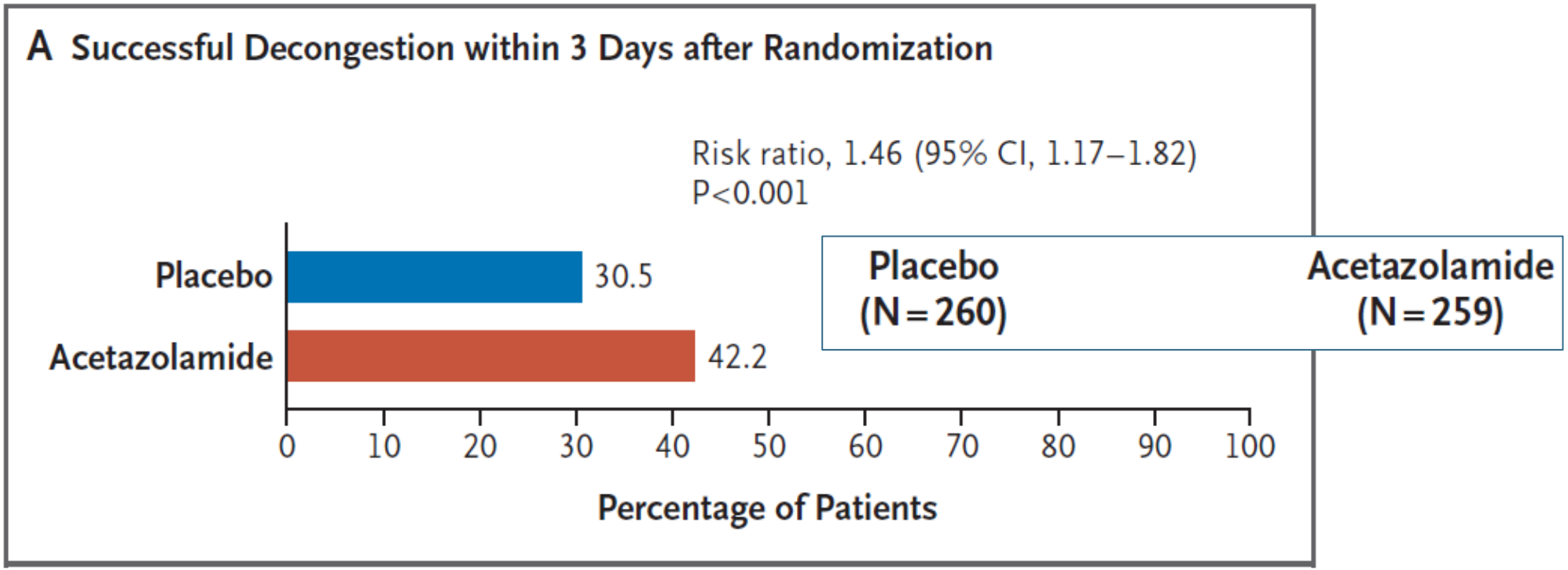
Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=260)	Acetazolamide (N=259)	Total (N=519)
Age — yr	78.5±8.8	77.9 ±9.0	78.2±8.9
Left ventricular ejection fraction			
Mean — %	43±15	43±15	43±15
≤40% — no. (%)	111 (42.7)	113 (43.6)	224 (43.2)

N Engl J Med. 2022 Aug 27

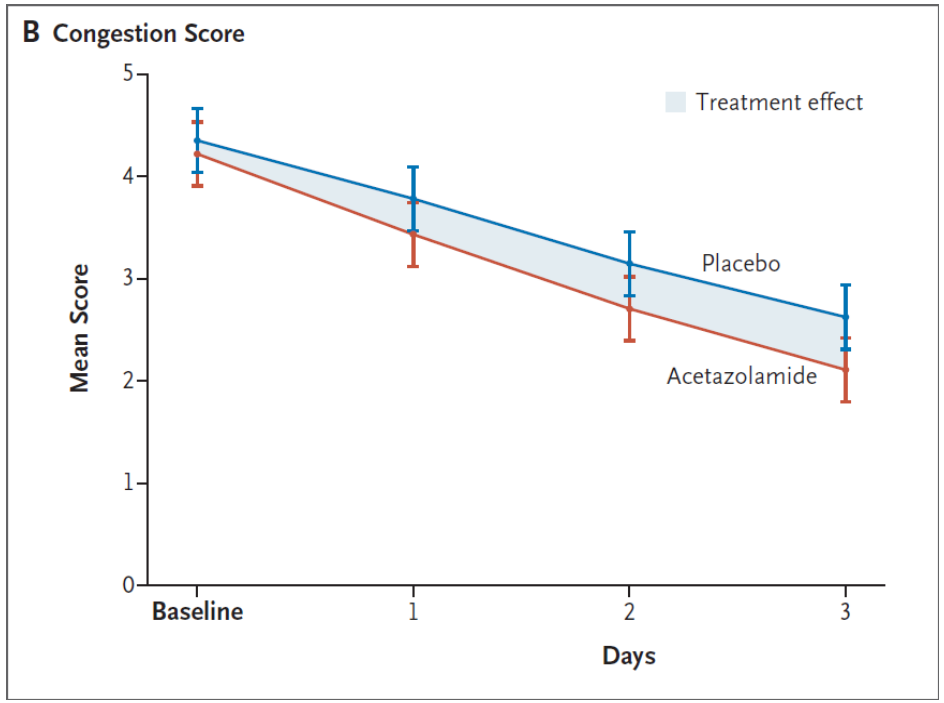
ADVOR trial

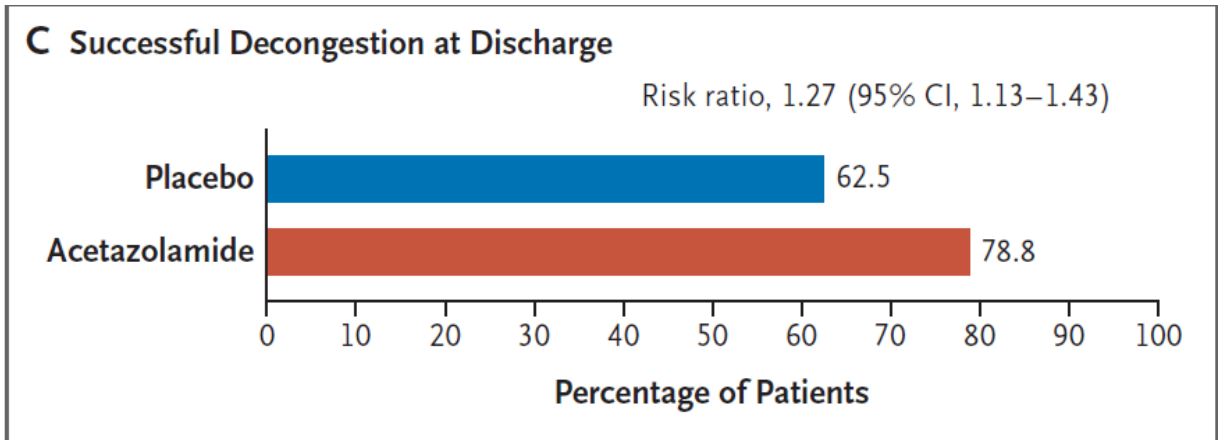
- **Primary end point**
  - **Successful decongestion** - Defined as the absence of signs of volume overload (i.e., no more than trace edema, no residual pleural effusion, and no residual ascites) within 3 days after randomization without an indication for escalation of decongestive therapy



N Engl J Med. 2022 Aug 27

ADVOR trial



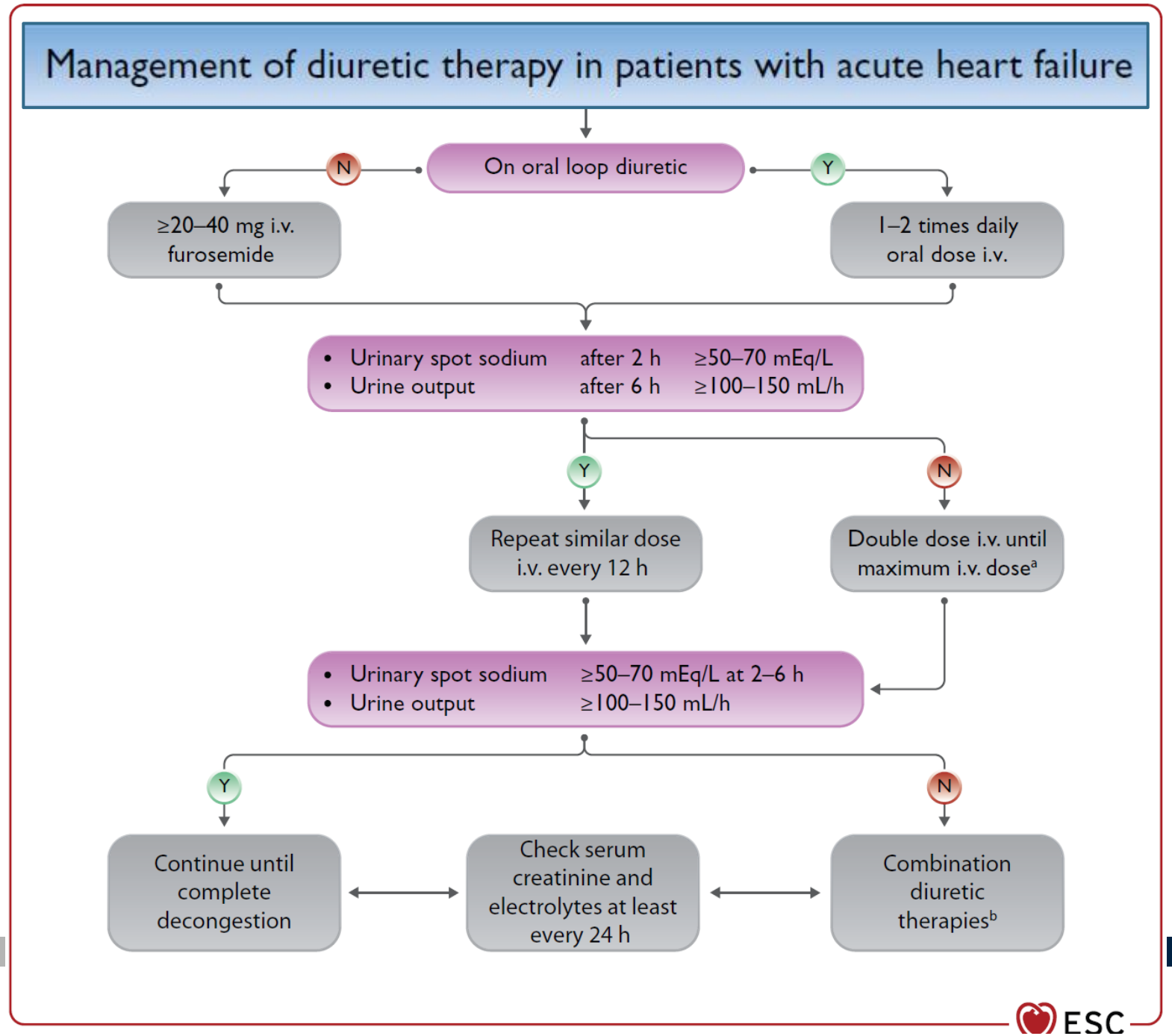


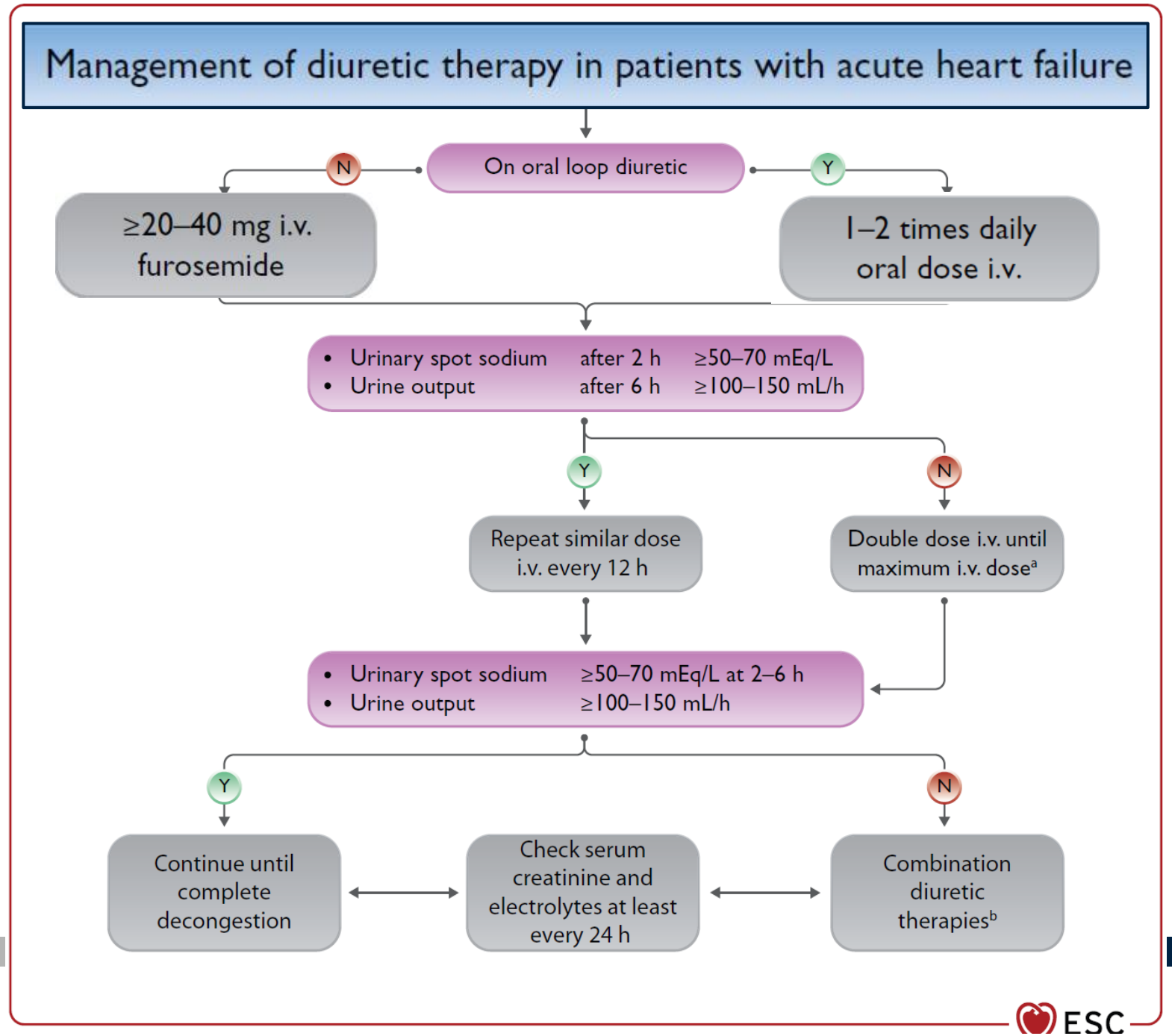
N Engl J Med. 2022 Aug 27

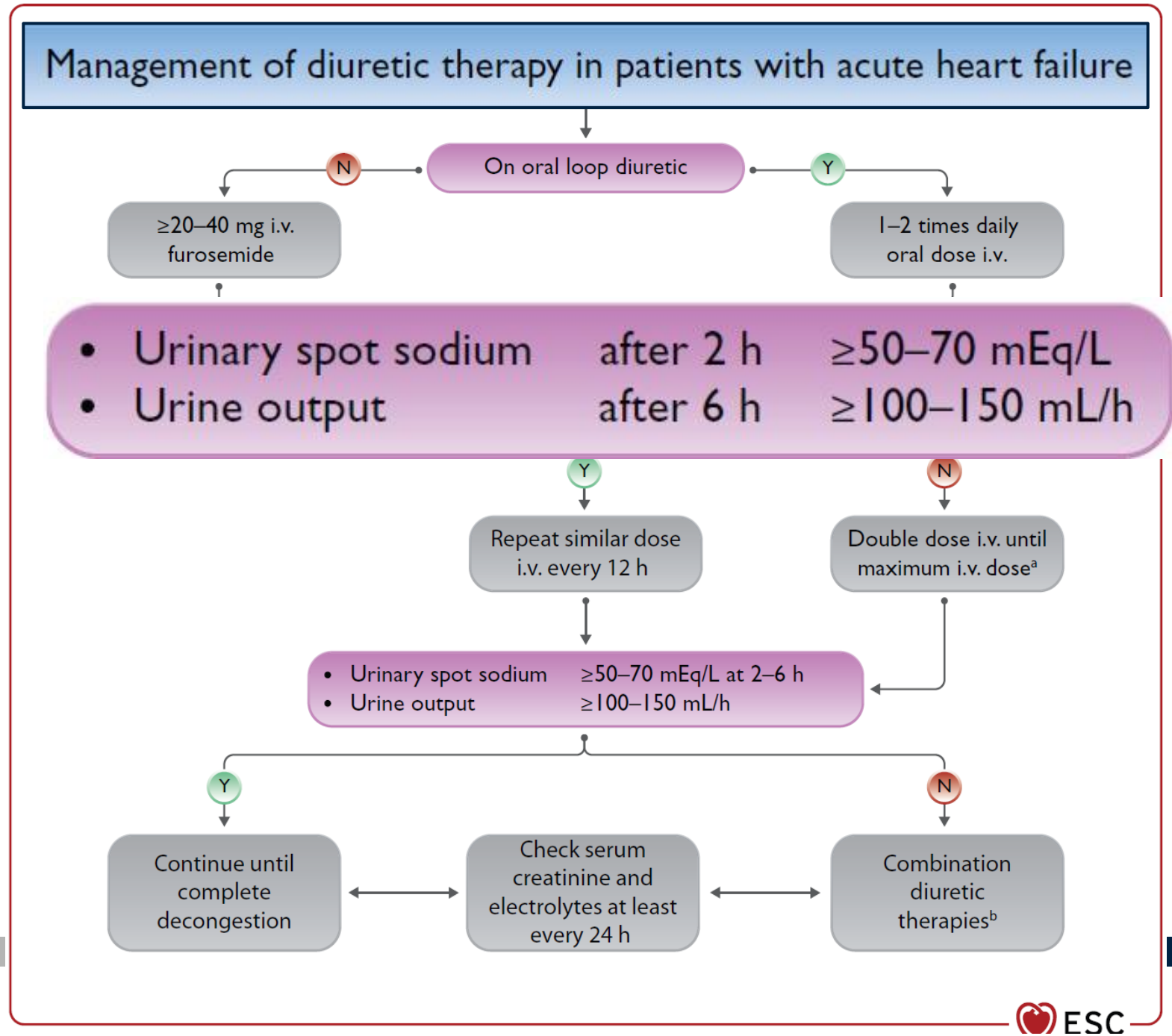
ADVOR trial

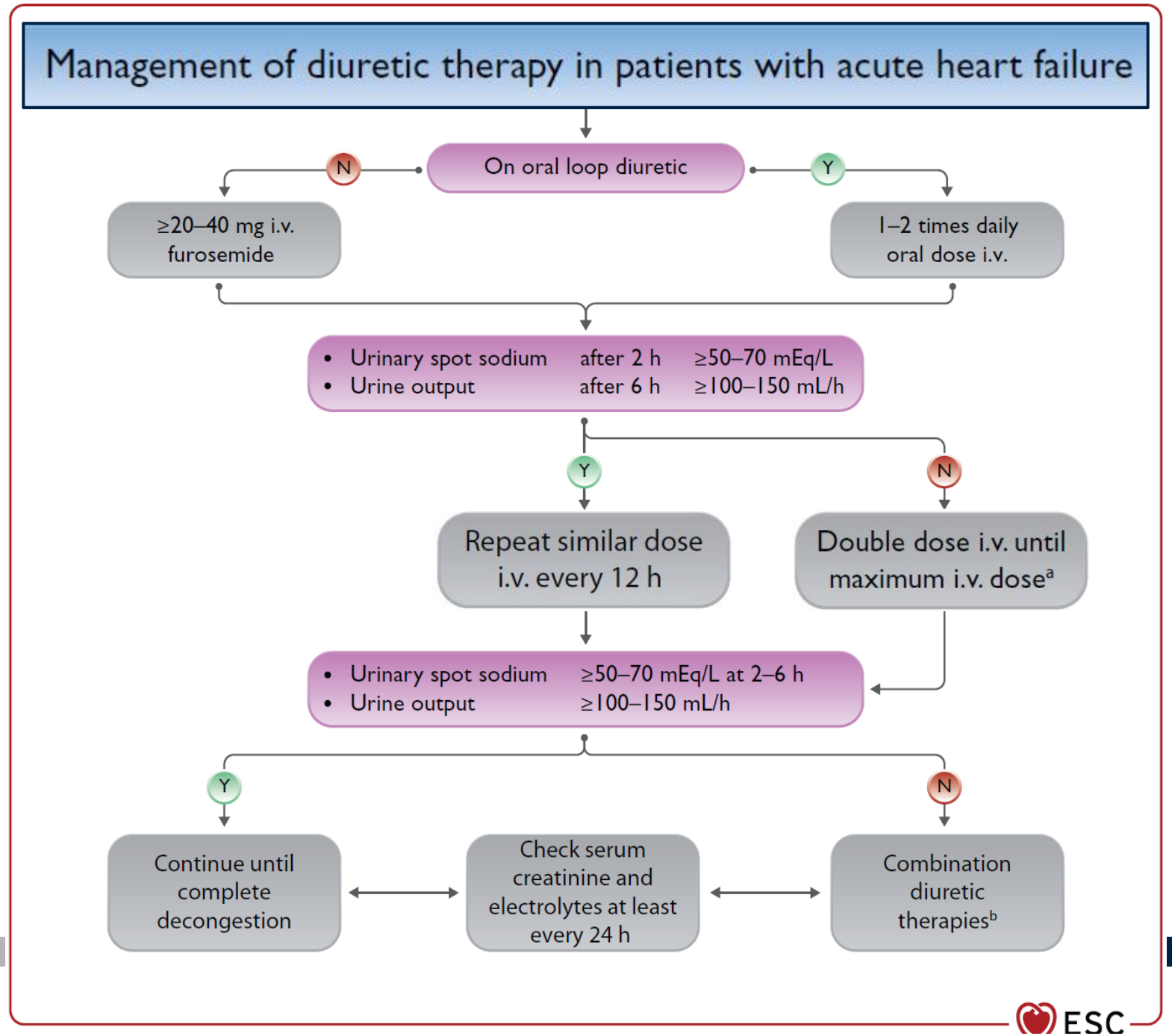
- In patients with acute decompensated heart failure and volume overload, t**he addition of acetazolamide to standardized intravenous loop-diuretic** therapy was **associated** with a higher incidence of **successful decongestion** within 3 days after randomization
- In addition:
  - **Shorter hospital stay**
  - More likely to be discharged without residual signs of volume overload
- **No difference in the risk of death** from any cause **or rehospitalization** for heart failure between the two trial groups
- The addition of acetazolamide to loop-diuretic therapy was not associated with an increased incidence of **adverse events**
- Patients who were receiving a higher maintenance dose of loop diuretics appeared to have less benefit than those who were receiving a lower maintenance dose

N Engl J Med. 2022 Aug 27


Management of diuretic therapy in patients with acute heart failure
On oral loop diuretic
N
Y
≥20–40 mg i.v. furosemide
1–2 times daily oral dose i.v.
• Urinary spot sodium after 2 h ≥50–70 mEq/L
• Urine output after 6 h ≥100–150 mL/h
Y
N
Repeat similar dose i.v. every 12 h
Double dose i.v. until maximum i.v. dose[a]
• Urinary spot sodium ≥50–70 mEq/L at 2–6 h
• Urine output ≥100–150 mL/h
Y
N
Continue until complete decongestion
Check serum creatinine and electrolytes at least every 24 h
Combination diuretic therapies[b]


Management of diuretic therapy in patients with acute heart failure
On oral loop diuretic
N
Y
≥20–40 mg i.v. furosemide
1–2 times daily oral dose i.v.
• Urinary spot sodium after 2 h ≥50–70 mEq/L
• Urine output after 6 h ≥100–150 mL/h
Y
N
Repeat similar dose i.v. every 12 h
Double dose i.v. until maximum i.v. dose[a]
• Urinary spot sodium ≥50–70 mEq/L at 2–6 h
• Urine output ≥100–150 mL/h
Y
N
Continue until complete decongestion
Check serum creatinine and electrolytes at least every 24 h
Combination diuretic therapies[b]


Management of diuretic therapy in patients with acute heart failure
On oral loop diuretic
N
Y
≥20–40 mg i.v. furosemide
1–2 times daily oral dose i.v.
• Urinary spot sodium after 2 h ≥50–70 mEq/L
• Urine output after 6 h ≥100–150 mL/h
Y
N
Repeat similar dose i.v. every 12 h
Double dose i.v. until maximum i.v. dose[a]
• Urinary spot sodium ≥50–70 mEq/L at 2–6 h
• Urine output ≥100–150 mL/h
Y
N
Continue until complete decongestion
Check serum creatinine and electrolytes at least every 24 h
Combination diuretic therapies[b]


Management of diuretic therapy in patients with acute heart failure
On oral loop diuretic
N
Y
≥20–40 mg i.v. furosemide
1–2 times daily oral dose i.v.
• Urinary spot sodium after 2 h ≥50–70 mEq/L
• Urine output after 6 h ≥100–150 mL/h
Y
N
Repeat similar dose i.v. every 12 h
Double dose i.v. until maximum i.v. dose[a]
• Urinary spot sodium ≥50–70 mEq/L at 2–6 h
• Urine output ≥100–150 mL/h
Y
N
Continue until complete decongestion
Check serum creatinine and electrolytes at least every 24 h
Combination diuretic therapies[b]

Vasodilators

Nitrates

- IV **nitroglycerin or nitroprusside** can be used in acute HF to acutely relieve symptoms of pulmonary congestion
- Overall, there are **NO data** that suggest that intravenous nitrates **improve outcomes** in the patient hospitalized with HF
- Tachyphylaxis may develop within 24 hours
- Up to 20% of those with HF may develop resistance to even high doses
- **Sodium nitroprusside**:
  - Potentially of value in **severely congested patients with elevated SVR or severe MV regurgitation** complicating LV dysfunction
  - May cause **hypotension** -> **arterial line** is typically required
  - Longer infusions of the drug have been associated with **thiocyanate** and **cyanide toxicity**, particularly in the setting of renal insufficiency and significant hepatic disease

Circulation. 2022;145:e895–e1032

ORIGINAL ARTICLE

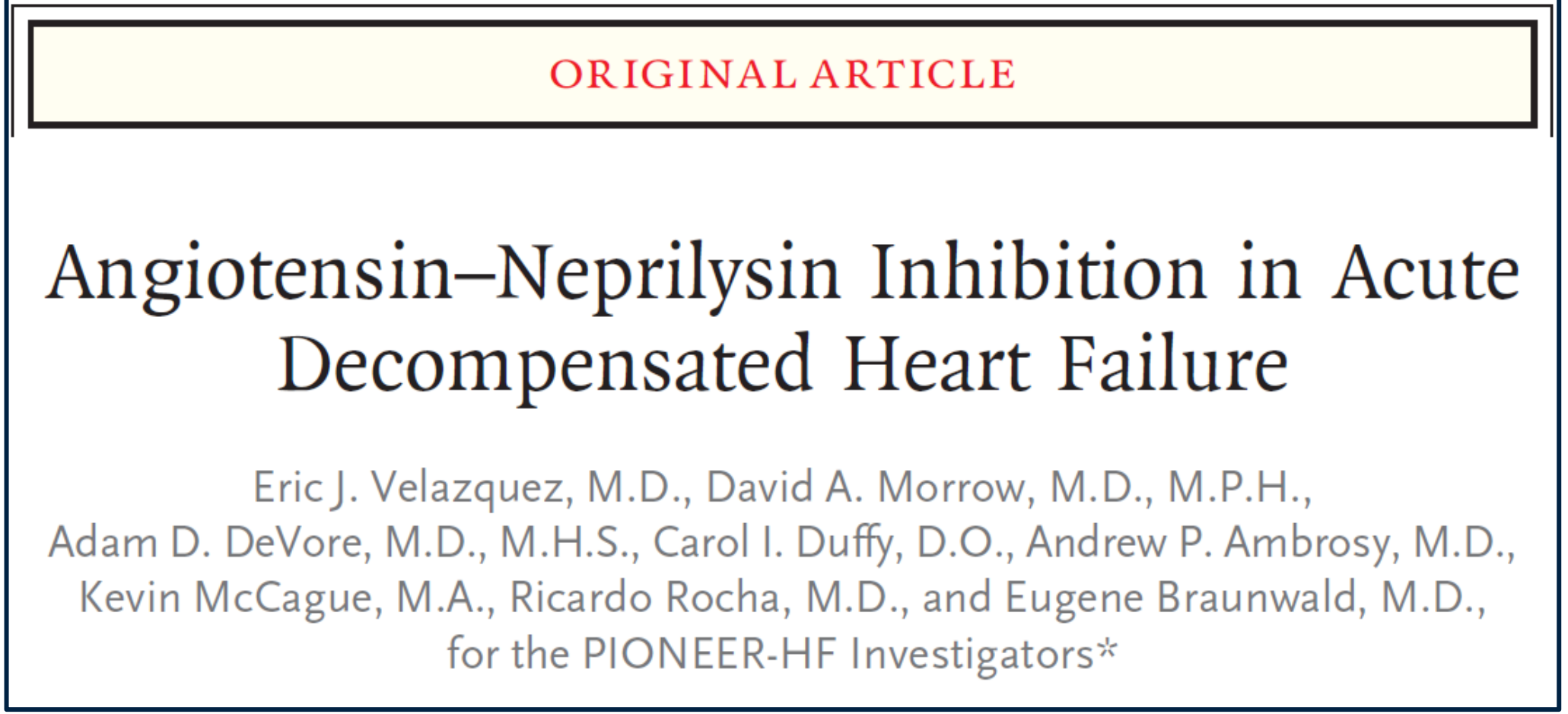
Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure

Eric J. Velazquez, M.D., David A. Morrow, M.D., M.P.H., Adam D. DeVore, M.D., M.H.S., Carol I. Duffy, D.O., Andrew P. Ambrosy, M.D., Kevin McCague, M.A., Ricardo Rocha, M.D., and Eugene Braunwald, M.D., for the PIONEER-HF Investigators*

Inclusion criteria

- Admitted with primary diagnosis of acute decompensated heart failure
- LVEF ≤ 40%
- NT-proBNP >1600 pg/ml or BNP > 400 pg/ml

N Engl J med 380;6


ORIGINAL ARTICLE

Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure

Eric J. Velazquez, M.D., David A. Morrow, M.D., M.P.H., Adam D. DeVore, M.D., M.H.S., Carol I. Duffy, D.O., Andrew P. Ambrosy, M.D., Kevin McCague, M.A., Ricardo Rocha, M.D., and Eugene Braunwald, M.D., for the PIONEER-HF Investigators*

- Patients were enrolled no less than 24 hours and up to 10 days after initial presentation to the hospital, **while they were still hospitalized**
- **Before randomization, patients were required to be hemodynamically stable**

N Engl J med 380;6

ORIGINAL ARTICLE

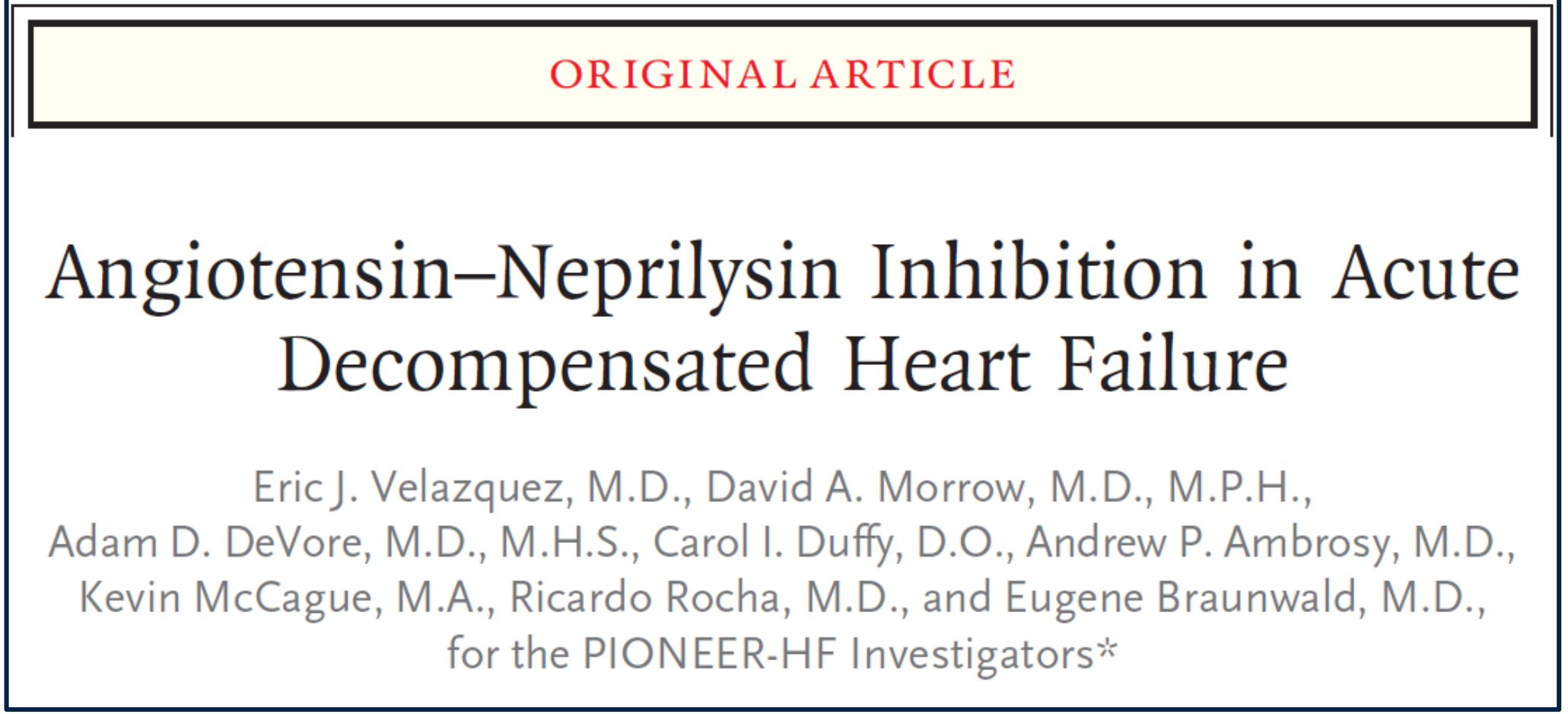
Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure

Eric J. Velazquez, M.D., David A. Morrow, M.D., M.P.H., Adam D. DeVore, M.D., M.H.S., Carol I. Duffy, D.O., Andrew P. Ambrosy, M.D., Kevin McCague, M.A., Ricardo Rocha, M.D., and Eugene Braunwald, M.D., for the PIONEER-HF Investigators*

- Patients were enrolled no less than 24 hours and up to 10 days after initial presentation to the hospital, while they were still hospitalized
- Before randomization, patients were required to be hemodynamically stable

Randomized: sacubitril–valsartan or enalapril

N Engl J med 380;6


ORIGINAL ARTICLE

Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure

Eric J. Velazquez, M.D., David A. Morrow, M.D., M.P.H., Adam D. DeVore, M.D., M.H.S., Carol I. Duffy, D.O., Andrew P. Ambrosy, M.D., Kevin McCague, M.A., Ricardo Rocha, M.D., and Eugene Braunwald, M.D., for the PIONEER-HF Investigators*

- The **primary efficacy outcome** was the time-averaged proportional **change in the NT-proBNP concentration** from baseline through weeks 4 and 8

N Engl J med 380;6

PIONEER-HF

Variable	Sacubitril–Valsartan (N=440)	Enalapril (N=441)
Age — yr		
Median	61	63
Interquartile range	51–71	54–72
Female sex — no. (%)	113 (25.7)	133 (30.2)
Race — no. (%)†		
Black	158 (35.9)	158 (35.8)
White	261 (59.3)	254 (57.6)
Body-mass index‡		
Median	30.5	30.0
Interquartile range	25.9–37.1	25.8–36.3
Previous heart failure — no. (%)	298 (67.7)	278 (63.0)
Previous use of medication — no. (%)		
ACE inhibitor or ARB	208 (47.3)	214 (48.5)
Beta-blocker	262 (59.5)	263 (59.6)
MRA	48 (10.9)	40 (9.1)
Loop diuretic	262 (59.5)	240 (54.4)
Hydralazine	30 (6.8)	33 (7.5)
Nitrate	43 (9.8)	40 (9.1)
Digoxin	41 (9.3)	35 (7.9)

N Engl J med 380;6

PIONEER-HF

Variable	Sacubitril–Valsartan (N=440)	Enalapril (N=441)
Age — yr		
Median	61	63
Interquartile range	51–71	54–72
Female sex — no. (%)	113 (25.7)	133 (30.2)
Race — no. (%)†		
Black	158 (35.9)	158 (35.8)
White	261 (59.3)	254 (57.6)
Body-mass index‡		
Median	30.5	30.0
Interquartile range	25.9–37.1	25.8–36.3
Previous heart failure — no. (%)	298 (67.7)	278 (63.0)
Previous use of medication — no. (%)		
ACE inhibitor or ARB	208 (47.3)	214 (48.5)
Beta-blocker	262 (59.5)	263 (59.6)
MRA	48 (10.9)	40 (9.1)
Loop diuretic	262 (59.5)	240 (54.4)
Hydralazine	30 (6.8)	33 (7.5)
Nitrate	43 (9.8)	40 (9.1)
Digoxin	41 (9.3)	35 (7.9)

N Engl J med 380;6

PIONEER-HF

Variable	Sacubitril–Valsartan (N=440)	Enalapril (N=441)
Age — yr		
Median	61	63
Female sex — no. (%)	113 (25.7)	133 (30.2)
Race — no. (%)†		
Black	158 (35.9)	158 (35.8)
White	261 (59.3)	254 (57.6)
Body-mass index‡		
Median	30.5	30.0
Interquartile range	25.9–37.1	25.8–36.3
Previous heart failure — no. (%)	298 (67.7)	278 (63.0)
Previous use of medication — no. (%)		
ACE inhibitor or ARB	208 (47.3)	214 (48.5)
Beta-blocker	262 (59.5)	263 (59.6)
MRA	48 (10.9)	40 (9.1)
Loop diuretic	262 (59.5)	240 (54.4)
Hydralazine	30 (6.8)	33 (7.5)
Nitrate	43 (9.8)	40 (9.1)
Digoxin	41 (9.3)	35 (7.9)

N Engl J med 380;6

PIONEER-HF

Variable	Sacubitril–Valsartan (N=440)	Enalapril (N=441)
Age — yr		
Median	61	63
Interquartile range	51–71	54–72
Female sex — no. (%)	113 (25.7)	133 (30.2)
Race — no. (%)†		
Black	158 (35.9)	158 (35.8)
White	261 (59.3)	254 (57.6)
Body-mass index‡		
Median	30.5	30.0
Previous heart failure — no. (%)	298 (67.7)	278 (63.0)
Previous use of medication — no. (%)		
ACE inhibitor or ARB	208 (47.3)	214 (48.5)
Beta-blocker	262 (59.5)	263 (59.6)
MRA	48 (10.9)	40 (9.1)
Loop diuretic	262 (59.5)	240 (54.4)
Hydralazine	30 (6.8)	33 (7.5)
Nitrate	43 (9.8)	40 (9.1)
Digoxin	41 (9.3)	35 (7.9)

N Engl J med 380;6

PIONEER-HF

Variable	Sacubitril–Valsartan (N=440)	Enalapril (N=441)
Age — yr		
Median	61	63
Interquartile range	51–71	54–72
Female sex — no. (%)	113 (25.7)	133 (30.2)
Race — no. (%)†		
Black	158 (35.9)	158 (35.8)
White	261 (59.3)	254 (57.6)
Body-mass index‡		
Median	30.5	30.0
Interquartile range	25.9–37.1	25.8–36.3
Previous heart failure — no. (%)	298 (67.7)	278 (63.0)
Previous use of medication — no. (%)		
ACE inhibitor or ARB	208 (47.3)	214 (48.5)
NT-proBNP at screening — pg/ml¶		
Median	4821	4710
Hydralazine	30 (6.8)	33 (7.5)
Nitrate	43 (9.8)	40 (9.1)
Digoxin	41 (9.3)	35 (7.9)

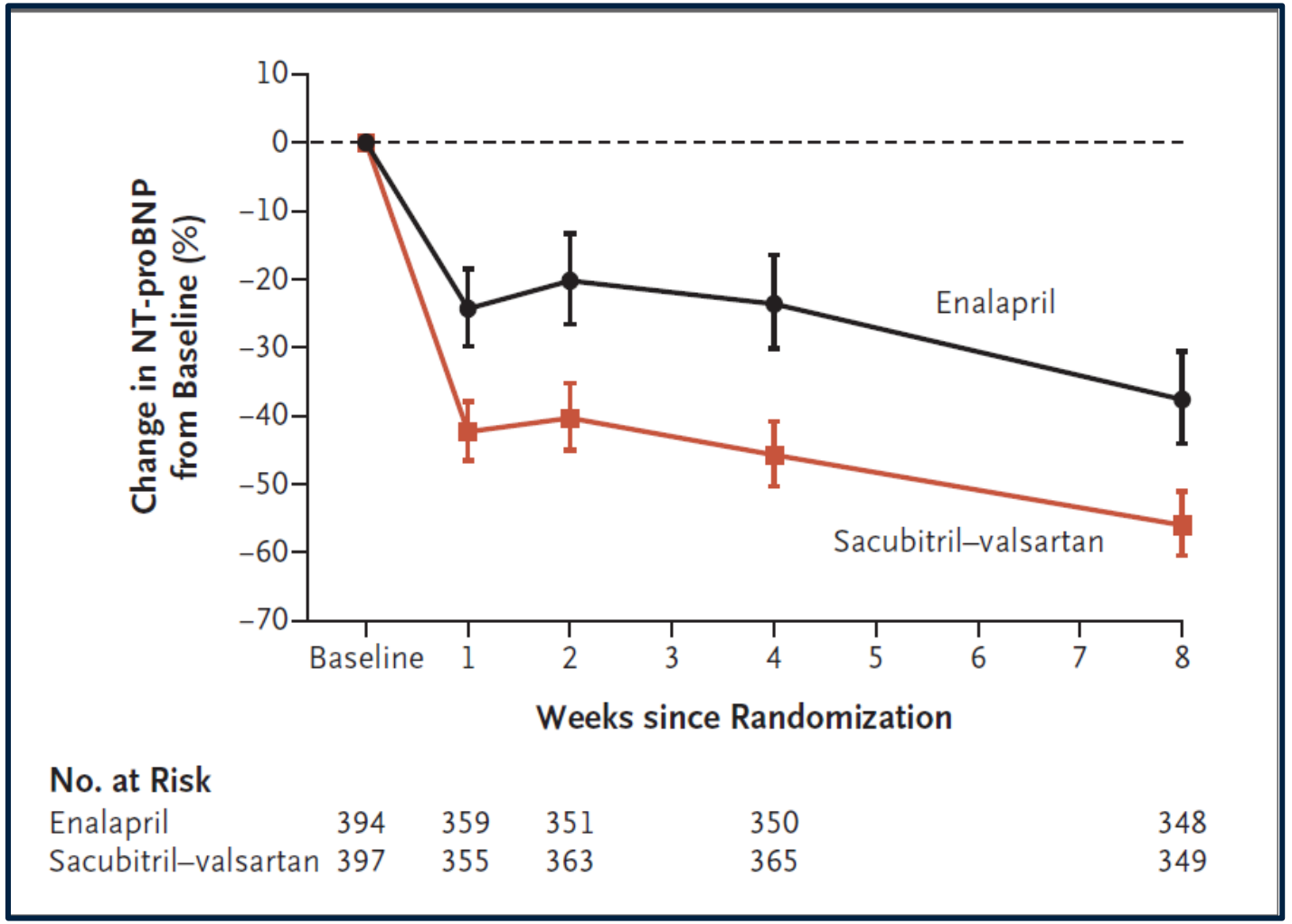
N Engl J med 380;6

PIONEER-HF

Variable	Sacubitril–Valsartan (N=440)	Enalapril (N=441)
Age — yr		
Median	61	63
Interquartile range	51–71	54–72
Female sex — no. (%)	113 (25.7)	133 (30.2)
Race — no. (%)†		
Black	158 (35.9)	158 (35.8)
White	261 (59.3)	254 (57.6)
Body-mass index‡		
Median	30.5	30.0
Interquartile range	25.9–37.1	25.8–36.3
Previous heart failure — no. (%)	298 (67.7)	278 (63.0)
Previous use of medication — no. (%)		
ACE inhibitor or ARB	208 (47.3)	214 (48.5)
Beta-blocker	262 (59.5)	263 (59.6)
MRA	48 (10.9)	40 (9.1)
Left ventricular ejection fraction — %¶		
Median	24	25
Nitrate	43 (9.8)	40 (9.1)
Digoxin	41 (9.3)	35 (7.9)

N Engl J med 380;6

PIONEER-HF



N Engl J med 380;6

Secondary Efficacy and Safety Endpoints

Outcome	Sacubitril–Valsartan (N=440)	Enalapril (N=441)	Sacubitril–Valsartan vs. Enalapril
Key safety outcomes — no. (%)			**Relative risk (95% CI)**
Worsening renal function†	60 (13.6)	65 (14.7)	0.93 (0.67 to 1.28)
Hyperkalemia	51 (11.6)	41 (9.3)	1.25 (0.84 to 1.84)
Symptomatic hypotension	66 (15.0)	56 (12.7)	1.18 (0.85 to 1.64)
Angioedema	1 (0.2)	6 (1.4)	0.17 (0.02 to 1.38)
Secondary biomarker outcomes — % (95% CI)‡			**Ratio of change (95% CI)**
Change in high-sensitivity troponin T concentration	−36.6 (−40.8 to −32.0)	−25.2 (−30.2 to −19.9)	0.85 (0.77 to 0.94)
Change in B-type natriuretic peptide concentration	−28.7 (−35.5 to −21.3)	−33.1 (−39.5 to −25.9)	1.07 (0.92 to 1.23)
Change in ratio of B-type natriuretic peptide to NT-proBNP	35.2 (28.8 to 42.0)	−8.3 (−3.6 to −12.7)	1.48 (1.38 to 1.58)
Exploratory clinical outcomes — no. (%)			**Hazard ratio (95% CI)§**
Composite of clinical events	249 (56.6)	264 (59.9)	0.93 (0.78 to 1.10)
Death	10 (2.3)	15 (3.4)	0.66 (0.30 to 1.48)
Rehospitalization for heart failure	35 (8.0)	61 (13.8)	0.56 (0.37 to 0.84)
Implantation of left ventricular assist device	1 (0.2)	1 (0.2)	0.99 (0.06 to 15.97)
Inclusion on list for heart transplantation	0	0	NA
Unplanned outpatient visit leading to use of intravenous diuretics	2 (0.5)	2 (0.5)	1.00 (0.14 to 7.07)
Use of additional drug for heart failure	78 (17.7)	84 (19.0)	0.92 (0.67 to 1.25)
Increase in dose of diuretics of >50%	218 (49.5)	222 (50.3)	0.98 (0.81 to 1.18)
Composite of serious clinical events¶	41 (9.3)	74 (16.8)	0.54 (0.37 to 0.79)

N Engl J med 380;6

Secondary Efficacy and Safety Endpoints

	Sacubitril–Valsartan	Enalapril	Sacubitril–Valsartan vs.
Key safety outcomes — no. (%)			**Relative risk (95% CI)**
Worsening renal function†	60 (13.6)	65 (14.7)	0.93 (0.67 to 1.28)
Hyperkalemia	51 (11.6)	41 (9.3)	1.25 (0.84 to 1.84)
Symptomatic hypotension	66 (15.0)	56 (12.7)	1.18 (0.85 to 1.64)
Angioedema	1 (0.2)	6 (1.4)	0.17 (0.02 to 1.38)
Secondary biomarker outcomes — % (95% CI)‡			**Ratio of change (95% CI)**
Change in high-sensitivity troponin T concentration	−36.6 (−40.8 to −32.0)	−25.2 (−30.2 to −19.9)	0.85 (0.77 to 0.94)
Change in B-type natriuretic peptide concentration	−28.7 (−35.5 to −21.3)	−33.1 (−39.5 to −25.9)	1.07 (0.92 to 1.23)
Change in ratio of B-type natriuretic peptide to NT-proBNP	35.2 (28.8 to 42.0)	−8.3 (−3.6 to −12.7)	1.48 (1.38 to 1.58)
Exploratory clinical outcomes — no. (%)			**Hazard ratio (95% CI)§**
Composite of clinical events	249 (56.6)	264 (59.9)	0.93 (0.78 to 1.10)
Death	10 (2.3)	15 (3.4)	0.66 (0.30 to 1.48)
Rehospitalization for heart failure	35 (8.0)	61 (13.8)	0.56 (0.37 to 0.84)
Implantation of left ventricular assist device	1 (0.2)	1 (0.2)	0.99 (0.06 to 15.97)
Inclusion on list for heart transplantation	0	0	NA
Unplanned outpatient visit leading to use of intravenous diuretics	2 (0.5)	2 (0.5)	1.00 (0.14 to 7.07)
Use of additional drug for heart failure	78 (17.7)	84 (19.0)	0.92 (0.67 to 1.25)
Increase in dose of diuretics of >50%	218 (49.5)	222 (50.3)	0.98 (0.81 to 1.18)
Composite of serious clinical events¶	41 (9.3)	74 (16.8)	0.54 (0.37 to 0.79)

N Engl J med 380;6

Secondary Efficacy and Safety Endpoints

Outcome	Sacubitril–Valsartan (N=440)	Enalapril (N=441)	Sacubitril–Valsartan vs. Enalapril
Key safety outcomes — no. (%)			**Relative risk (95% CI)**
Worsening renal function†	60 (13.6)	65 (14.7)	0.93 (0.67 to 1.28)
Hyperkalemia	51 (11.6)	41 (9.3)	1.25 (0.84 to 1.84)
Symptomatic hypotension	66 (15.0)	56 (12.7)	1.18 (0.85 to 1.64)
Angioedema	1 (0.2)	6 (1.4)	0.17 (0.02 to 1.38)
Secondary biomarker outcomes — % (95% CI)‡			**Ratio of change (95% CI)**
Change in high-sensitivity troponin T concentration	−36.6 (−40.8 to −32.0)	−25.2 (−30.2 to −19.9)	0.85 (0.77 to 0.94)
Death	10 (2.3)	15 (3.4)	0.66 (0.30 to 1.48)
Change in ratio of B-type natriuretic peptide to NT-proBNP	35.2 (28.8 to 42.0)	−8.3 (−3.6 to −12.7)	1.48 (1.38 to 1.58)
Exploratory clinical outcomes — no. (%)			**Hazard ratio (95% CI)§**
Composite of clinical events	249 (56.6)	264 (59.9)	0.93 (0.78 to 1.10)
Death	10 (2.3)	15 (3.4)	0.66 (0.30 to 1.48)
Rehospitalization for heart failure	35 (8.0)	61 (13.8)	0.56 (0.37 to 0.84)
Implantation of left ventricular assist device	1 (0.2)	1 (0.2)	0.99 (0.06 to 15.97)
Inclusion on list for heart transplantation	0	0	NA
Unplanned outpatient visit leading to use of intravenous diuretics	2 (0.5)	2 (0.5)	1.00 (0.14 to 7.07)
Use of additional drug for heart failure	78 (17.7)	84 (19.0)	0.92 (0.67 to 1.25)
Increase in dose of diuretics of >50%	218 (49.5)	222 (50.3)	0.98 (0.81 to 1.18)
Composite of serious clinical events¶	41 (9.3)	74 (16.8)	0.54 (0.37 to 0.79)

N Engl J med 380;6

Secondary Efficacy and Safety Endpoints

Outcome	Sacubitril–Valsartan (N=440)	Enalapril (N=441)	Sacubitril–Valsartan vs. Enalapril
Key safety outcomes — no. (%)			**Relative risk (95% CI)**
Worsening renal function†	60 (13.6)	65 (14.7)	0.93 (0.67 to 1.28)
Hyperkalemia	51 (11.6)	41 (9.3)	1.25 (0.84 to 1.84)
Symptomatic hypotension	66 (15.0)	56 (12.7)	1.18 (0.85 to 1.64)
Angioedema	1 (0.2)	6 (1.4)	0.17 (0.02 to 1.38)
Secondary biomarker outcomes — % (95% CI)‡			**Ratio of change (95% CI)**
Change in high-sensitivity troponin T concentration	−36.6 (−40.8 to −32.0)	−25.2 (−30.2 to −19.9)	0.85 (0.77 to 0.94)
Change in B-type natriuretic peptide concentration	−28.7 (−35.5 to −21.3)	−33.1 (−39.5 to −25.9)	1.07 (0.92 to 1.23)
Change in ratio of B-type natriuretic peptide to NT-proBNP	35.2 (28.8 to 42.0)	−8.3 (−3.6 to −12.7)	1.48 (1.38 to 1.58)
Exploratory clinical outcomes — no. (%)			**Hazard ratio (95% CI)§**
Rehospitalization for heart failure	35 (8.0)	61 (13.8)	0.56 (0.37 to 0.84)
Rehospitalization for heart failure	35 (8.0)	61 (13.8)	0.56 (0.37 to 0.84)
Implantation of left ventricular assist device	1 (0.2)	1 (0.2)	0.99 (0.06 to 15.97)
Inclusion on list for heart transplantation	0	0	NA
Unplanned outpatient visit leading to use of intravenous diuretics	2 (0.5)	2 (0.5)	1.00 (0.14 to 7.07)
Use of additional drug for heart failure	78 (17.7)	84 (19.0)	0.92 (0.67 to 1.25)
Increase in dose of diuretics of >50%	218 (49.5)	222 (50.3)	0.98 (0.81 to 1.18)
Composite of serious clinical events¶	41 (9.3)	74 (16.8)	0.54 (0.37 to 0.79)

N Engl J med 380;6

PIONEER-HF

- The initiation of sacubitril– valsartan therapy after hemodynamic stabilization led to **a greater reduction in the NT-proBNP concentration** than enalapril therapy, a difference that was evident by the first week

- The rates of renal dysfunction, hyperkalemia, and symptomatic hypotension did not differ significantly between the sacubitril–valsartan group and the enalapril group

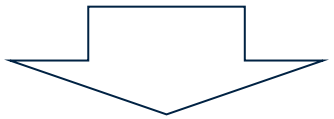
- In an analysis of exploratory clinical outcomes, the in-hospital initiation of sacubitril–valsartan therapy was associated with a **lower rate of rehospitalization for heart failure at 8 weeks** than enalapril therapy

N Engl J med 380;6

Vasopressors Vs. Inotropes

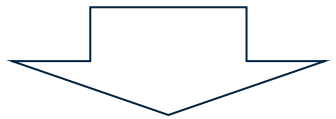
Vasopressors

- Increase **peripheral vasoconstriction** to increase mean arterial pressure



Increase cardiac afterload, wall stress, and myocardial oxygen consumption

- Impair microcirculation

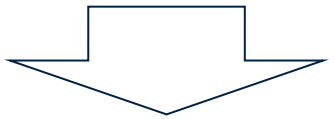


Worsen peripheral ischemia

Vasopressors Vs. Inotropes

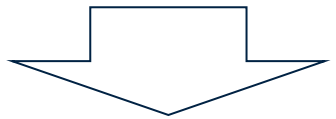
Vasopressors

- Increase peripheral vasoconstriction to increase mean arterial pressure



Increase cardiac afterload, wall stress, and **myocardial oxygen consumption**

- Impair microcirculation

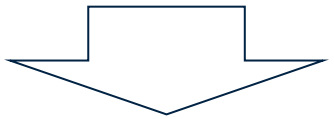


Worsen peripheral ischemia

Vasopressors Vs. Inotropes

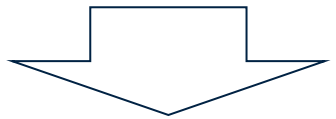
Vasopressors

- Increase peripheral vasoconstriction to increase mean arterial pressure



Increase cardiac afterload, wall stress, and myocardial oxygen consumption

- **Impair microcirculation**

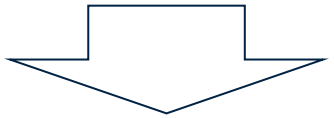


Worsen peripheral ischemia

Vasopressors Vs. Inotropes

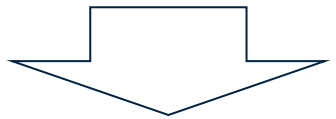
Vasopressors

- Increase peripheral vasoconstriction to increase mean arterial pressure



Increase cardiac afterload, wall stress, and myocardial oxygen consumption

- Impair microcirculation



Worsen peripheral ischemia

Inotropes

- Increase ventricular contractility and CO
- Reduce filling pressures
- Preserve end-organ perfusion

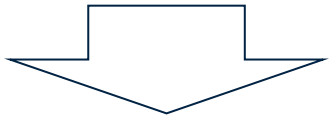
But……

- Increase myocardial oxygen demand → ischemic burden
- Malignant arrhythmias

Vasopressors Vs. Inotropes

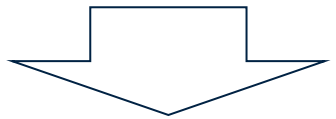
Vasopressors

- Increase peripheral vasoconstriction to increase mean arterial pressure



Increase cardiac afterload, wall stress, and myocardial oxygen consumption

- Impair microcirculation



Worsen peripheral ischemia

Inotropes

- Increase ventricular contractility and CO
- Reduce filling pressures
- Preserve end-organ perfusion

But……

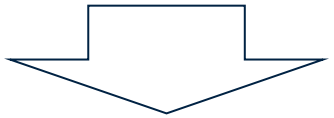
- Increase myocardial oxygen demand → ischemic burden
- Malignant arrhythmias

These agents should be used in the lowest possible doses for the shortest duration

Vasopressors Vs. Inotropes

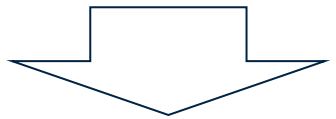
Vasopressors

- Increase peripheral vasoconstriction to increase mean arterial pressure



Increase cardiac afterload, wall stress, and myocardial oxygen consumption

- Impair microcirculation



Worsen peripheral ischemia

Inotropes

- Increase ventricular contractility and CO
- Reduce filling pressures
- Preserve end-organ perfusion

But……

- Increase myocardial oxygen demand → ischemic burden
- Malignant arrhythmias

Dobutamine
Milrinone
Levosimendan

These agents should be used in the lowest possible doses for the shortest duration

Dobutamine

- Synthetic catecholamine
- Racemic mixture of two stereoisomers
  - Levo isomer – beta adrenergic activity
  - Dextro isomer – alpha adrenergic activity
- **Decreases afterload while increasing inotropy**
- **Short-acting** – Plasma half life about 2 minutes
- **Side effects**
  - Arrhythmias
  - Ischemia/angina
  - Hypotension
  - Tachycardia – especially as dose increased
  - Nausea, headache, palpitations

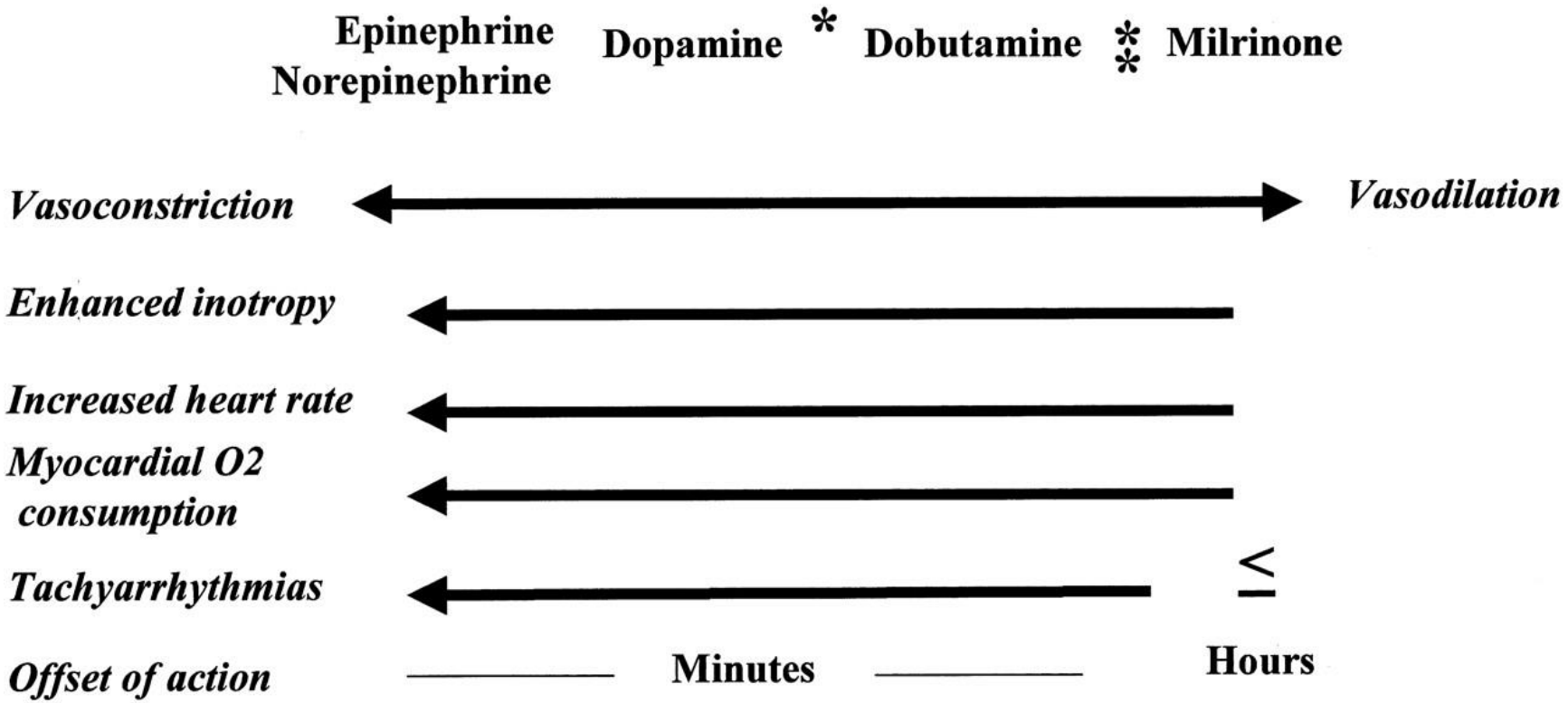
Phosphodiesterase Inhibitors

- **Milrinone** is a specific **phosphodiesterase III inhibitors**
- **Increase contractility** without an increase in heart rate especially at low dose
- Act **independently of beta receptors**
- **Potent vasodilator** including the venous capacitance vessels and pulmonary vascular bed
  - Significant hypotension can occur if filling pressures are not elevated due to the venodilator properties of PDE inhibitors dropping pre-load (**avoid use in "dehydrated" patients**)
- Long half life of 2.3 hours
- Milrinone is 80% **eliminated by the kidney**
  - Renal failure will effectively increase the dose of milrinone and increase risk of toxicity and side-effects
  - In renal failure decrease the infusion rate by about 50%

Levosimendan

- A cardiac myofilament **calcium sensitizer**
- Levosimendan **increases cardiac contractility** by increasing calcium sensitivity rather than by increasing intracellular ionic free calcium
- Physiologic effects:
  - Increases CO and SV
  - Decreases PCWP
  - Decreases mean PA pressures
  - Decreases SVR
- No evidence of the development of tolerance
- **Extended plasma half-life** → the hemodynamic effects persist for several days after termination of the infusion

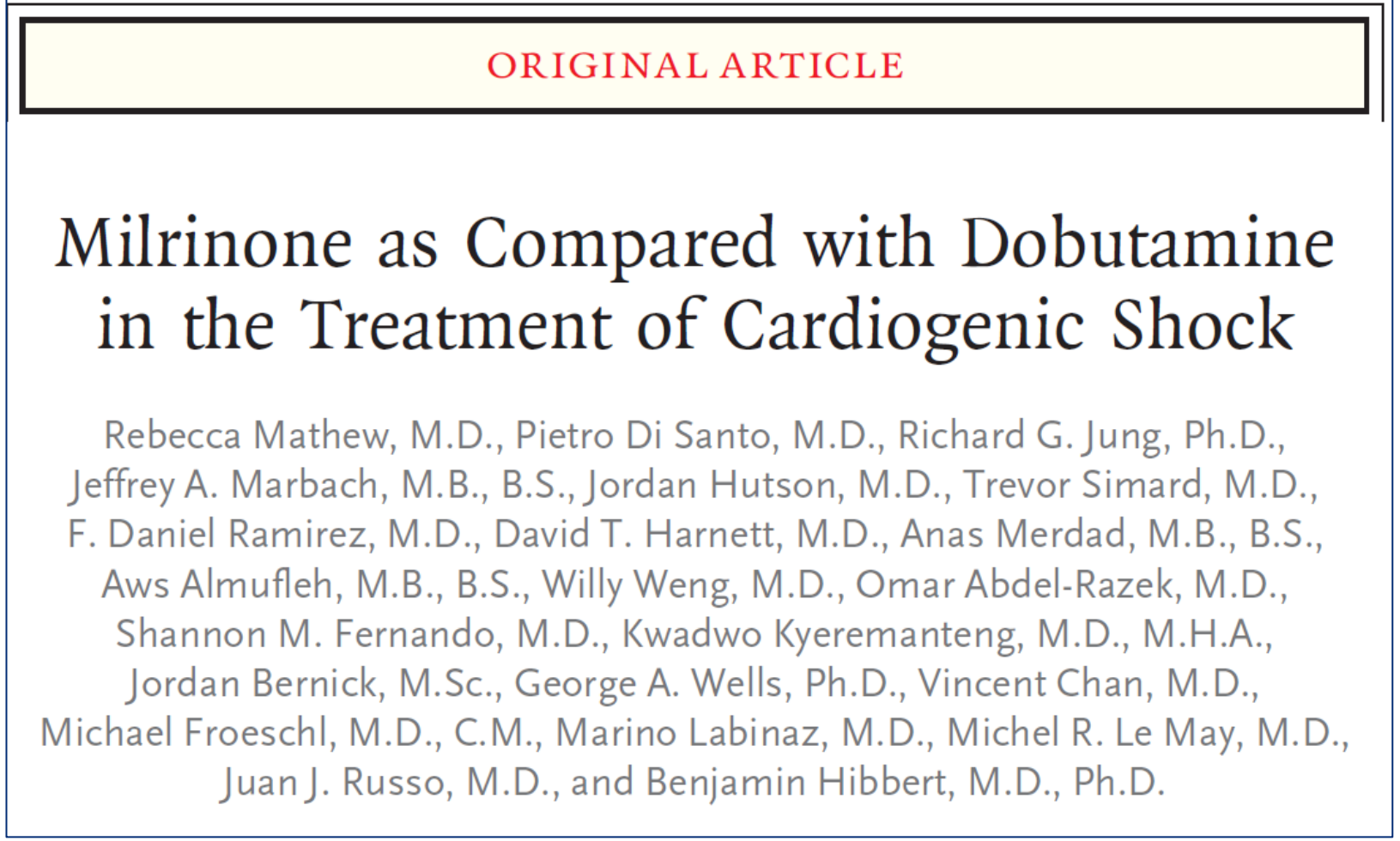
Another Way of Looking at Inotropes



* Low doses (1-3 mcg) of dopamine and dobutamine have very similar clinical effects when used in heart failure.

** Relative inotropy of milrinone may be greater after prolonged beta-adrenergic stimulation

Lynne Warner Stevenson Circulation. 2003;108:367-372


ORIGINAL ARTICLE

Milrinone as Compared with Dobutamine in the Treatment of Cardiogenic Shock

Rebecca Mathew, M.D., Pietro Di Santo, M.D., Richard G. Jung, Ph.D., Jeffrey A. Marbach, M.B., B.S., Jordan Hutson, M.D., Trevor Simard, M.D., F. Daniel Ramirez, M.D., David T. Harnett, M.D., Anas Merdad, M.B., B.S., Aws Almufleh, M.B., B.S., Willy Weng, M.D., Omar Abdel-Razek, M.D., Shannon M. Fernando, M.D., Kwadwo Kyeremanteng, M.D., M.H.A., Jordan Bernick, M.Sc., George A. Wells, Ph.D., Vincent Chan, M.D., Michael Froeschl, M.D., C.M., Marino Labinaz, M.D., Michel R. Le May, M.D., Juan J. Russo, M.D., and Benjamin Hibbert, M.D., Ph.D.

DOREMI trial

- Randomized, double-blind clinical trial of milrinone as compared with dobutamine in patients with cardiogenic shock

N Engl J Med 2021; 385:516-525

DOREMI trial

- The **primary outcome** was the **composite** of **in-hospital death** from any cause, **resuscitated cardiac arrest**, receipt of a **cardiac transplant or mechanical circulatory support**, **nonfatal myocardial infarction**, **transient ischemic attack or stroke** diagnosed by a neurologist, or **initiation of renal replacement therapy**

N Engl J Med 2021; 385:516-525

DOREMI trial

Characteristic	Milrinone (N = 96)	Dobutamine (N = 96)
Age — yr	68.9±13.8	72.0±11.3
Female sex — no. (%)	36 (38)	34 (35)
Median body-mass index (IQR)†	26.4 (23.7–31.0)	26.0 (22.5–30.5)
Race — no. (%)‡		
White	86 (90)	79 (82)
Non-White	10 (10)	17 (18)
Left ventricular function		
Median left ventricular ejection fraction (IQR) — %	25 (20–40)	25 (20–40)
Cause of ventricular dysfunction — no. (%)		
Ischemic	66 (69)	62 (65)
Nonischemic	30 (31)	33 (34)
Coexisting conditions — no. (%)		
Previous myocardial infarction	39 (41)	29 (30)
Previous percutaneous coronary intervention	30 (31)	19 (20)
Previous coronary-artery bypass grafting	20 (21)	19 (20)
Previous stroke or transient ischemic attack	13 (14)	15 (16)
Atrial fibrillation	49 (51)	46 (48)
Chronic kidney disease§	38 (40)	40 (42)

N Engl J Med 2021; 385:516-525

DOREMI trial

Characteristic	Milrinone (N = 96)	Dobutamine (N = 96)
Age — yr	68.9±13.8	72.0±11.3
Female sex — no. (%)	36 (38)	34 (35)
Median body-mass index (IQR)†	26.4 (23.7–31.0)	26.0 (22.5–30.5)
Race — no. (%)‡		
White	86 (90)	79 (82)
Non-White	10 (10)	17 (18)
Left ventricular function		
Median left ventricular ejection fraction (IQR) — %	25 (20–40)	25 (20–40)
Cause of ventricular dysfunction — no. (%)		
Ischemic	66 (69)	62 (65)
Nonischemic	30 (31)	33 (34)
Coexisting conditions — no. (%)		
Previous myocardial infarction	39 (41)	29 (30)
Previous percutaneous coronary intervention	30 (31)	19 (20)
Previous coronary-artery bypass grafting	20 (21)	19 (20)
Previous stroke or transient ischemic attack	13 (14)	15 (16)
Atrial fibrillation	49 (51)	46 (48)
Chronic kidney disease§	38 (40)	40 (42)

N Engl J Med 2021; 385:516-525

DOREMI trial

Characteristic	Milrinone (N = 96)	Dobutamine (N = 96)
Age — yr	68.9±13.8	72.0±11.3
Female sex — no. (%)	36 (38)	34 (35)
Median body-mass index (IQR)†	26.4 (23.7–31.0)	26.0 (22.5–30.5)
Non-White	10 (10)	17 (18)
Left ventricular function		
Median left ventricular ejection fraction (IQR) — %	25 (20–40)	25 (20–40)
Cause of ventricular dysfunction — no. (%)		
Ischemic	66 (69)	62 (65)
Nonischemic	30 (31)	33 (34)
Coexisting conditions — no. (%)		
Previous myocardial infarction	39 (41)	29 (30)
Previous percutaneous coronary intervention	30 (31)	19 (20)
Previous coronary-artery bypass grafting	20 (21)	19 (20)
Previous stroke or transient ischemic attack	13 (14)	15 (16)
Atrial fibrillation	49 (51)	46 (48)
Chronic kidney disease§	38 (40)	40 (42)

Female sex — no. (%) 36 (38) 34 (35)

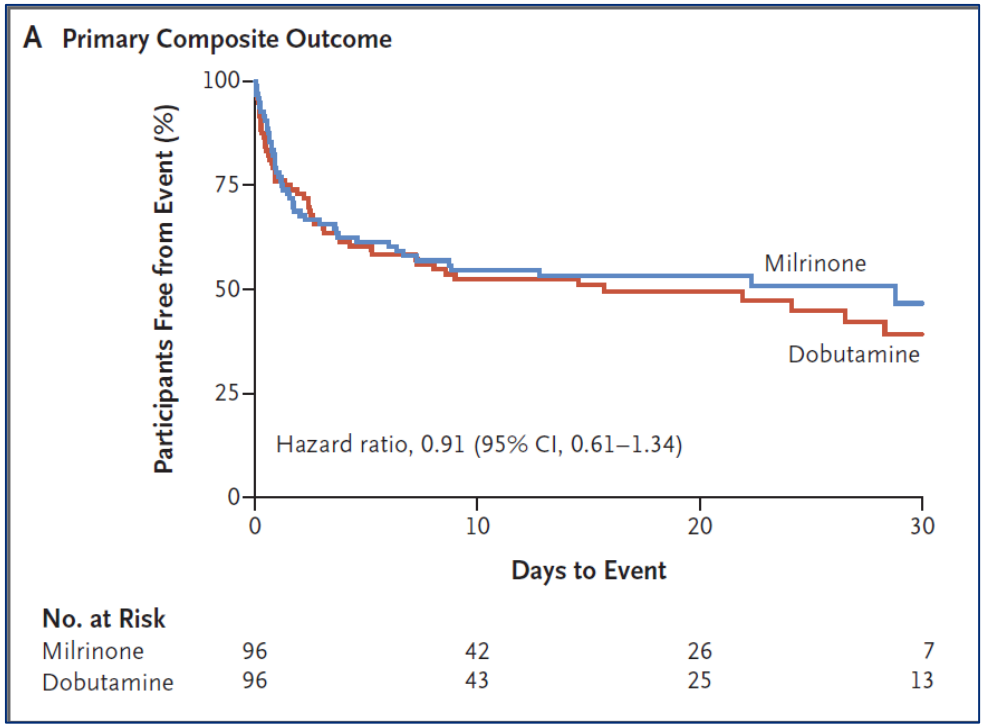
N Engl J Med 2021; 385:516-525

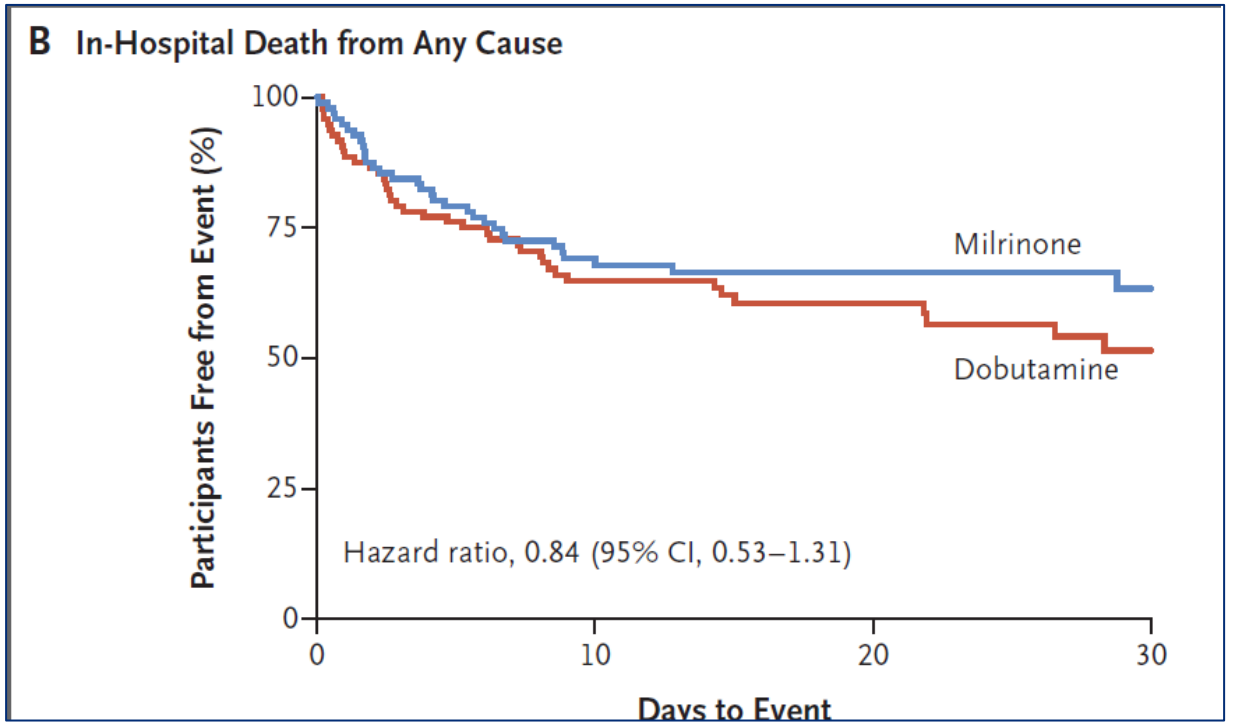
DOREMI trial

Characteristic	Milrinone (N = 96)	Dobutamine (N = 96)
Age — yr	68.9±13.8	72.0±11.3
Female sex — no. (%)	36 (38)	34 (35)
Median body-mass index (IQR)†	26.4 (23.7–31.0)	26.0 (22.5–30.5)
Race — no. (%)‡		
White	86 (90)	79 (82)
Non-White	10 (10)	17 (18)
Left ventricular function		
Cause of ventricular dysfunction — no. (%)		
Ischemic	66 (69)	62 (65)
Nonischemic	30 (31)	33 (34)
Previous myocardial infarction	39 (41)	29 (30)
Previous percutaneous coronary intervention	30 (31)	19 (20)
Previous coronary-artery bypass grafting	20 (21)	19 (20)
Previous stroke or transient ischemic attack	13 (14)	15 (16)
Atrial fibrillation	49 (51)	46 (48)
Chronic kidney disease§	38 (40)	40 (42)

N Engl J Med 2021; 385:516-525

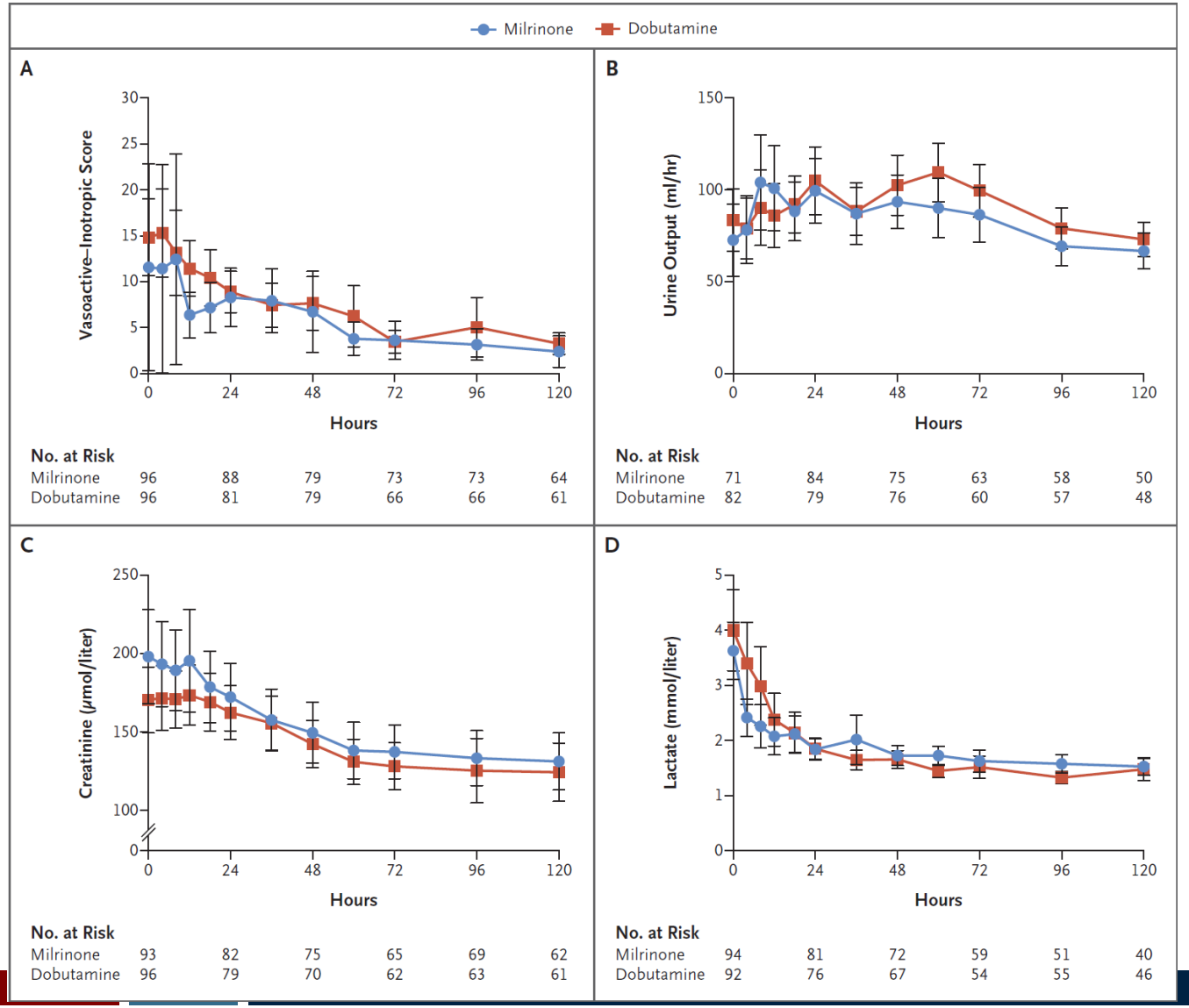
DOREMI trial





N Engl J Med 2021; 385:516-525

DOREMI trial



N Engl J Med 2021; 385:516-525

Levosimendan vs Dobutamine for Patients With Acute Decompensated Heart Failure

The SURVIVE Randomized Trial

- A randomized, double blind trial comparing the **efficacy and safety of intravenous levosimendan or dobutamine**

- Patients with **LVEF<30% admitted with ADHF requiring inotropic support** and at least one of the following:
  - Dyspnea at rest or mechanical ventilation for ADHF
  - Oliguria not as a result of hypovolemia
  - Pulmonary capillary wedge pressure of >18 mm Hg and/or cardiac index < 2.2 L/min per m2

JAMA. 2007;297:1883-1891

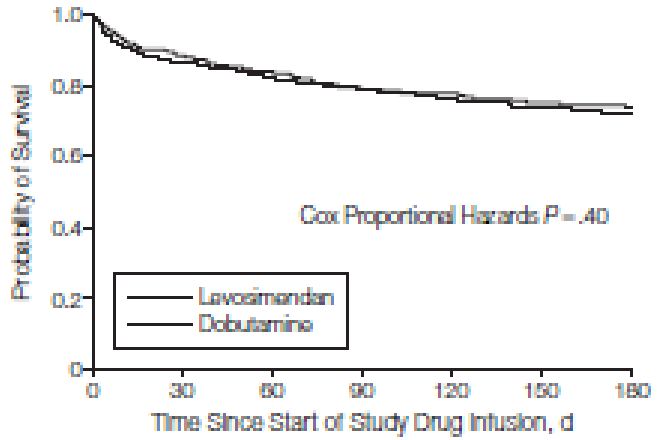
Levosimendan vs Dobutamine for Patients With Acute Decompensated Heart Failure

The SURVIVE Randomized Trial

- The **primary end point** of the study was all-cause mortality during the 180 days following randomization

663 pts in each group

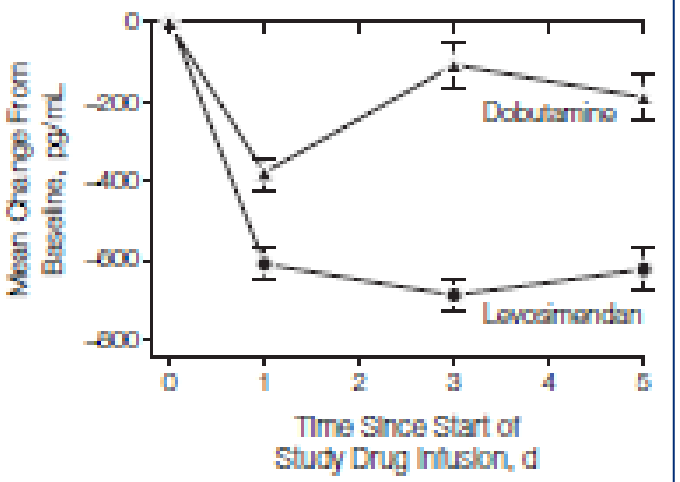
Figure 2. Effect of Dobutamine and Levosimendan Treatment on All-Cause Mortality During 180 Days Following the Start of Study Drug Infusion



No. at Risk

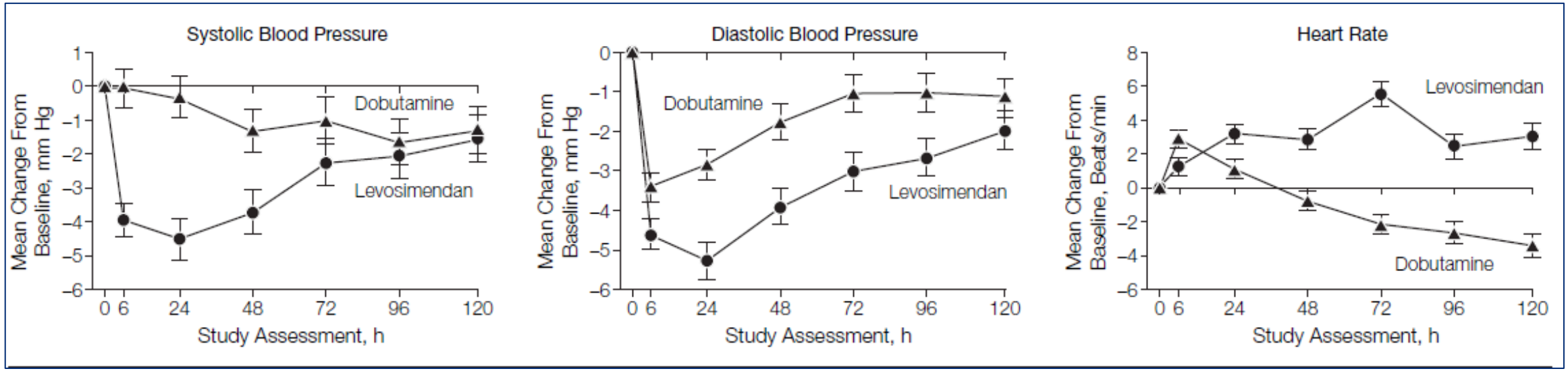
Levosimendan	664	608	586	525		462
Dobutamine	663	596	568	519		454

Figure 3. Mean Change From Baseline in B-Type Natriuretic Peptide Levels at 1, 3, and 5 Days by Treatment Group



Levosimendan vs Dobutamine for Patients With Acute Decompensated Heart Failure

The SURVIVE Randomized Trial



nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01659-1

Check for updates

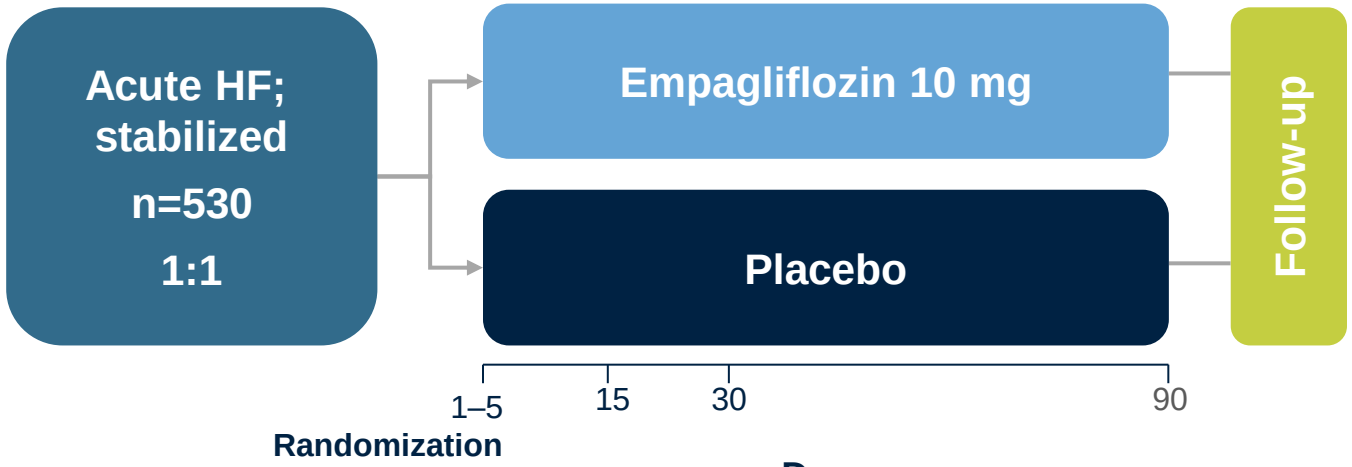
OPEN

The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial

Adriaan A. Voors[1]✉, Christiane E. Angermann[2], John R. Teerlink[3], Sean P. Collins[4], Mikhail Kosiborod[5,6,7,8], Jan Biegus[9], João Pedro Ferreira[10,11], Michael E. Nassif[5,6], Mitchell A. Psotka[12], Jasper Tromp[13], C. Jan Willem Borleffs[14], Changsheng Ma[15], Joseph Comin-Colet[16], Michael Fu[17], Stefan P. Janssens[18], Robert G. Kiss[19], Robert J. Mentz[20,21], Yasushi Sakata[22], Henrik Schirmer[23], Morten Schou[24], P. Christian Schulze[25], Lenka Spinarova[26], Maurizio Volterrani[27], Jerzy K. Wranicz[28], Uwe Zeymer[29], Shelley Zieroth[30], Martina Brueckmann[31,32], Jonathan P. Blatchford[33], Afshin Salsali[34,35] and Piotr Ponikowski[9]

EMPULSE Trial

EMPULSE studied the effect of empagliflozin in patients hospitalized for acute heart failure



Median time from hospital admission to randomization was **3 days**

INCLUSION

Currently **hospitalized** for the primary diagnosis of **AHF** (**de novo or decompensated chronic HF**), **regardless of EF**

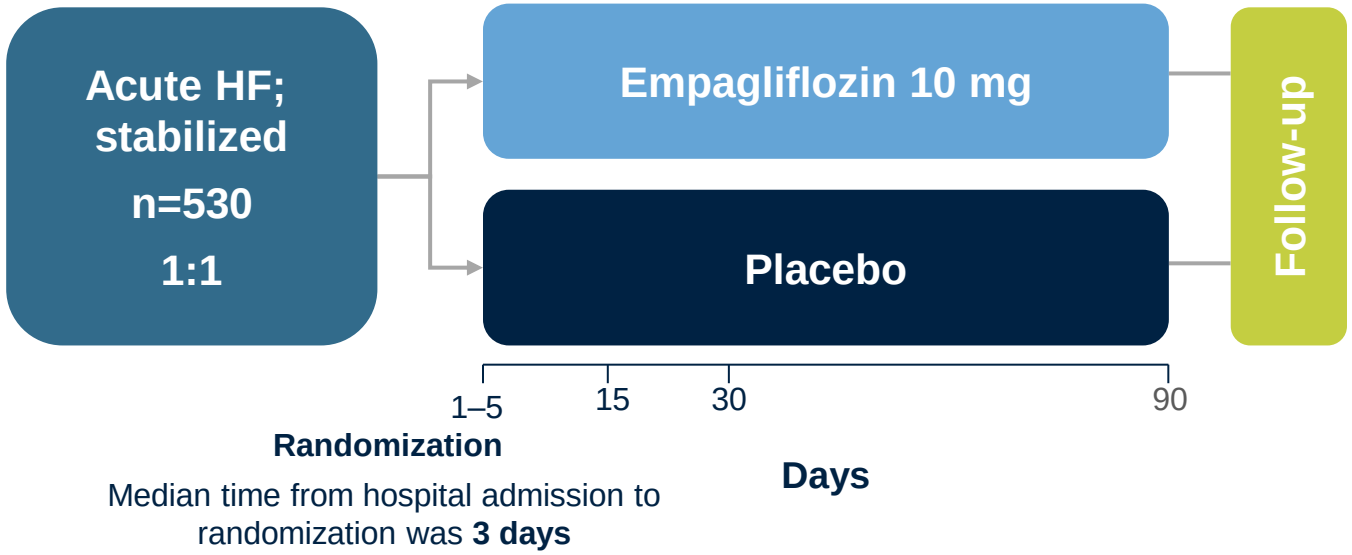
Randomization ≥24 hours and no later than 5 days after admission, as early as possible **after stabilization and while still in hospital**

Elevated NT-proBNP or BNP:

Without AF: NT-proBNP ≥1600 pg/mL or BNP ≥400 pg/mL

With AF: NT-proBNP ≥2400 pg/mL or BNP ≥600 pg/mL

EMPULSE studied the effect of empagliflozin in patients hospitalized for acute heart failure[1,2]



Median time from hospital admission to randomization was **3 days**

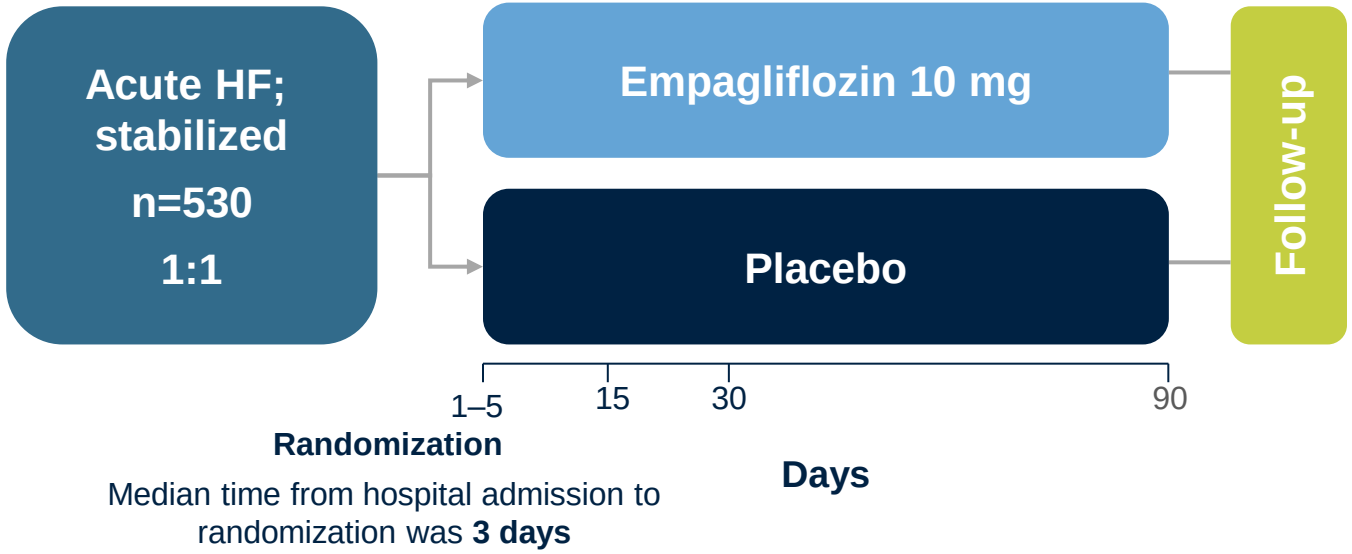
INCLUSION

Currently hospitalized for the primary diagnosis of AHF (de novo or decompensated chronic HF),

Patients with HFrEF and HFpEF were included
Patients with de novo or decompensated chronic HF were included

Elevated NT-proBNP or BNP:
Without AF: NT-proBNP ≥1600 pg/mL or BNP ≥400 pg/mL
With AF: NT-proBNP ≥2400 pg/mL or BNP ≥600 pg/mL

EMPULSE studied the effect of empagliflozin in patients hospitalized for acute heart failure[1,2]



Median time from hospital admission to randomization was **3 days**

INCLUSION

Currently hospitalized for the primary diagnosis of AHF (de novo or decompensated chronic HF),

Patients with HFrEF and HFpEF were included
Patients with de novo or decompensated chronic HF were included

Elevated NT-proBNP or BNP:
Without AF: NT-proBNP ≥1600 pg/mL or BNP ≥400 pg/mL
With AF: NT-proBNP ≥2400 pg/mL or BNP ≥600 pg/mL

Primary endpoint

- **Clinical benefit evaluated with a win ratio based on a composite of:**
  - Death
  - Number of HFEs (including HHFs, urgent HF visits and unplanned outpatient visits)
  - Time to first HFE
  - Change from baseline in KCCQ-TSS after 90 days of treatment

Statistical analysis of primary endpoint: The win ratio

The primary outcome was clinical benefit at 90 days, defined as a **hierarchical** composite outcome of time to all-cause death, the number of HFEs, time to first HFE, and a 5-point or greater difference in change from baseline in KCCQ-TSS after 90 days of treatment

Clinical benefit

Each patient from one treatment arm is compared with each patient from the other arm*

Win ratio = **Total number of wins in the empagliflozin group** / **Total number of wins in the placebo group**

1 Death
- Death is worse than no death
- Earlier death is worse

If neither patient is superior based on death

2 Number of HFEs†
- More HFEs is worse

If neither patient is superior based on death or number of HFEs

3 Time to first HFE†
- Earlier HFE is worse

If neither patient is superior based on 1–3

4 KCCQ-TSS mean change from baseline after 90 days
- More positive change is better
- Threshold for the difference is ≥5 for a win

*Stratified by HF status (i.e. de novo HF vs decompensated chronic HF). †Within common follow-up time; HFEs include HHF, urgent HF visits and unplanned outpatient visits. HF, heart failure; HFE, heart failure event; HHF, hospitalization for heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score. Tromp J *et al. Eur J Heart Fail.* 2021;23:826.

Nature Medicine | VOL 28 | March 2022 | 568–574

102

Baseline characteristics

Table 1 | Characteristics of the patients at baseline

	Empagliflozin ($n = 265$) Median (IQR) or n (%)	Placebo ($n = 265$) Median (IQR) or n (%)
Age (years)	71 (62–78)	70 (59–78)
Sex		
Men	179 (67.5)	172 (64.9)
Women	86 (32.5)	93 (35.1)
Race or ethnic group		
White	211 (79.6)	202 (76.2)
Black	21 (7.9)	33 (12.5)
Asian	32 (12.1)	25 (9.4)
Other/mixed race	1 (0.4)	4 (1.5)
Missing	0	1 (0.4)
Geographic region		
Europe	168 (63.4)	171 (64.5)
North America	66 (24.9)	69 (26.0)
Asia	31 (11.7)	25 (9.4)
NYHA class		
I	8 (3.0)	6 (2.3)
II	95 (35.8)	91 (34.3)
III	134 (50.6)	145 (54.7)
IV	26 (9.8)	23 (8.7)

Nature Medicine | VOL 28 | March 2022 | 568–574

Baseline characteristics

Table 1 | Characteristics of the patients at baseline

	Empagliflozin ($n=265$) Median (IQR) or n (%)	Placebo ($n=265$) Median (IQR) or n (%)
Age (years)	71 (62–78)	70 (59–78)
Sex		
Men	179 (67.5)	172 (64.9)
Women	86 (32.5)	93 (35.1)
Race or ethnic group		
White	211 (79.6)	202 (76.2)
Black	21 (7.9)	33 (12.5)
Asian	32 (12.1)	25 (9.4)
Other/mixed race	1 (0.4)	4 (1.5)
Missing	0	1 (0.4)
Geographic region		
Europe	168 (63.4)	171 (64.5)
North America	66 (24.9)	69 (26.0)
Asia	31 (11.7)	25 (9.4)
NYHA class		
I	8 (3.0)	6 (2.3)
II	95 (35.8)	91 (34.3)
III	134 (50.6)	145 (54.7)
IV	26 (9.8)	23 (8.7)

Nature Medicine | VOL 28 | March 2022 | 568–574

Baseline characteristics

Table 1 | Characteristics of the patients at baseline

	Empagliflozin ($n=265$) Median (IQR) or n (%)	Placebo ($n=265$) Median (IQR) or n (%)
Age (years)	71 (62-78)	70 (59-78)
Sex		
Men	179 (67.5)	172 (64.9)
Women	86 (32.5)	93 (35.1)
Left ventricular ejection fraction (%)	31.0 (23.0-45.0)	32.0 (22.5-49.0)
≤40%	182 (68.7)	172 (64.9)
>40%	76 (28.7)	93 (35.1)
Other/mixed race	1 (0.4)	4 (1.5)
Missing	0	1 (0.4)
Geographic region		
Europe	168 (63.4)	171 (64.5)
North America	66 (24.9)	69 (26.0)
Asia	31 (11.7)	25 (9.4)
NYHA class		
I	8 (3.0)	6 (2.3)
II	95 (35.8)	91 (34.3)
III	134 (50.6)	145 (54.7)
IV	26 (9.8)	23 (8.7)

Nature Medicine | VOL 28 | March 2022 | 568–574

Baseline characteristics

Table 1 | Characteristics of the patients at baseline

	Empagliflozin ($n=265$) Median (IQR) or n (%)	Placebo ($n=265$) Median (IQR) or n (%)
Age (years)	71 (62–78)	70 (59–78)
Sex		
Men	179 (67.5)	172 (64.9)
Women	86 (32.5)	93 (35.1)
Race or ethnic group		
White	211 (79.6)	202 (76.2)
Black	21 (7.9)	33 (12.5)
Asian	32 (12.1)	25 (9.4)
Other/mixed race	1 (0.4)	4 (1.5)
Missing	0	1 (0.4)
Medical history		
Diabetes	124 (46.8)	116 (43.8)
North America	66 (24.9)	69 (26.0)
Asia	31 (11.7)	25 (9.4)
NYHA class		
I	8 (3.0)	6 (2.3)
II	95 (35.8)	91 (34.3)
III	134 (50.6)	145 (54.7)
IV	26 (9.8)	23 (8.7)

Nature Medicine | VOL 28 | March 2022 | 568–574

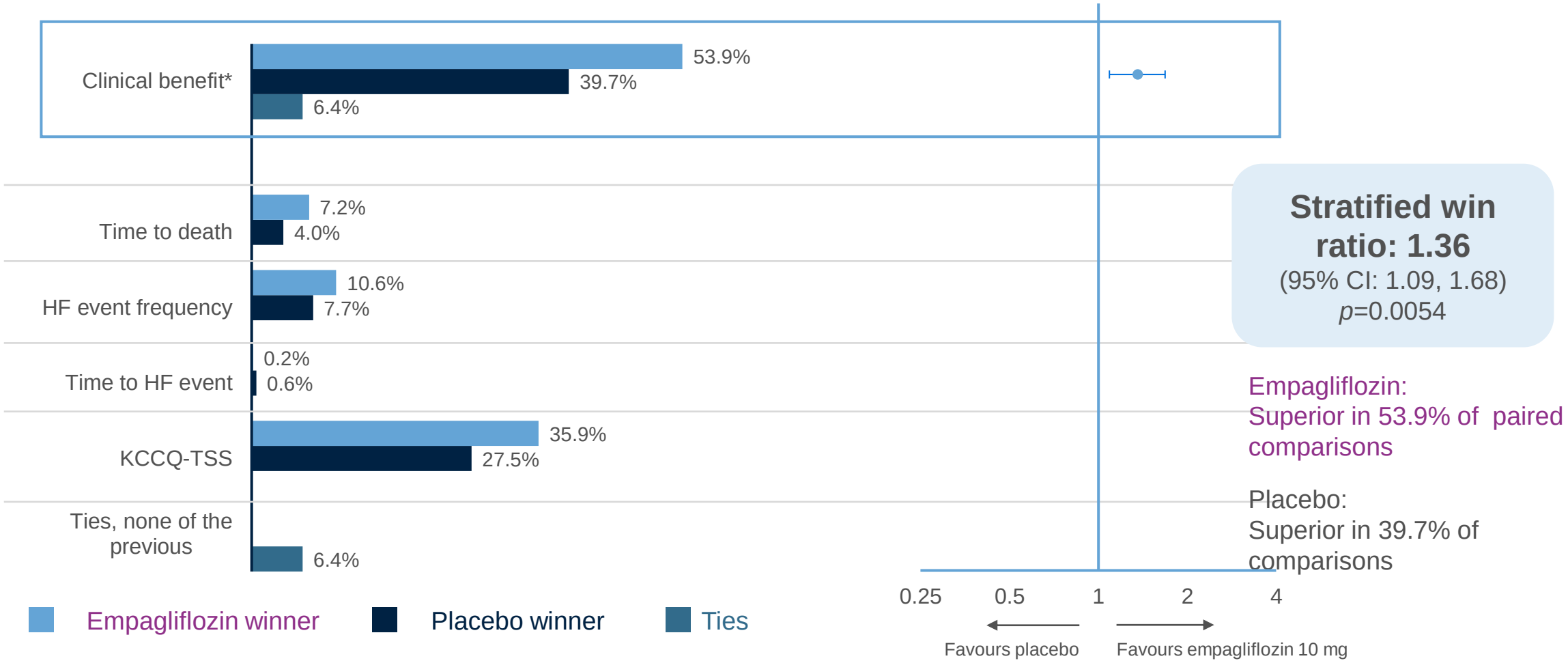
Baseline characteristics

Table 1 | Characteristics of the patients at baseline

	Empagliflozin ($n = 265$) Median (IQR) or n (%)	Placebo ($n = 265$) Median (IQR) or n (%)
Age (years)	71 (62–78)	70 (59–78)
Sex		
Men	179 (67.5)	172 (64.9)
Women	86 (32.5)	93 (35.1)
Race or ethnic group		
White	211 (79.6)	202 (76.2)
Black	21 (7.9)	33 (12.5)
Asian	32 (12.1)	25 (9.4)
Other/mixed race	1 (0.4)	4 (1.5)
Missing	0	1 (0.4)
Geographic region		
Europe	168 (63.4)	171 (64.5)
North America	66 (24.9)	69 (26.0)
Heart failure status		
Decompensated CHF	177 (66.8)	178 (67.2)
Acute de novo	88 (33.2)	87 (32.8)
IV	26 (9.8)	23 (8.7)

Nature Medicine | VOL 28 | March 2022 | 568–574

EMPULSE: Patients treated with empagliflozin were 36% more likely to experience a clinical benefit than those who received placebo



Stratified win ratio: 1.36
(95% CI: 1.09, 1.68)
p=0.0054

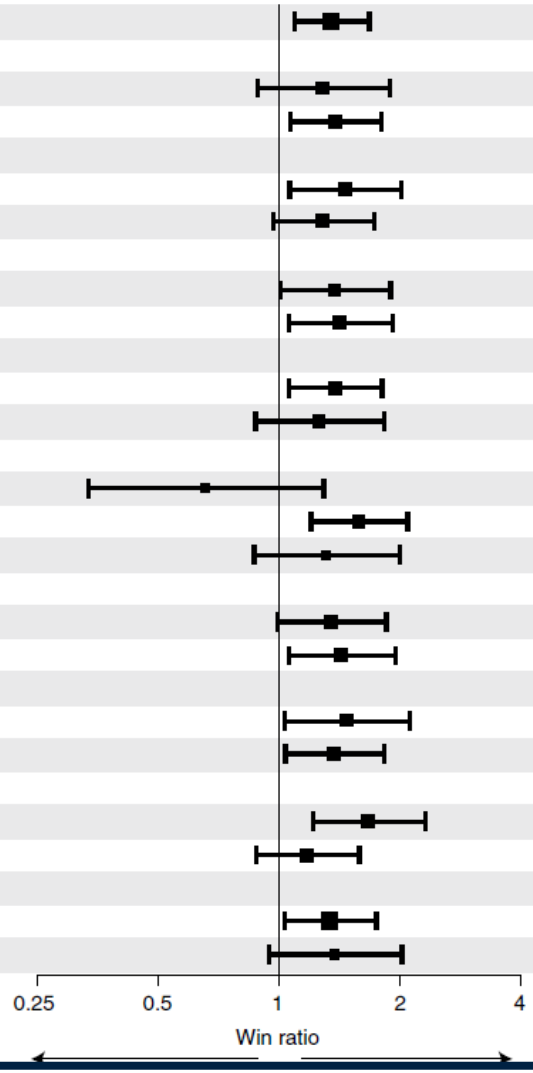
Empagliflozin:
Superior in 53.9% of paired comparisons

Placebo:
Superior in 39.7% of comparisons

Numbers reflect percentage of comparisons. For the components of the win ratio these numbers do not reflect randomized comparisons. *Composite of death, number of [illegible] HF visits and unplanned outpatient visits), time to first HFE and change from baseline in KCCQ-TSS after 90 days of treatment. CI, confidence interval; HF, heart failure; H[illegible] hospitalization for heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score. Voors AA et al. *Nat Med*. 2022; https://doi.org/10.10[illegible]
Nature Medicine | VOL 28 | March 2022 | 568–574

Primary efficacy outcome in all prespecified subgroups

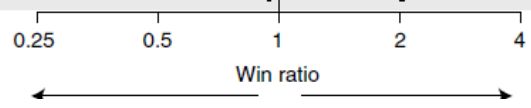
Subgroup	Empagliflozin	Placebo	Win ratio (95% CI)	Interaction *P* value
	Number of patients			
All patients	265	265	1.36 (1.09–1.68)	
Heart failure status				0.7590
De novo	88	87	1.29 (0.89–1.89)	
Decompensated chronic	177	178	1.39 (1.07–1.81)	
Baseline diabetes status				0.5683
Diabetic	124	116	1.47 (1.07–2.02)	
Non-diabetic	141	149	1.30 (0.97–1.73)	
Age				0.8889
<70 years	116	129	1.38 (1.01–1.90)	
≥70 years	149	136	1.43 (1.06–1.92)	
Sex				0.6923
Male	179	172	1.39 (1.06–1.81)	
Female	86	93	1.27 (0.88–1.83)	
Region				0.0602
Asia	31	25	0.66 (0.34–1.30)	
Europe	168	171	1.59 (1.20–2.09)	
North America	66	69	1.32 (0.87–2.00)	
Baseline NT-proBNP (pg ml^{-1})				0.7904
<Median	125	130	1.36 (0.99–1.85)	
≥Median	130	126	1.44 (1.06–1.96)	
Baseline eGFR (CKD-EPI)				0.7562
≥60 ml min^{-1} 1.73 m^{-2}	88	106	1.48 (1.04–2.13)	
<60 ml min^{-1} 1.73 m^{-2}	161	145	1.38 (1.04–1.83)	
Atrial fibrillation or flutter at baseline				0.1129
No	123	133	1.68 (1.22–2.32)	
Yes	142	132	1.18 (0.88–1.59)	
Baseline LVEF (%)				0.9008
HFrEF (LVEF ≤40%)	182	172	1.35 (1.04–1.75)	
HFpEF (LVEF >40%)	76	93	1.39 (0.95–2.03)	



Nature Medicine | VOL 28 | March 2022 | 568–574

Primary efficacy outcome in all prespecified subgroups

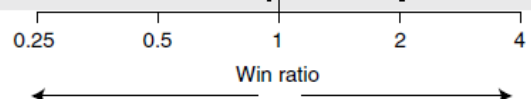
Subgroup	Empagliflozin	Placebo	Win ratio (95% CI)	Interaction *P* value
	Number of patients			
All patients	265	265	1.36 (1.09–1.68)	
Heart failure status				0.7590
De novo	88	87	1.29 (0.89–1.89)	
Decompensated chronic	177	178	1.39 (1.07–1.81)	
Non-diabetic	141	149	1.30 (0.97–1.73)	
Age				0.8889
<70 years	116	129	1.38 (1.01–1.90)	
≥70 years	149	136	1.43 (1.06–1.92)	
Sex				0.6923
Male	179	172	1.39 (1.06–1.81)	
Female	86	93	1.27 (0.88–1.83)	
Region				0.0602
Asia	31	25	0.66 (0.34–1.30)	
Europe	168	171	1.59 (1.20–2.09)	
North America	66	69	1.32 (0.87–2.00)	
Baseline NT-proBNP (pg ml^{-1})				0.7904
<Median	125	130	1.36 (0.99–1.85)	
≥Median	130	126	1.44 (1.06–1.96)	
Baseline eGFR (CKD-EPI)				0.7562
≥60 ml min^{-1} 1.73 m^{-2}	88	106	1.48 (1.04–2.13)	
<60 ml min^{-1} 1.73 m^{-2}	161	145	1.38 (1.04–1.83)	
Atrial fibrillation or flutter at baseline				0.1129
No	123	133	1.68 (1.22–2.32)	
Yes	142	132	1.18 (0.88–1.59)	
Baseline LVEF (%)				0.9008
HFrEF (LVEF ≤40%)	182	172	1.35 (1.04–1.75)	
HFpEF (LVEF >40%)	76	93	1.39 (0.95–2.03)	



Nature Medicine | VOL 28 | March 2022 | 568–574

Primary efficacy outcome in all prespecified subgroups

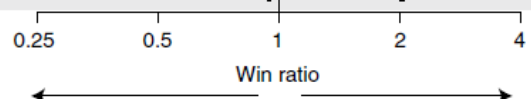
Subgroup	Empagliflozin	Placebo	Win ratio (95% CI)	Interaction *P* value
	Number of patients			
All patients	265	265	1.36 (1.09–1.68)	
Heart failure status				0.7590
De novo	88	87	1.29 (0.89–1.89)	
Decompensated chronic	177	178	1.39 (1.07–1.81)	
Baseline diabetes status				0.5683
Diabetic	124	116	1.47 (1.07–2.02)	
Non-diabetic	141	149	1.30 (0.97–1.73)	
Age				0.8889
<70 years	116	129	1.38 (1.01–1.90)	
≥70 years	149	136	1.43 (1.06–1.92)	
Female	86	93	1.27 (0.88–1.83)	
Region				0.0602
Asia	31	25	0.66 (0.34–1.30)	
Europe	168	171	1.59 (1.20–2.09)	
North America	66	69	1.32 (0.87–2.00)	
Baseline NT-proBNP (pg ml^{-1})				0.7904
<Median	125	130	1.36 (0.99–1.85)	
≥Median	130	126	1.44 (1.06–1.96)	
Baseline eGFR (CKD-EPI)				0.7562
≥60 ml min^{-1} 1.73 m^{-2}	88	106	1.48 (1.04–2.13)	
<60 ml min^{-1} 1.73 m^{-2}	161	145	1.38 (1.04–1.83)	
Atrial fibrillation or flutter at baseline				0.1129
No	123	133	1.68 (1.22–2.32)	
Yes	142	132	1.18 (0.88–1.59)	
Baseline LVEF (%)				0.9008
HFrEF (LVEF ≤40%)	182	172	1.35 (1.04–1.75)	
HFpEF (LVEF >40%)	76	93	1.39 (0.95–2.03)	



Nature Medicine | VOL 28 | March 2022 | 568–574

Primary efficacy outcome in all prespecified subgroups

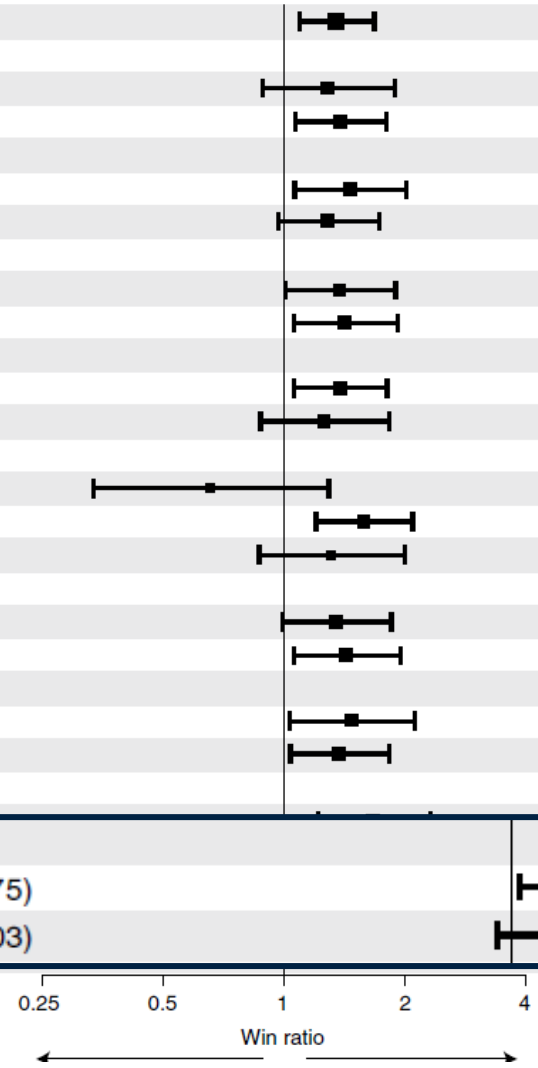
Subgroup	Empagliflozin	Placebo	Win ratio (95% CI)	Interaction *P* value
	Number of patients			
All patients	265	265	1.36 (1.09–1.68)	
Heart failure status				0.7590
De novo	88	87	1.29 (0.89–1.89)	
Decompensated chronic	177	178	1.39 (1.07–1.81)	
Baseline diabetes status				0.5683
Diabetic	124	116	1.47 (1.07–2.02)	
Non-diabetic	141	149	1.30 (0.97–1.73)	
Age				0.8889
<70 years	116	129	1.38 (1.01–1.90)	
≥70 years	149	136	1.43 (1.06–1.92)	
Sex				0.6923
Male	179	172	1.39 (1.06–1.81)	
Female	86	93	1.27 (0.88–1.83)	
Europe	168	171	1.59 (1.20–2.09)	
North America	66	69	1.32 (0.87–2.00)	
Baseline NT-proBNP (pg ml^{-1})				0.7904
<Median	125	130	1.36 (0.99–1.85)	
≥Median	130	126	1.44 (1.06–1.96)	
Baseline eGFR (CKD-EPI)				0.7562
≥60 ml min^{-1} 1.73 m^{-2}	88	106	1.48 (1.04–2.13)	
<60 ml min^{-1} 1.73 m^{-2}	161	145	1.38 (1.04–1.83)	
Atrial fibrillation or flutter at baseline				0.1129
No	123	133	1.68 (1.22–2.32)	
Yes	142	132	1.18 (0.88–1.59)	
Baseline LVEF (%)				0.9008
HFrEF (LVEF ≤40%)	182	172	1.35 (1.04–1.75)	
HFpEF (LVEF >40%)	76	93	1.39 (0.95–2.03)	



Nature Medicine | VOL 28 | March 2022 | 568–574

Primary efficacy outcome in all prespecified subgroups

Subgroup	Empagliflozin	Placebo	Win ratio (95% CI)	Interaction *P* value
	Number of patients			
All patients	265	265	1.36 (1.09–1.68)	
Heart failure status				0.7590
De novo	88	87	1.29 (0.89–1.89)	
Decompensated chronic	177	178	1.39 (1.07–1.81)	
Baseline diabetes status				0.5683
Diabetic	124	116	1.47 (1.07–2.02)	
Non-diabetic	141	149	1.30 (0.97–1.73)	
Age				0.8889
<70 years	116	129	1.38 (1.01–1.90)	
≥70 years	149	136	1.43 (1.06–1.92)	
Sex				0.6923
Male	179	172	1.39 (1.06–1.81)	
Female	86	93	1.27 (0.88–1.83)	
Region				0.0602
Asia	31	25	0.66 (0.34–1.30)	
Europe	168	171	1.59 (1.20–2.09)	
North America	66	69	1.32 (0.87–2.00)	
Baseline NT-proBNP (pg ml^{-1})				0.7904
<Median	125	130	1.36 (0.99–1.85)	
≥Median	130	126	1.44 (1.06–1.96)	
Baseline eGFR (CKD-EPI)				0.7562
≥60 ml min^{-1} 1.73 m^{-2}	88	106	1.48 (1.04–2.13)	
<60 ml min^{-1} 1.73 m^{-2}	161	145	1.38 (1.04–1.83)	
Atrial fibrillation or flutter at baseline				0.1129
Baseline LVEF (%)				0.9008
HFrEF (LVEF ≤40%)	182	172	1.35 (1.04–1.75)	
HFpEF (LVEF >40%)	76	93	1.39 (0.95–2.03)	



Nature Medicine | VOL 28 | March 2022 | 568–574

Adverse Events

Category of AEs	Empagliflozin 10 mg N (%)	Placebo N (%)
Number of patients	260 (100.0)	264 (100.0)
Patients with any AEs	182 (70.0)	204 (77.3)
Severe AEs	39 (15.0)	54 (20.5)
Investigator defined drug-related AEs	30 (11.5)	27 (10.2)
AEs leading to discontinuation of study medication	22 (8.5)	34 (12.9)
Serious AEs	84 (32.3)	115 (43.6)
Results in death	9 (3.5)	17 (6.4)
Is life threatening	12 (4.6)	14 (5.3)
Persistent or significant disability/incapacity	0	1 (0.4)
Requires or prolongs hospitalization	64 (24.6)	87 (33.0)
Congenital anomaly or birth defect	0	0
Other medically important serious event	33 (12.7)	48 (18.2)
AEs of special interest		
Hepatic injury (narrow SMQ)	10 (3.8)	13 (4.9)
Acute renal failure (narrow SMQ)	20 (7.7)	32 (12.1)
Ketoacidosis (narrow SMQ)	0	0

Adverse Events

Category of AEs	Empagliflozin 10 mg N (%)	Placebo N (%)
Number of patients	260 (100.0)	264 (100.0)
Patients with any AEs	182 (70.0)	204 (77.3)
Severe AEs	39 (15.0)	54 (20.5)
Investigator defined drug-related AEs	30 (11.5)	27 (10.2)
AEs leading to discontinuation of study medication	22 (8.5)	34 (12.9)
Serious AEs	84 (32.3)	115 (43.6)
Results in death	9 (3.5)	17 (6.4)
Is life threatening	12 (4.6)	14 (5.3)
Persistent or significant disability/incapacity	0	1 (0.4)
Requires or prolongs hospitalization	64 (24.6)	87 (33.0)
Congenital anomaly or birth defect	0	0
Other medically important serious event	33 (12.7)	48 (18.2)
AEs of special interest		
Hepatic injury (narrow SMQ)	10 (3.8)	13 (4.9)
Acute renal failure (narrow SMQ)	20 (7.7)	32 (12.1)
Ketoacidosis (narrow SMQ)	0	0

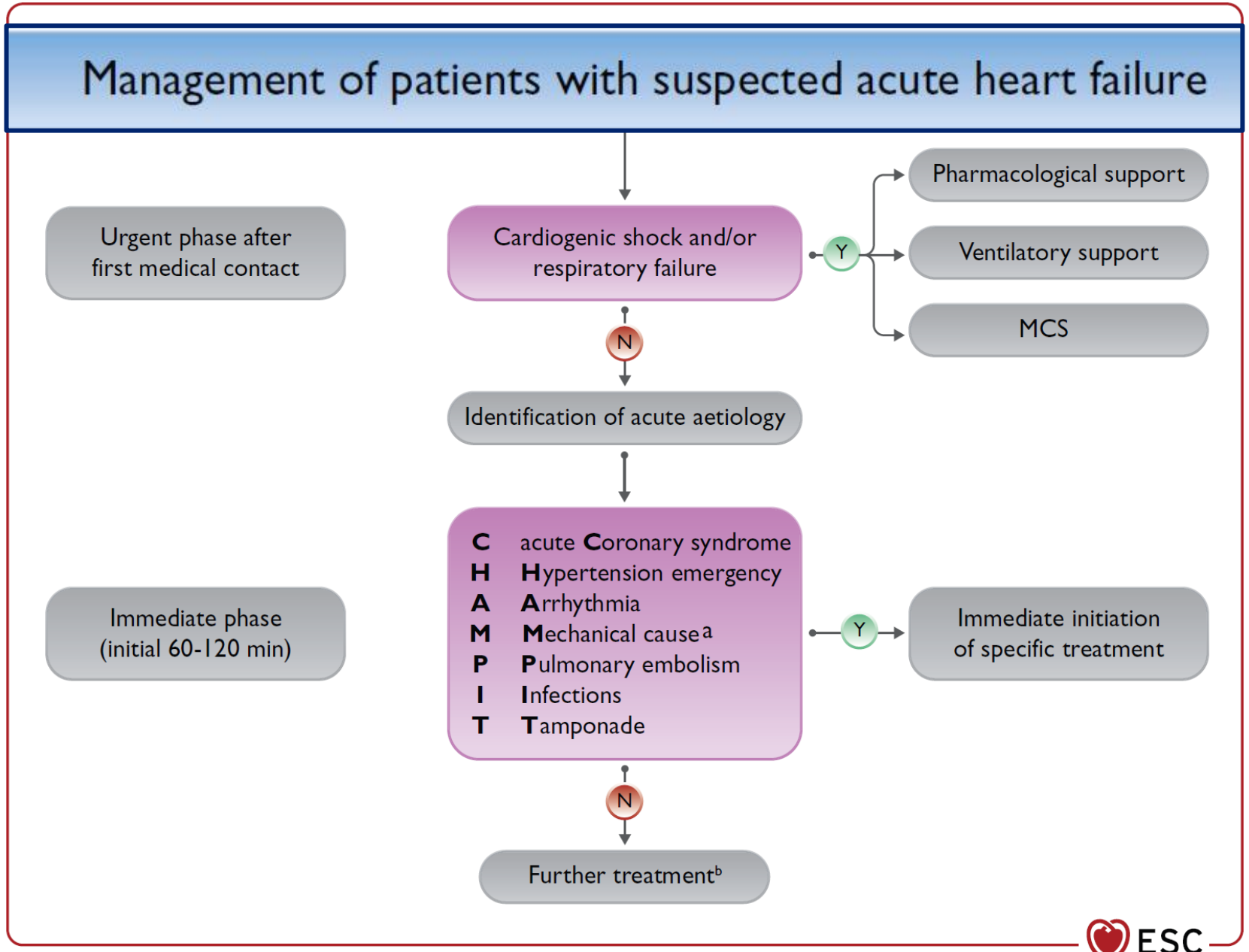
Adverse Events

Category of AEs	Empagliflozin 10 mg N (%)	Placebo N (%)
Number of patients	260 (100.0)	264 (100.0)
Patients with any AEs	182 (70.0)	204 (77.3)
Severe AEs	39 (15.0)	54 (20.5)
Investigator defined drug-related AEs	30 (11.5)	27 (10.2)
AEs leading to discontinuation of study medication	22 (8.5)	34 (12.9)
Serious AEs	84 (32.3)	115 (43.6)
Results in death	9 (3.5)	17 (6.4)
Is life threatening	12 (4.6)	14 (5.3)
Persistent or significant disability/incapacity	0	1 (0.4)
Requires or prolongs hospitalization	64 (24.6)	87 (33.0)
Congenital anomaly or birth defect	0	0
Other medically important serious event	33 (12.7)	48 (18.2)
Hepatic injury (narrow SMQ)	10 (3.8)	13 (4.9)
Acute renal failure (narrow SMQ)	20 (7.7)	32 (12.1)
Ketoacidosis (narrow SMQ)	0	0

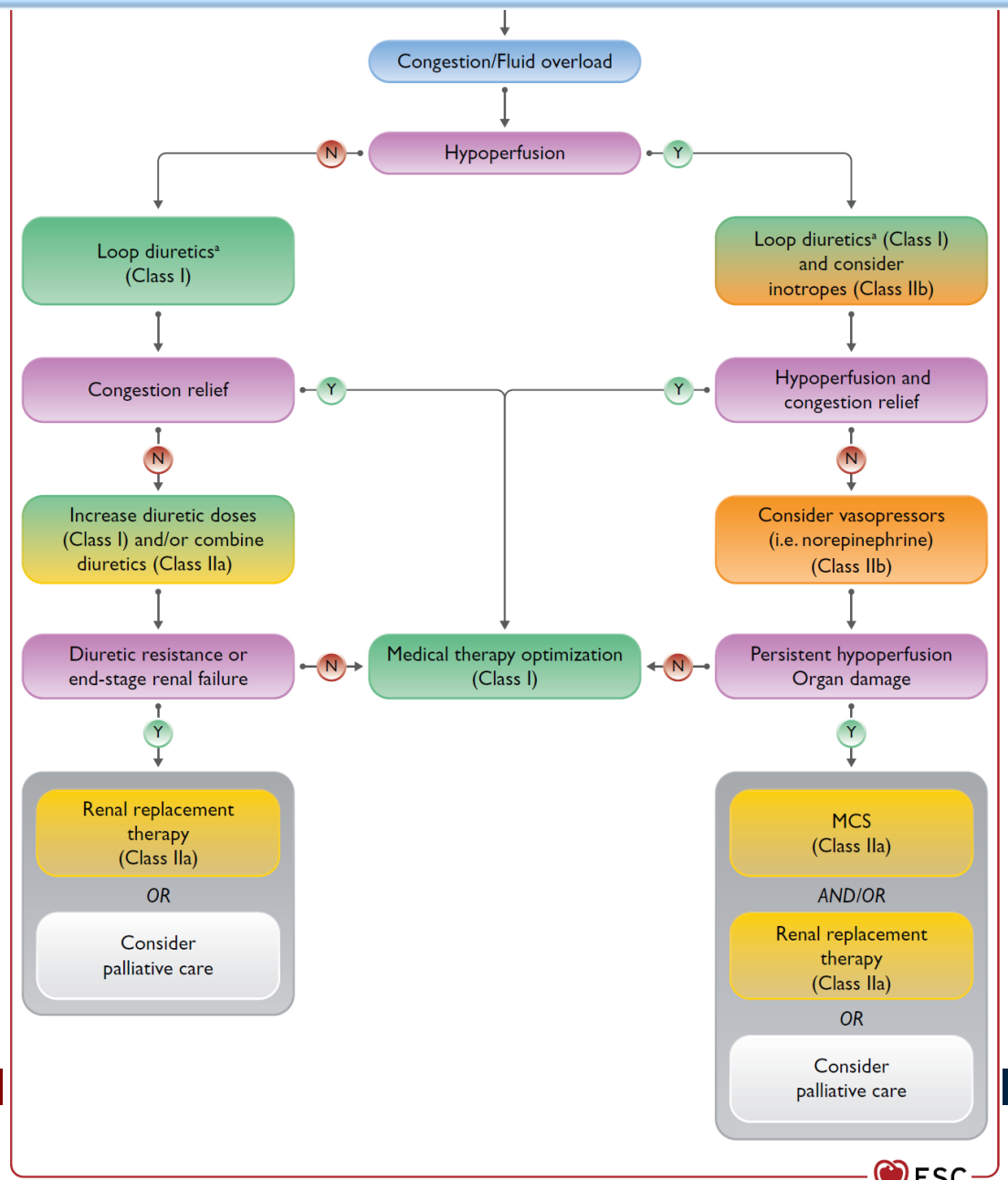
Efficacy and safety of dapagliflozin in acute heart failure: Rationale and design of the DICTATE-AHF trial

Zachary L Cox, PharmD [a,b], Sean P Collins, MD, MSc [c], Mark Aaron, MD [d], Gabriel A Hernandez, MD [e], A Thomas McRae III, MD [f], Beth T Davidson, DNP [f], Mike Fowler, MD [g], Christopher J Lindsell, PhD [h], Frank E Harrell Jr, PhD [h], Cathy A Jenkins, MS [h], Christina Kampe, MAcc [c], Karen F Miller, RN, MPA [c], William B Stubblefield, MD [c], and JoAnn Lindenfeld, MD [i] *Nashville, TN; and Jackson, MS*

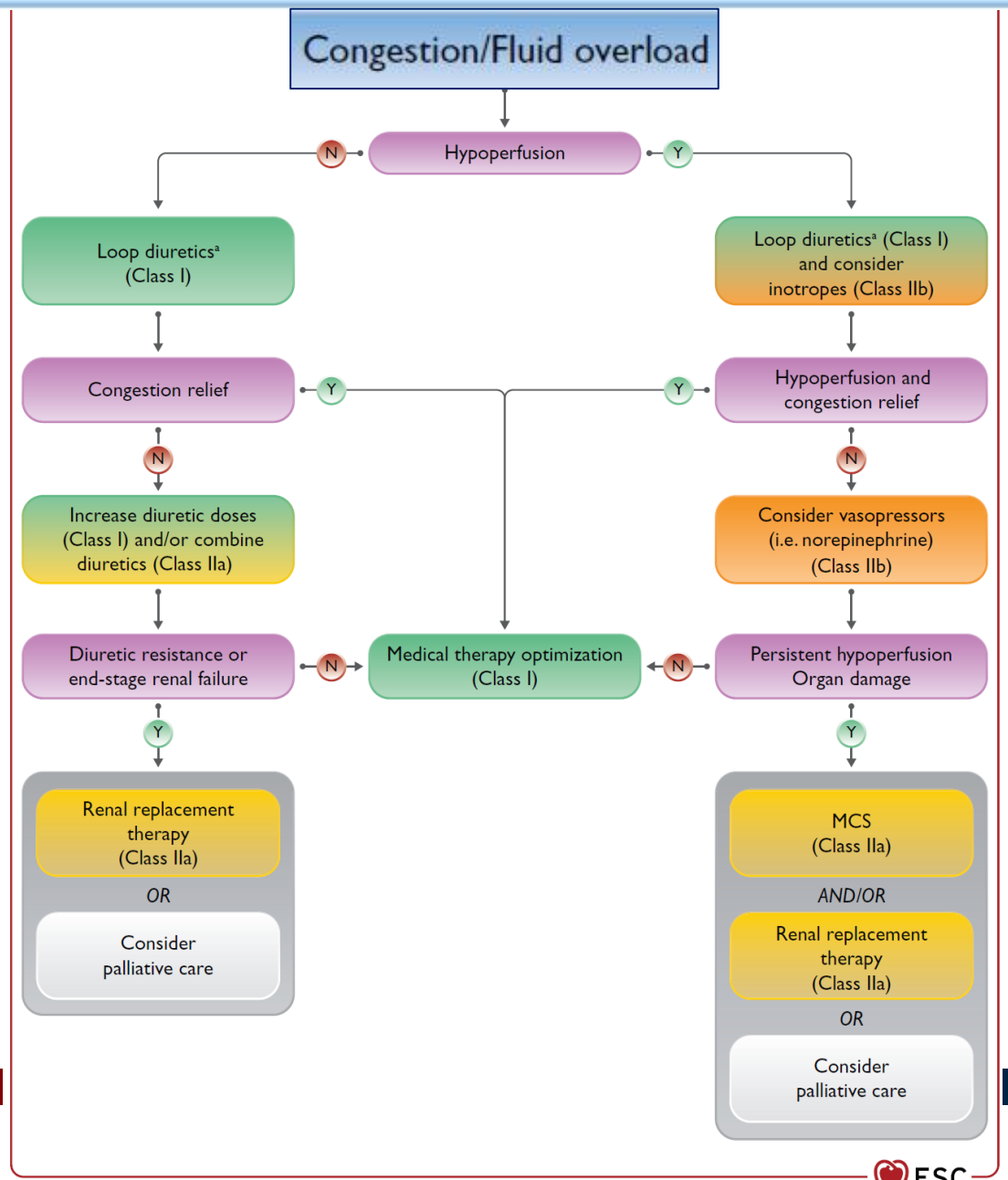
Am Heart J 2021;232:116–124.


Management of patients with suspected acute heart failure
Urgent phase after first medical contact
Cardiogenic shock and/or respiratory failure
Y
Pharmacological support
Ventilatory support
MCS
N
Identification of acute aetiology
Immediate phase (initial 60-120 min)
C acute Coronary syndrome
H Hypertension emergency
A Arrhythmia
M Mechanical cause[a]
P Pulmonary embolism
I Infections
T Tamponade
Y
Immediate initiation of specific treatment
N
Further treatment[b]

Management of patients with acute decompensated heart failure

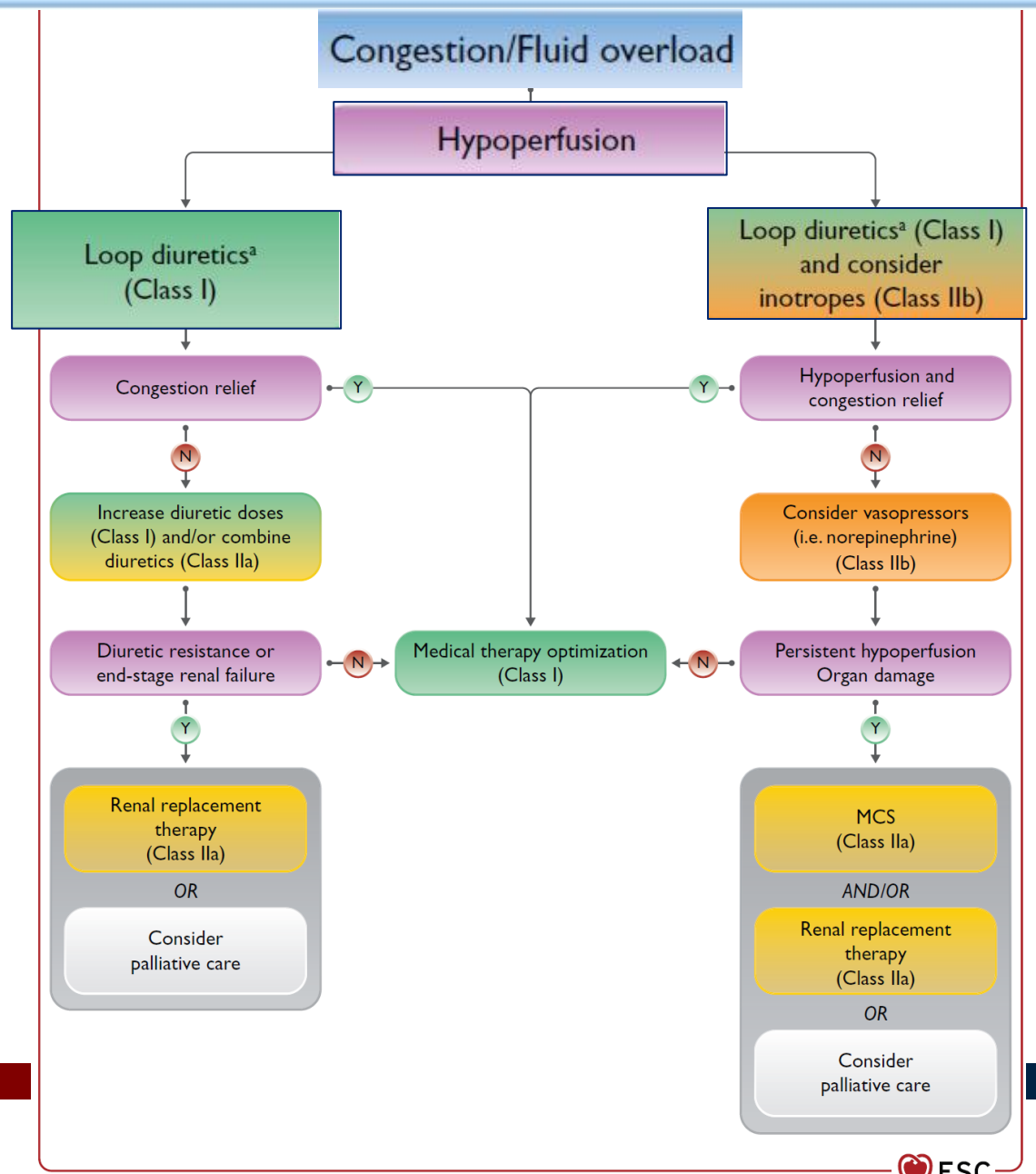


Management of patients with acute decompensated heart failure

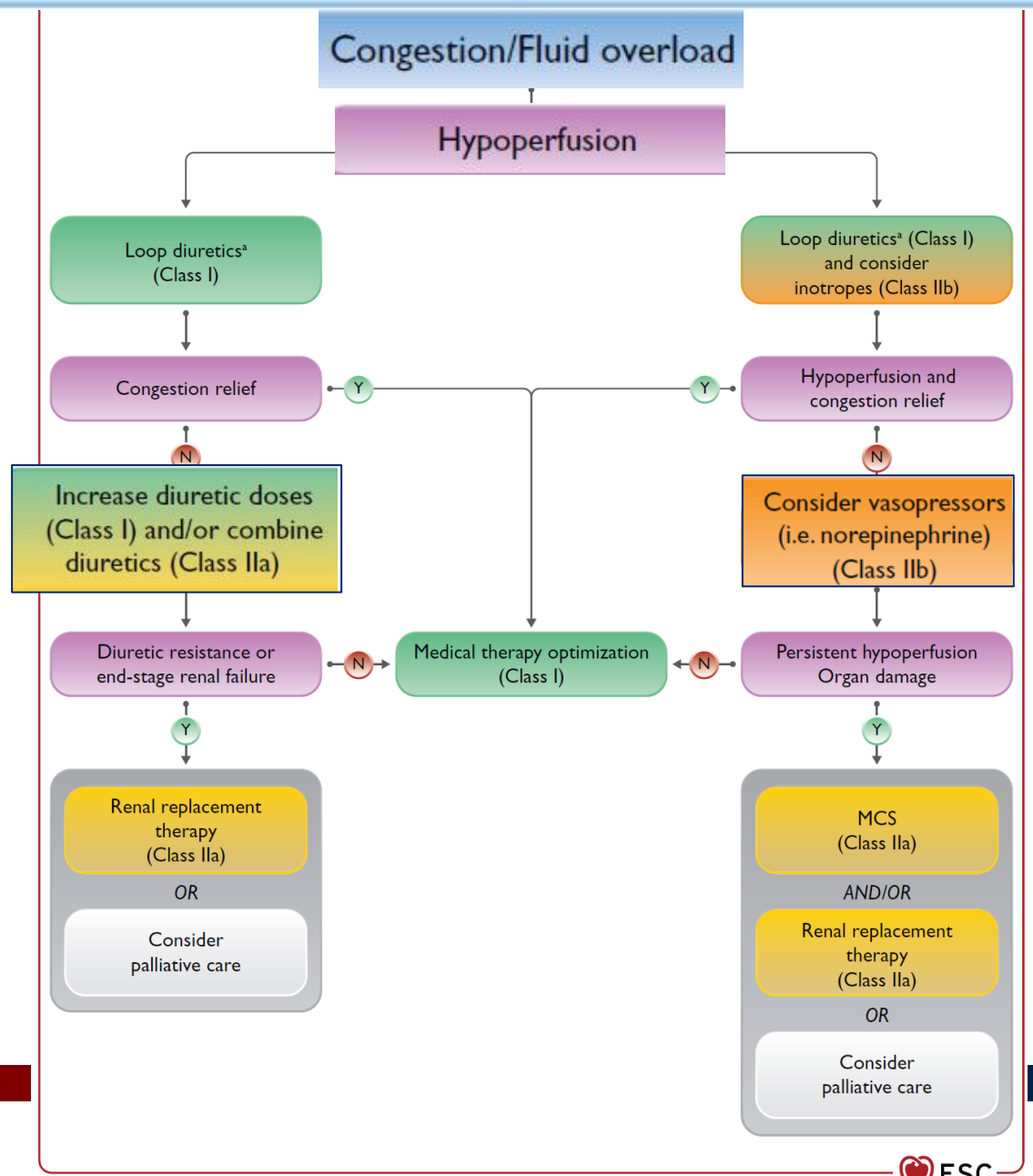


ESC

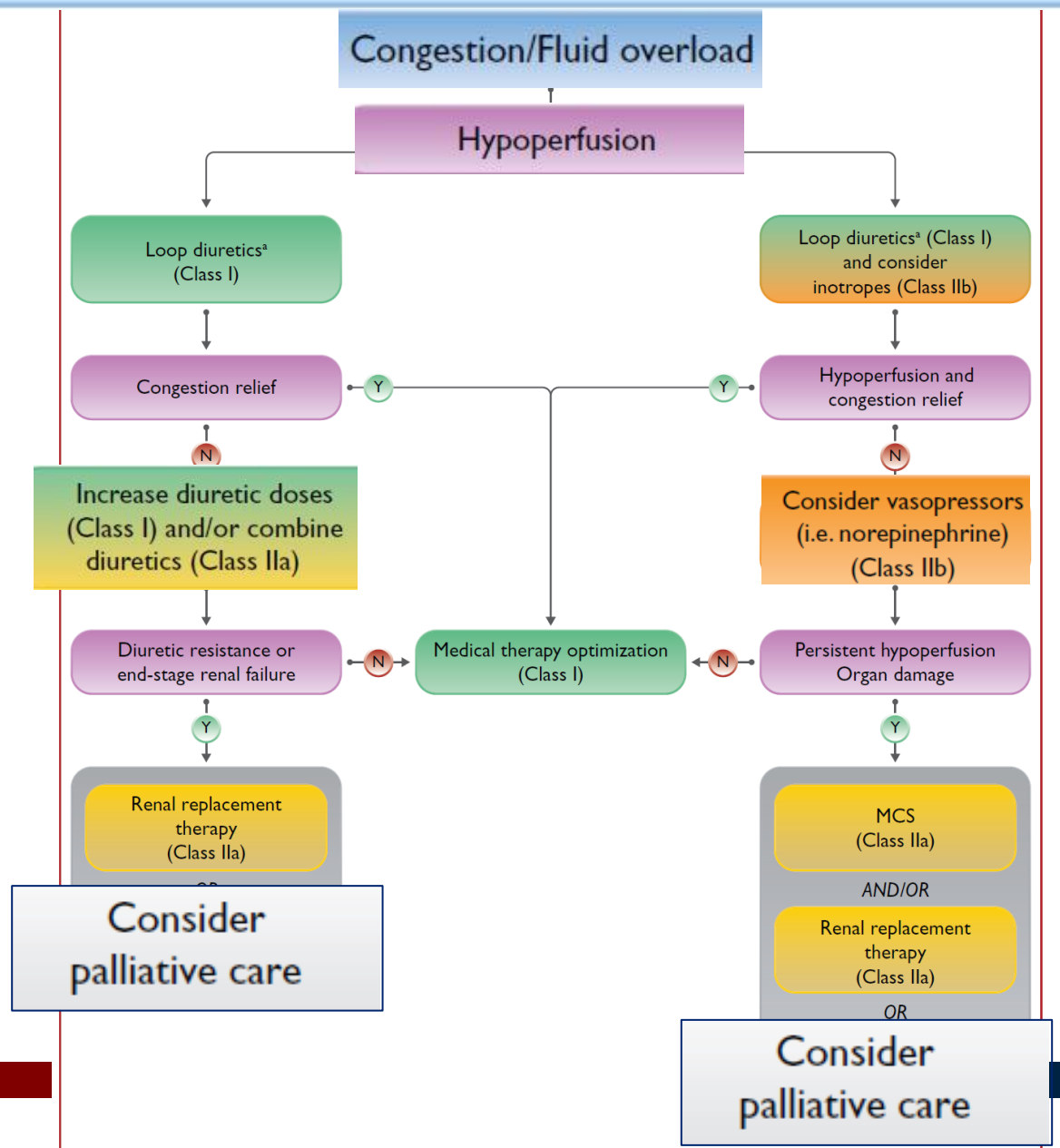
Management of patients with acute decompensated heart failure



Management of patients with acute decompensated heart failure



Management of patients with acute decompensated heart failure



Thank you……

ebirati@pmc.gov.il
054-9188639

Cardiogenic Shock – Definition

Clinical Criteria

SBP <90 mm Hg for >30 min:
a. Or mean BP <60 mm Hg for >30 min
b. Or requirement of vasopressors to maintain sys BP ≥90 mm Hg or mean BP ≥60 mm Hg
Hypoperfusion defined by:
c. Decreased mentation
d. Cold extremities, livedo reticularis
e. Urine output <30 mL/h
f. Lactate >2 mmol/L

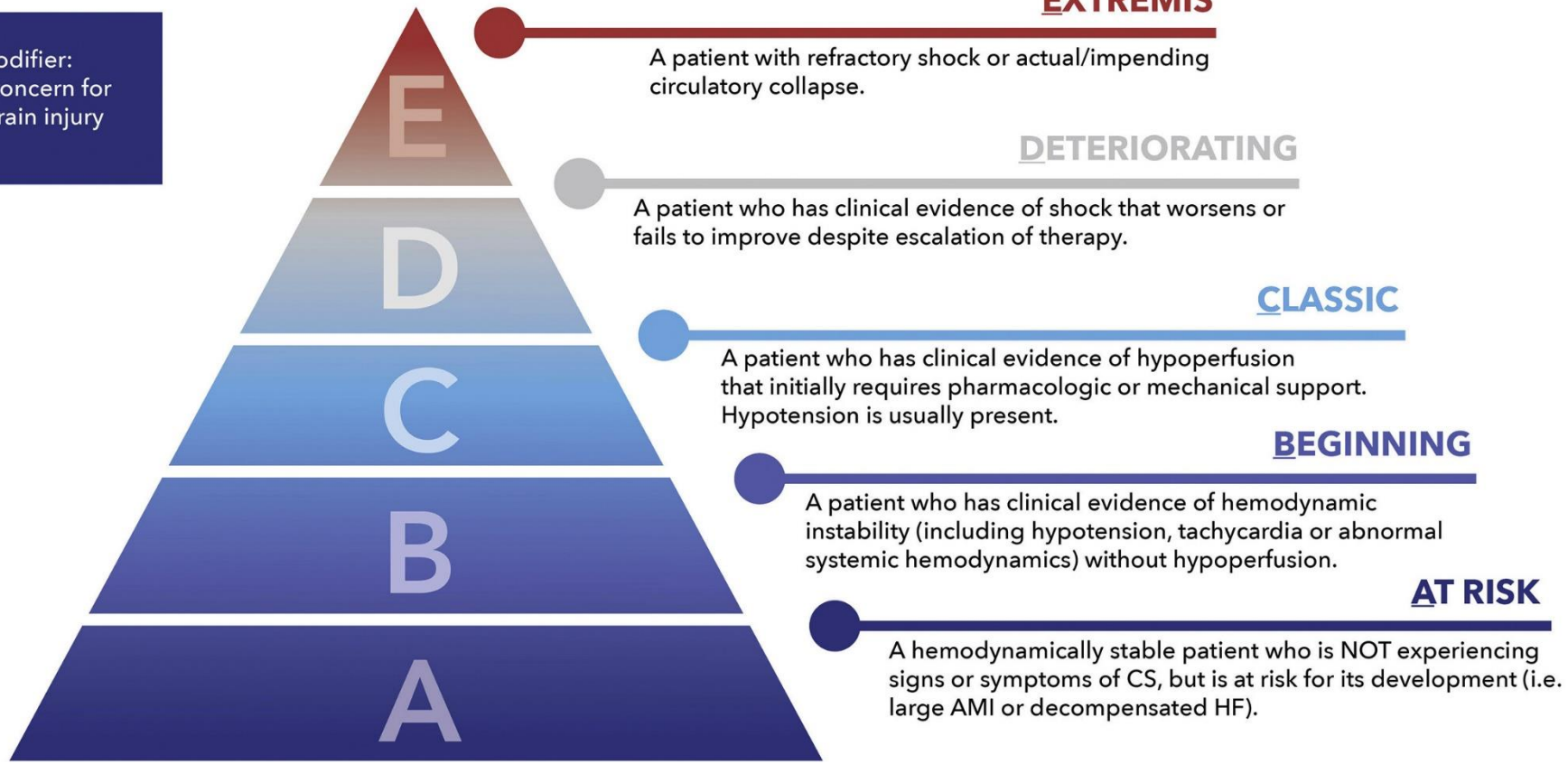
Hemodynamic Criteria

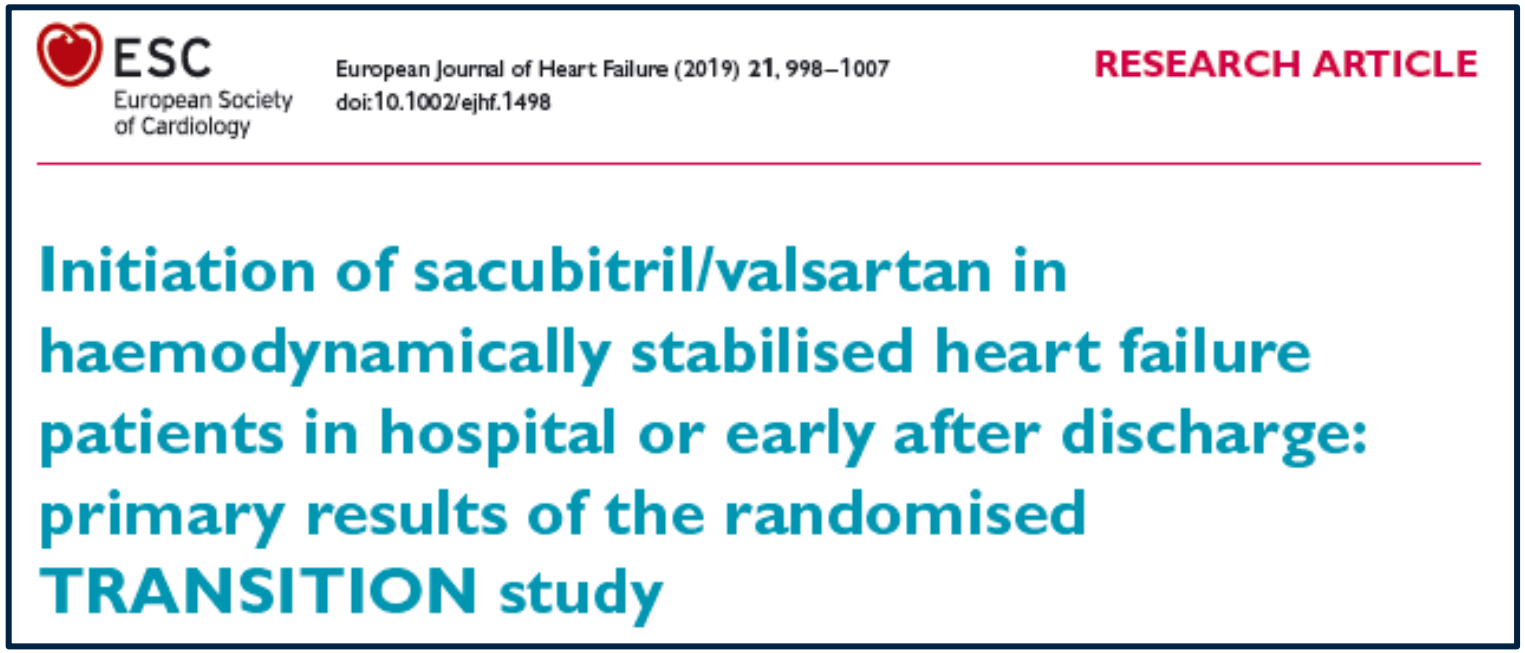
SBP <90 mm Hg or mean BP <60 mm Hg
2. Cardiac index <2.2 L/min/m^2
3. Pulmonary capillary wedge pressure >15 mm Hg
4. Other hemodynamic considerations a. Cardiac power output ([CO x MAP]/451) <0.6 W b. Shock index (HR/systolic BP) >1.0 c. RV shock i. Pulmonary artery pulse index [(PASP-PADP)/CVP] <1.0 ii. CVP >15 mm Hg iii. CVP-PCW >0.6

Circulation. 2022;145:e895–e1032

SCAI stages

(A) Modifier:
CA with concern for anoxic brain injury

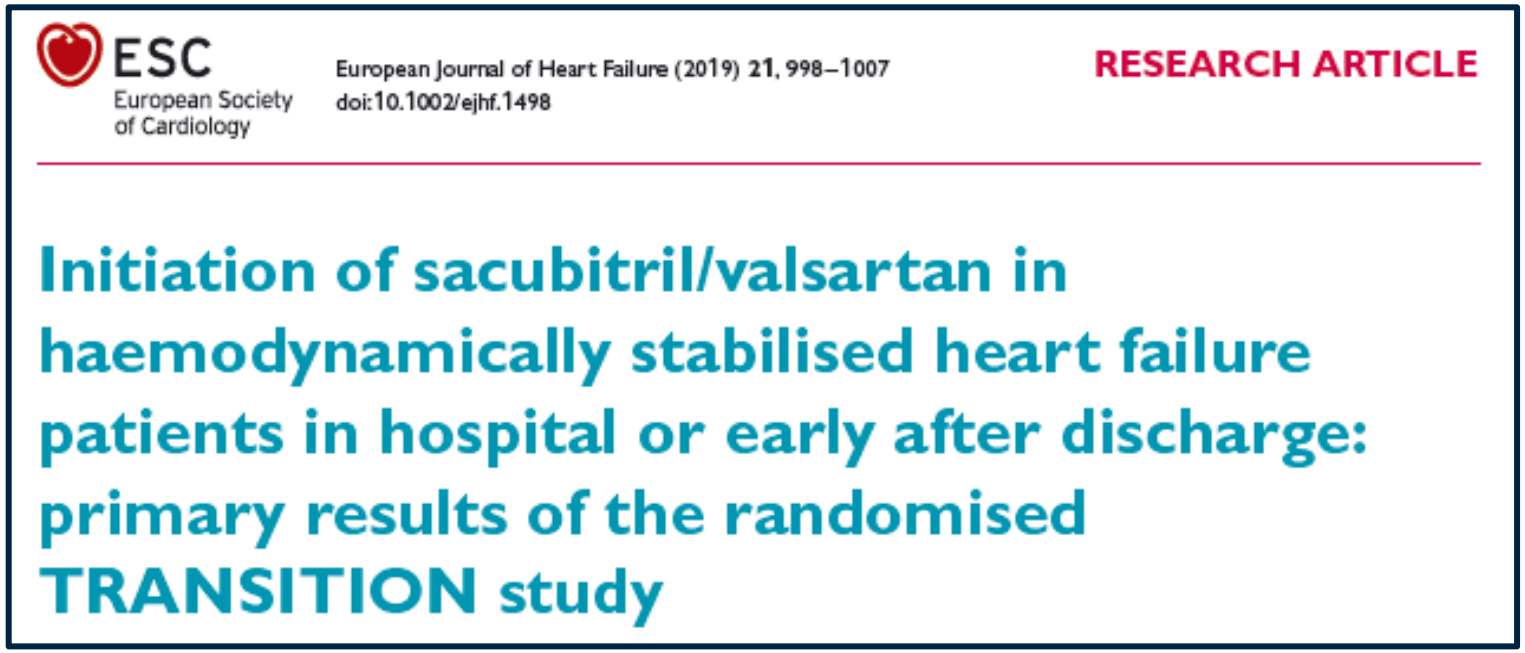




Inclusion Criteria:

- Hospitalized for an episode of ADHF (de novo HF or due to exacerbation of chronic HF), with New York Heart Association (NYHA) class II–IV, blood pressure ≥100 mmHg and left-ventricular ejection fraction (LVEF) ≤40%

European Journal of Heart Failure (2019) 21, 998–1007



- Randomized 1:1 to start sacubitril/valsartan either pre- or post-discharge
  - Pre-discharge group received the first dose of sacubitril/valsartan no later than 12 h before discharge and ≤7 days after randomisation
  - Post-discharge group received the first dose of sacubitril/valsartan at any time between days 1 and 14 post-discharge

European Journal of Heart Failure (2019) 21, 998–1007

Drug	Infusion rate
Dobutamine	2–20 μg/kg/min (beta+)
Dopamine	3–5 μg/kg/min; inotropic (beta+) >5 μg/kg/min: inotropic (beta+), vasopressor (alpha+)
Milrinone	0.375–0.75 μg/kg/min
Enoximone	5–20 μg/kg/min
Levosimendan	0.1 μg/kg/min, which can be decreased to 0.05 or increased to 0.2 μg/kg/min
Norepinephrine	0.2–1.0 μg/kg/min
Epinephrine	0.05–0.5 μg/kg/min

JACC: Heart Failure
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 1, No. 2, 2013
ISSN 2213-1779/$36.00
http://dx.doi.org/10.1016/j.jchf.2012.12.004

CLINICAL RESEARCH

Effect of Levosimendan on the Short-Term Clinical Course of Patients With Acutely Decompensated Heart Failure

Milton Packer, MD,* Wilson Colucci, MD,† Lloyd Fisher, PHD,‡ Barry M. Massie, MD,§ John R. Teerlink, MD,§ James Young, MD,‖ Robert J. Padley, MD,¶ Roopal Thakkar, MD,¶ Leticia Delgado-Herrera, RPH,¶ Jeffrey Salon, MD,¶ Chris Garratt, MB, CHB,# Bidan Huang, PHD,¶ Toni Sarapohja, MSC,# for the REVIVE Heart Failure Study Group

Dallas, Texas; Boston, Massachusetts; Seattle, Washington; San Francisco, California; Cleveland, Ohio; Abbott Park, Illinois; and Espoo, Finland

- The REVIVE I and II trials enrolled 700 patients who were hospitalized for the treatment of ADHF and remained dyspneic at rest despite treatment with intravenous diuretics
- For the **primary endpoint** in both trials, the clinical course of each patient during the first 5 days was characterized as "**improved**," "**unchanged**," or "**worse**" – **Not significant**

J Am Coll Cardiol HF 2013;1:103–11

REVIVE trial

- Secondary endpoint

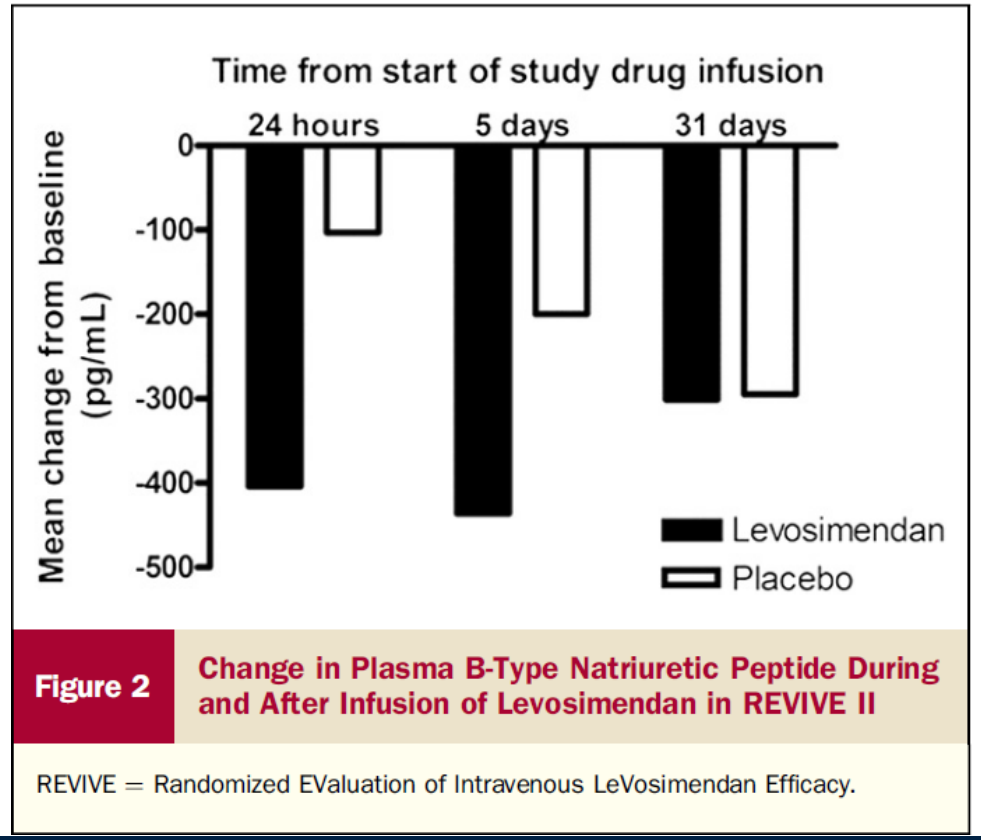
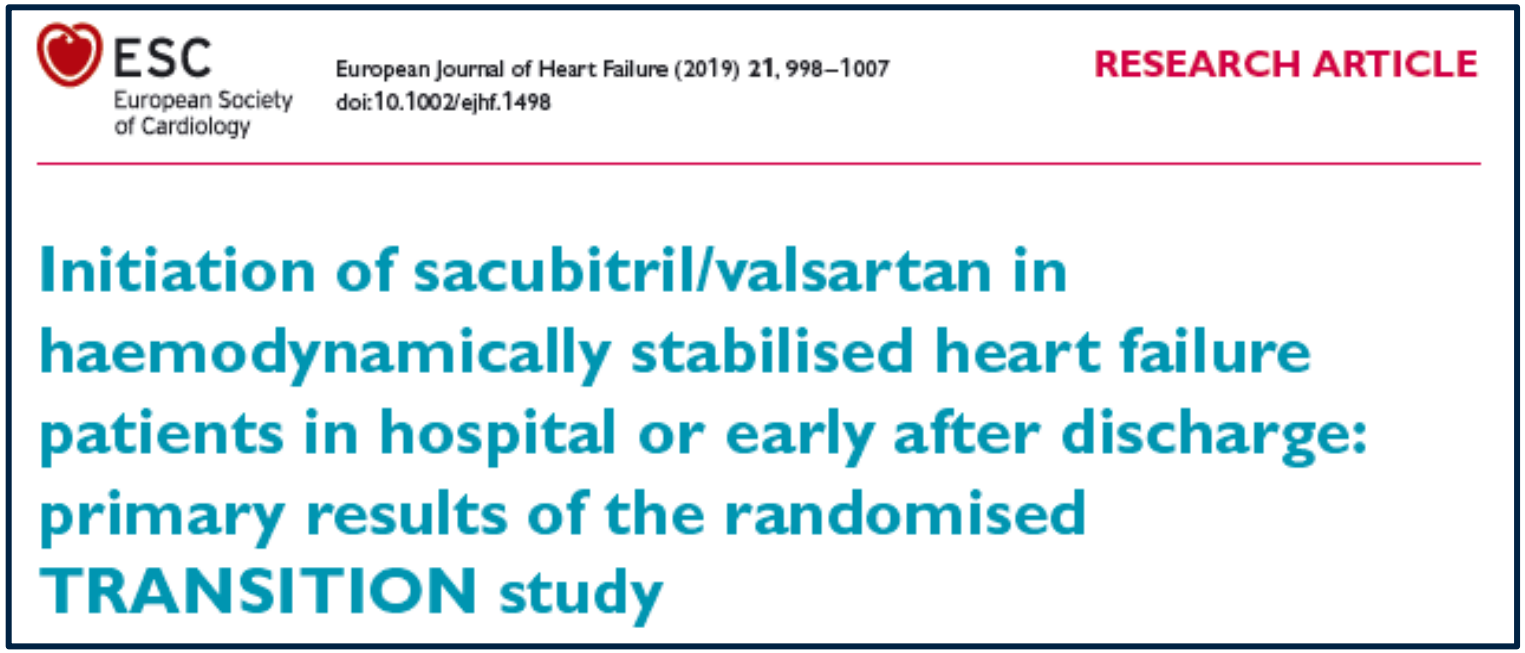


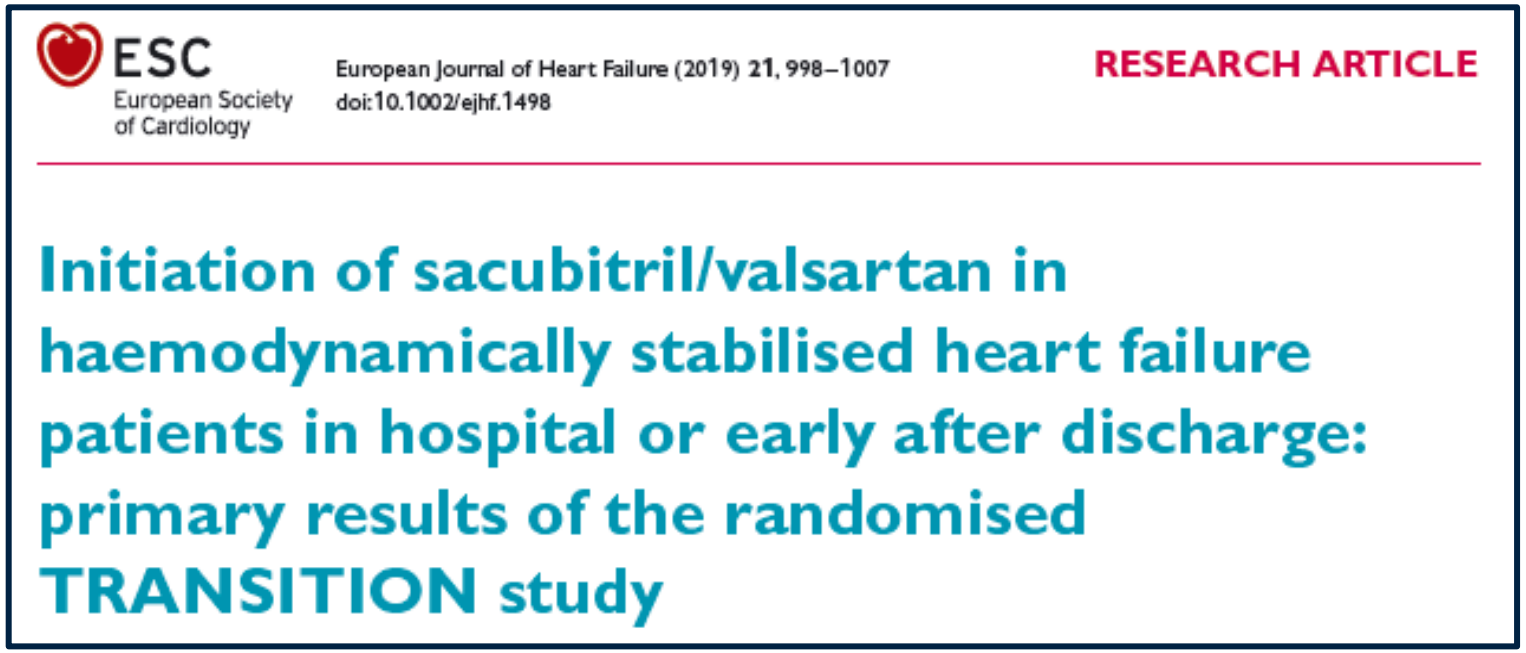
Figure 2 **Change in Plasma B-Type Natriuretic Peptide During and After Infusion of Levosimendan in REVIVE II**

REVIVE = Randomized EValuation of Intravenous LeVosimendan Efficacy.



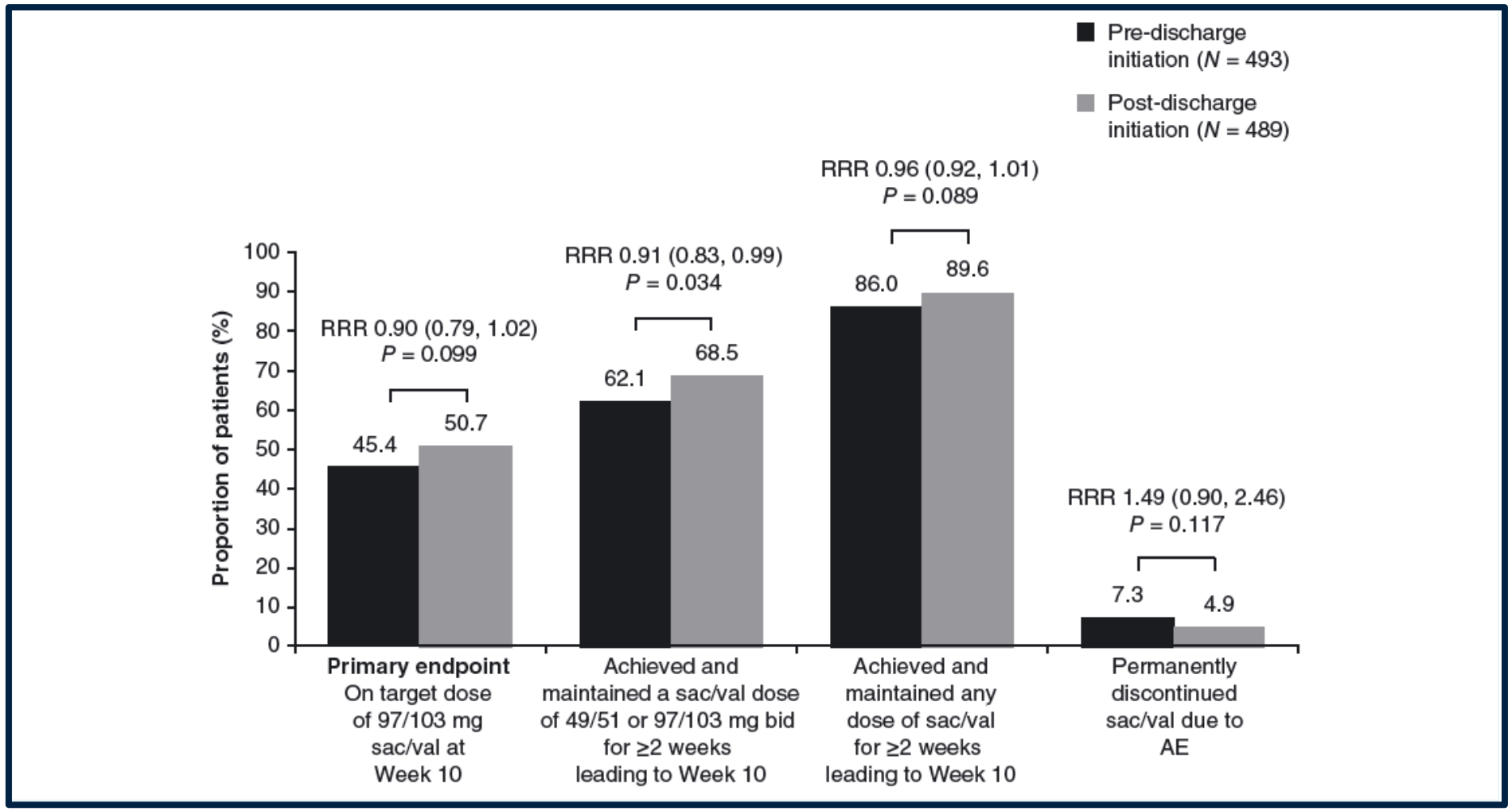
- The primary endpoint was the proportion of patients attaining 97/103 mg bid target dose after 10 weeks

European Journal of Heart Failure (2019) 21, 998–1007



- 500 patients were randomized to pre-discharge initiation and 502 to post-discharge initiation
- Median time from admission to first dose of study drug was 7 days in the pre-discharge group and 10 days in the post-discharge group
- The target dose of sacubitril/valsartan was reached in about 48% of patients

European Journal of Heart Failure (2019) 21, 998–1007


Pre-discharge initiation (N = 493)
Post-discharge initiation (N = 489)
Proportion of patients (%)
100
90
80
70
60
50
40
30
20
10
0
RRR 0.90 (0.79, 1.02)
P = 0.099
45.4
50.7
RRR 0.91 (0.83, 0.99)
P = 0.034
62.1
68.5
RRR 0.96 (0.92, 1.01)
P = 0.089
86.0
89.6
RRR 1.49 (0.90, 2.46)
P = 0.117
7.3
4.9
Primary endpoint
On target dose of 97/103 mg sac/val at Week 10
Achieved and maintained a sac/val dose of 49/51 or 97/103 mg bid for ≥2 weeks leading to Week 10
Achieved and maintained any dose of sac/val for ≥2 weeks leading to Week 10
Permanently discontinued sac/val due to AE

Summary of Adrenergic Agents

Drug	Mean Arterial Pressure (MAP)	Pulmonary Capillary Wedge Pressure (PCWP)	Cardiac Output (CO)	Systemic Vascular Resistance (SVR)	Heart Rate (HR)
Dobutamine	↓↔	↓↔	↑↑↑	↓	↑
Dopamine	↑↑ High	↑↔	↑↑	↓↔Low ↑↑ High	↑
Isoproterenol	↓↓	↓↓	↑↑↑	↓↓↓	↑↑↑
Norepinepherine	↑↑↑	↑↔	↑	↑↑↑	↑↔
Epinepherine	↑↑	↑↔	↑↑	↑	↑↑↑

Receptor Actions of Catecholamines

Adenoreceptor	Site	Action
Beta $_1$	Myocardium	Increase contractility
	Sinoatrial Node	Increase heart rate
	AV Node	Increase conduction
Beta$_2$	Arterioles	Vasodilation
	Lungs	Bronchodilation
Alpha	Periperal Arterioles	Vasoconstriction

Adrenergic Receptor Activity of Sympathomimetic Amines

Agent	Alpha Peripheral	$Beta_1$ Cardiac	$Beta_2$ Peripheral
Norepinepherine	++++	++++	0
Epinipherine	++++	++++	++
Dopamine	++++	++++	++
Isoproterenol	0	++++	++++
Dobutamine	+	++++	+