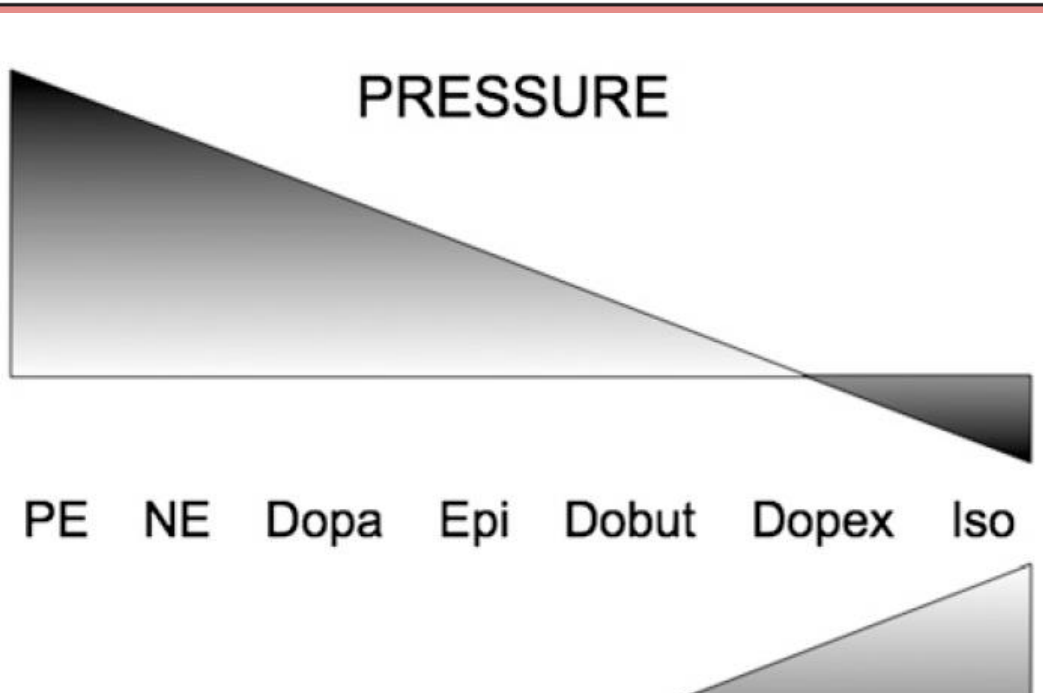
Inotropi e vasopressori nel paziente con SCA

Giovanni Chiarini

Inotropi e vasopressori

Medication	Mecha	HR	CO	SVR
Dobutamine	β1 > β2	↑	↑↑	↓
Milrinone	PDE-3 i	↑	↑↑	↓↓
Levosimendan	Calciun	0	↑↑	↓↓
Epinephrine	β1 = β2	↑	↑↑↑	↓
Norepinephrine	β1 > α	0 or ↓	0	↑↑
Dopamine	Modera	↑	↑↑	0 or ↓
Dopamine	High do	↑↑	↑	↑↑
Phenylephrine	α1	↓	↓	↑
Vasopressin	V1	0	0	↑↑



CURRENT OPINION

Pharmacologic therapies for acute cardiogenic shock

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Concise Clinical Review

Vasoactive Drugs in Circulatory Shock

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Inotropi e vasopressori: AHA STEMI

Compared with IABP, LV assist devices may provide superior hemodynamic support and serve as more effective bridges to recovery or transplantation, though experience with their use in this setting is limited.[463,464] Medical support with inotropes and vasopressor agents should be individualized and guided by invasive hemodynamic monitoring. Use of dopamine in this setting may be associated with excess hazard.[465]

may be considered in patients with refractory cardiogenic shock. (*Level of Evidence: C*)

Cardiogenic shock in patients with STEMI may be caused by extensive LV infarction or by mechanical complications, including papillary muscle rupture, ventricular septal rupture, free-wall rupture with tamponade, and RV infarction. The onset of cardiogenic shock due to mechanical compli-

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465. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med. 2010;362:779–89.

ies can be justified. In the SHOCK trial, mortality rates at 6 and 1 year were significantly lower in patients allocated to emergency revascularization than in patients who received immediate medical stabilization.[212,354] Nearly two thirds of the patients in the medical stabilization group received

Inotropi e vasopressori: ESC STEMI

Similarly, vasopressors and inotropes are used due to their favourable haemodynamic effects, but none have produced consistent symptomatic improvement and many induced a reduction in survival that may be associated with the deleterious cellular effects of these drugs.[299] A recent randomized trial compared norepinephrine with dopamine in 1679 patients with shock, including 280 with cardiogenic shock. Dopamine was associated with higher mortality in the cardiogenic shock subgroup and more adverse events—mainly arrhythmic events—for the overall cohort.[300] Therefore, when blood pressure is low, norepinephrine should be the first choice. It should be used at the lowest possible dose and titrated until the systolic arterial pressure rises to at least 80 mmHg. Subsequently—and because its beta-2-adrenergic effect—dobutamine can be given simultaneously to improve contractility.

represents an alternative for patients on chronic beta-blocker th
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cially in patients with hyponatraemia.

300. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, Brasseur A, Defrance P, Gottignies P, Vincent JL. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010;**362**:779–789.

Inotropi e vasopressori: ESC STEMI

Recommendations	Class [a]	Level [b]	Ref [c]
Treatment of cardiogenic shock (Killip class IV)			
Oxygen/mechanical respiratory support is indicated according to blood gasses.	I	C	-
Urgent echocardiography/Doppler must be performed to detect mechanical complications, assess systolic function and loading conditions.	I	C	-
High-risk patients must be transferred early to tertiary centres.	I	C	-
Emergency revascularization with either PCI or CABG in suitable patients must be considered.	I	B	100
Fibrinolysis should be considered if revascularization is unavailable.	IIa	C	-
Intra-aortic balloon pumping may be considered.	IIb	B	1, 98, 305
LV assist devices may be considered for circulatory support in patients in refractory shock.	IIb	C	-
Haemodynamic assessment with balloon floating catheter may be considered.	IIb	B	316
Inotropic/vasopressor agents should be considered: • Dopamine	IIa	C	-
• Dobutamine	IIa	C	-
• Norepinephrine (preferred over dopamine when blood pressure is low).	IIb	B	300, 317
Early revascularization must be considered if the patient has not been previously revascularized.	I	C	-

Inotropi e vasopressori: AHA NSTEMI

7.2.2. Cardiogenic Shock: Recommendation

Class I

1. **Early revascularization is recommended in suitable**

patients with NSTEMI, suggesting the presence of true posterior MI.[595] Dopamine in patients with cardiogenic shock may be associated with increased mortality compared with norepinephrine.[596] The use of percutaneous ventricular assist devices

Dopamine in patients with cardiogenic shock may be associated with increased mortality compared with norepinephrine.[596]

amenable to PCI, and at the time of surgical repair of a mechanical defect (eg, septal, papillary muscle, free-wall rupture). Age alone is not a contraindication to urgent revascularization for cardiogenic shock.[589,590] Mortality after cardiogenic shock has steadily improved,[591] including in older adults,[589,590] with 30-day mortality ranging from approximately 40% with milder forms of shock[268] to >45% with refractory shock.[592] Approximately 30% of patients in the IABP-SHOCK (Intra-Aortic Balloon Pump in Cardiogenic Shock) II trial presented with NSTEMI,[368] and 22% of patients in the TRIUMPH (Tilarginine Acetate Injection in a Randomized International Study in Unstable Acute Myocardial

596. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med. 2010;362:779–89.

underwent cardiac catheterization, and in-hospital revascularization was performed in 47% of this group.

In-hospital mortality of all patients with shock was 59%.[594] Patients with NSTEMI developed cardiogenic shock later than patients with STEMI, and had higher-risk clinical characteristics, more extensive CAD, and more recurrent ischemia and infarction before developing shock compared with patients with STEMI, and shock developed later in patients with NSTEMI.[151] Patients with NSTEMI constituted >17% of those in the SHOCK trial registry.[595] They were also older and had more comorbidities but had comparable mortality to patients with STEMI. The left circumflex coronary artery was the culprit vessel in 30% of

Inotropi e vasopressori: AHA HF

Parenteral inotropes, however, remain as an option to help the subset of patients with HF who are refractory to other therapies and are suffering consequences from end-organ hypoperfusion. Inotropes should be considered only in such patients with systolic dysfunction who have low cardiac index and evidence of systemic hypoperfusion and/or congestion (Table 26).

Table 26. Intravenous Inotropic Agents Used in Management of HF

Inotropic Agent	Dose (mcg/kg) Bolus	Dose (mcg/kg) Infusion (/min)	Drug Kinetics and Metabolism	Effects CO	Effects HR	Effects SVR	Effects PVR	Adverse Effects	Special Considerations
Adrenergic agonists									
Dopamine	N/A	5 to 10	$t_{1/2}$: 2 to 20 min R,H,P	↑	↑	↔	↔	T, HA, N, tissue necrosis	Caution: MAO-I
	N/A	10 to 15		↑	↑	↑	↔		
Dobutamine	N/A	2.5 to 5	$t_{1/2}$: 2 to 3 min H	↑	↑	↓	↔	↑/↓BP, HA, T, N, F, hypersensitivity	Caution: MAO-I; CI: sulfite allergy
	N/A	5 to 20		↑	↑	↔	↔		
PDE inhibitor									
Milrinone	N/R	0.125 to 0.75	$t_{1/2}$: 2.5 h H	↑	↑	↓	↓	T, ↓BP	Renal dosing, monitor LFTs

BP indicates blood pressure; CI, contraindication; CO, cardiac output; F, fever; H, hepatic; HA, headache; HF, heart failure; HR, heart rate; LFT, liver function test; MAO-I, monoamine oxidase inhibitor; N, nausea; N/A, not applicable; N/R, not recommended; P, plasma; PDE, phosphodiesterase; PVR, pulmonary vascular resistance; R, renal; SVR, systemic vascular resistance; T, tachyarrhythmias; and $t_{1/2}$, elimination half-life.

Inotropi e vasopressori: ESC HF

Inotropes

Use of an inotrope such as dobutamine (*Table 21*) should usually be reserved for patients with such severe reduction in cardiac output that vital organ perfusion is compromised. Such patients are almost always hypotensive ('shocked'). Inotropes cause sinus tachycardia and may induce myocardial ischaemia and arrhythmias. There is long-standing concern that they may increase mortality. There is pharmacological rationale to use levosimendan (or a phosphodiesterase III inhibitor such as milrinone) if it is felt necessary to counteract the effect of a beta-blocker.

Vasopressors

Drugs with prominent peripheral arterial vasoconstrictor action such as norepinephrine (*Table 21*) are sometimes given to severely ill patients with marked hypotension. These agents are given to raise blood pressure and redistribute cardiac output from the extremities to the vital organs. However, this is at the expense of an increase in LV afterload, and these agents have adverse effects similar to those of inotropes (and the most commonly used of these agents, norepinephrine and epinephrine, have inotropic activity). Their use should be restricted to patients with persistent hypoperfusion despite adequate cardiac filling pressures.

Dopamine

In large doses (>5 μg/kg/min) dopamine has inotropic and vasoconstrictor activity. At lower doses (<3 μg/kg/min) dopamine may have a selective renal arterial vasodilator activity and promote natriuresis, although this is uncertain. Dopamine may cause hypoxaemia.[229] Arterial oxygen saturation should be monitored, and supplemental oxygen administrated as required.

Table 21 Drugs used to treat acute heart failure that are positive inotropes or vasopressors or both

	Bolus	Infusion rate
Dobutamine	No	2–20 μg/kg/min (β+)
Dopamine	No	<3 μg/kg/min: renal effect (δ+)
		3–5 μg/kg/min; inotropic (β+)
		>5 μg/kg/min: (β+), vasopressor (α+)
Milrinone	25–75 μg/kg over 10–20 min	0.375–0.75 μg/kg/min
Enoximone	0.5–1.0 mg/kg over 5–10 min	5–20 μg/kg/min
Levosimedan[a]	12 μg/kg over 10 min (optional)[b]	0.1 μg/kg/min, which can be decreased to 0.05 or increased to 0.2 μg/kg/min
Norepinephrine	No	0.2–1.0 μg/kg/min
Epinephrine	Bolus: 1 mg can be given i.v. during resuscitation, repeated every 3–5 min	0.05–0.5 μg/kg/min

[a]Also a vasodilator.

[b]Bolus not recommended in hypotensive patients (systolic blood pressure <90 mmHg).

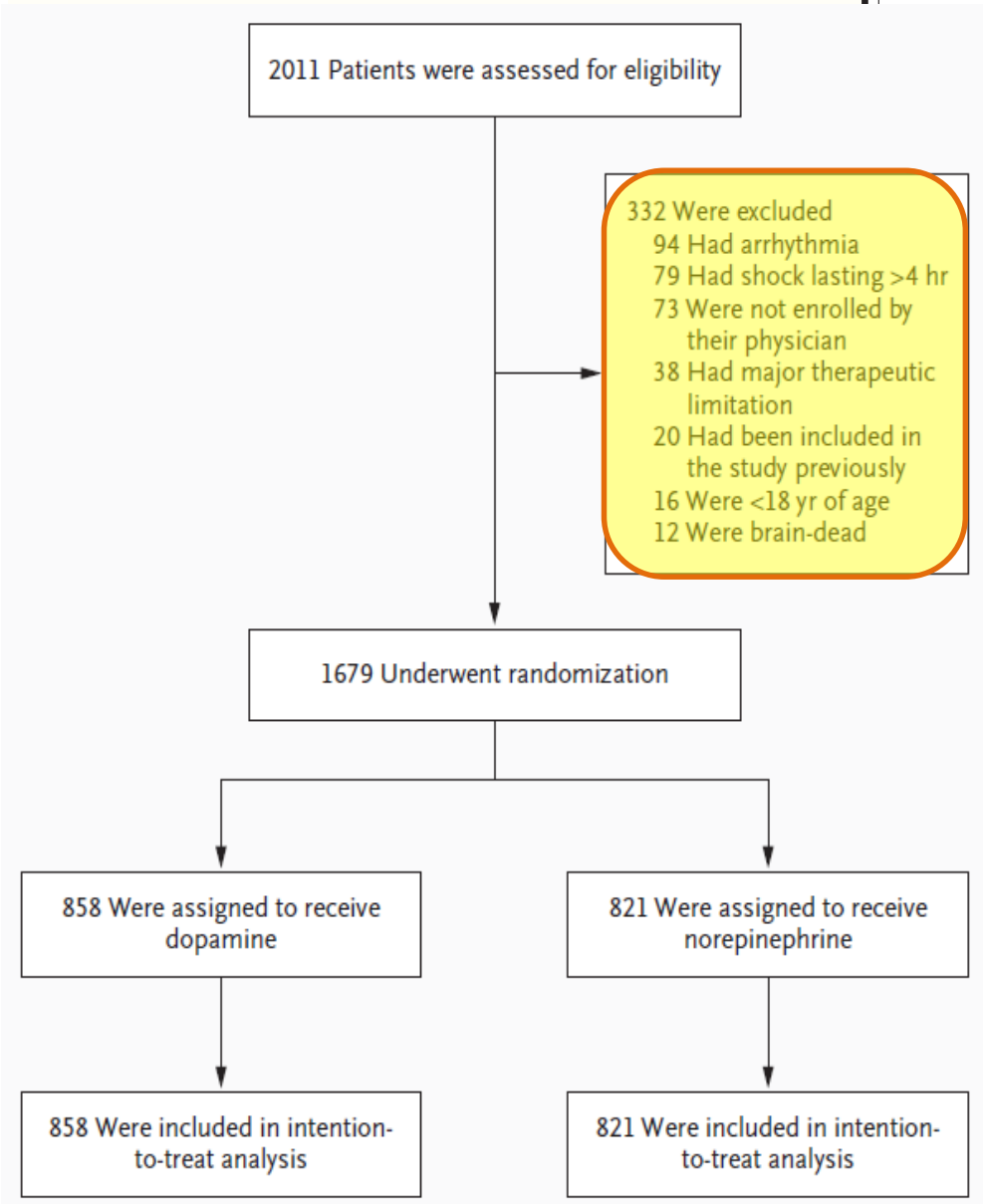
α = alpha adrenoceptor; β = beta adrenoceptor; δ = dopamine receptor.

Noradrenalina vs Dopamina

The NEW ENGLAND

STUDY PATIENTS

We conducted this multicenter trial between December 19, 2003, and October 6, 2007, in eight centers in Belgium, Austria, and Spain. All patients 18 years of age or older in whom a vasopressor agent was required for the treatment of shock were included in the study. The patient was considered to be in shock if the mean arterial pressure was less than 70 mm Hg or the systolic blood pressure was less than 100 mm Hg despite the fact that an adequate amount of fluids (at least 1000 ml of crystalloids or 500 ml of colloids) had been administered (unless there was an elevation in the central venous pressure to >12 mm Hg or in pulmonary-artery occlusion pressure to >14 mm Hg) and if there were signs of tissue hypoperfusion (e.g., altered mental state, mottled skin, urine output of <0.5 ml per kilogram of body weight for 1 hour, or a serum lactate level of >2 mmol per liter). Patients were excluded if they were younger than 18 years of age; had already received a vasopressor agent (dopamine, norepinephrine, epinephrine, or phenylephrine) for more than 4 hours during the current episode of shock; had a serious arrhythmia, such as rapid atrial fibrillation (>160 beats per minute) or ventricular tachycardia; or had been declared brain-dead.



Noradrenalina vs Dopamina

Cause of shock — no. (%)		
Sepsis	542 (63.2)	502 (61.1)
Lungs	278 (32.4)	246 (30.0)
Abdomen	138 (16.1)	135 (16.4)
Urine	51 (5.9)	42 (5.1)
Catheter	14 (1.6)	10 (1.2)
Endocardium	9 (1.0)	11 (1.3)
Mediastinum	10 (1.2)	15 (1.8)
Soft tissues	11 (1.3)	13 (1.6)
Other	15 (1.7)	20 (2.4)
Cardiogenic source	135 (15.7)	145 (17.6)
Myocardial infarction	75 (8.7)	86 (10.5)
Dilated cardiomyopathy	25 (2.9)	19 (2.3)
Tamponade	2 (0.2)	7 (0.9)
Pulmonary embolism	10 (1.2)	8 (1.0)
Valvular disease	4 (0.5)	5 (0.6)
After cardiopulmonary bypass	19 (2.2)	20 (2.4)
Other		
Hypovolemia	138 (16.1)	125 (15.2)
Hemorrhage	130 (15.2)	116 (14.1)
Trauma	17 (2.0)	23 (2.8)
Gastrointestinal bleeding	31 (3.6)	22 (2.7)
Bleeding at surgical site	64 (7.5)	57 (6.9)
Other	18 (2.1)	14 (1.7)
Dehydration	8 (0.9)	9 (1.1)
Other	48 (5.9)	44 (5.0)
Spinal	6 (0.7)	8 (1.0)
Peridural§	13 (1.5)	4 (0.5)
Intoxication-related¶	7 (0.8)	4 (0.5)
Anaphylactic	3 (0.3)	4 (0.5)
Miscellaneous	13 (1.5)	29 (3.5)

60% SHOCK SETTICO

16% SHOCK CARDIOGENO

15% SHOCK IPOVOLEMICO

Noradrenalina vs Dopamina

Table 2. Mortality Rates.*

Time Period	Dopamine	Norepinephrine	Odds Ratio (95% CI)†	P Value
	percent mortality			
During stay in intensive care unit	50.2	45.9	1.19 (0.98–1.44)	0.07
During hospital stay	59.4	56.6	1.12 (0.92–1.37)	0.24
At 28 days	52.5	48.5	1.17 (0.97–1.42)	0.10
At 6 mo	63.8	62.9	1.06 (0.86–1.31)	0.71
At 12 mo	65.9	63.0	1.15 (0.91–1.46)	0.34

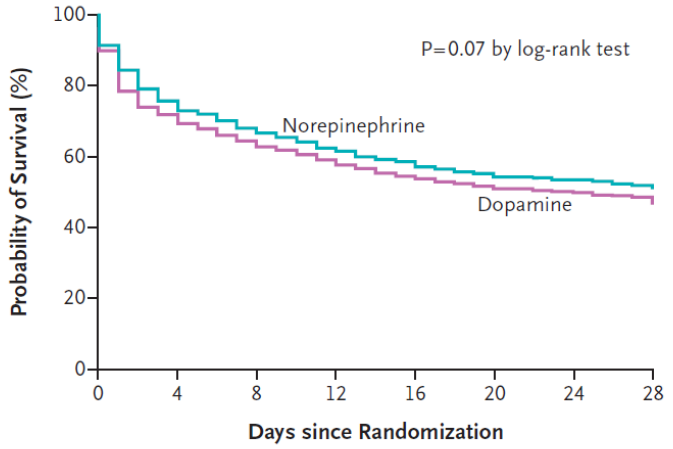


Figure 2. Kaplan–Meier Curves for 28-Day Survival in the Intention-to-Treat Population.

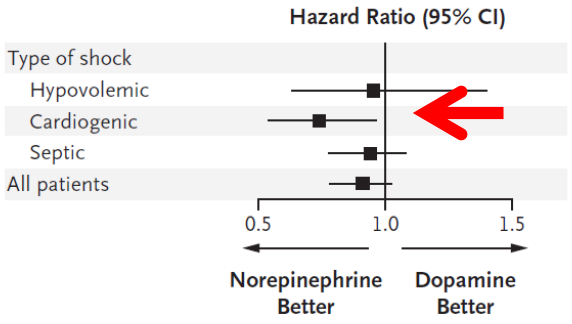


Figure 3. Forest Plot for Predefined Subgroup Analysis According to Type of Shock.

A total of 1044 patients were in septic shock (542 in the dopamine group and 502 in the norepinephrine group), 280 were in cardiogenic shock (135 in the dopamine group and 145 in the norepinephrine group), and 263 were in hypovolemic shock (138 in the dopamine group and 125 in the norepinephrine group). The P value for interaction was 0.87.

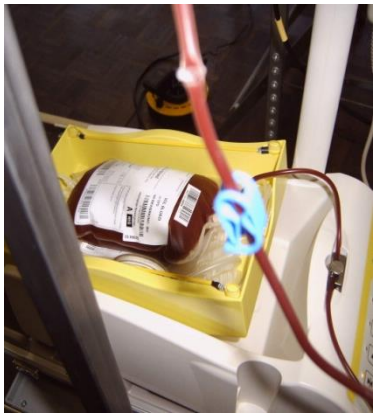
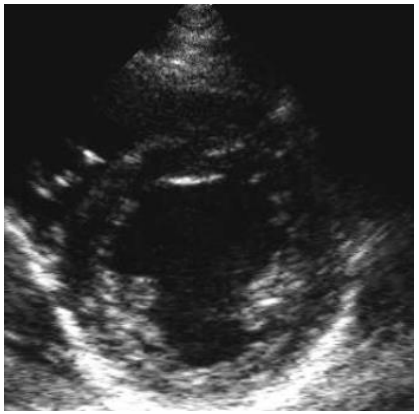
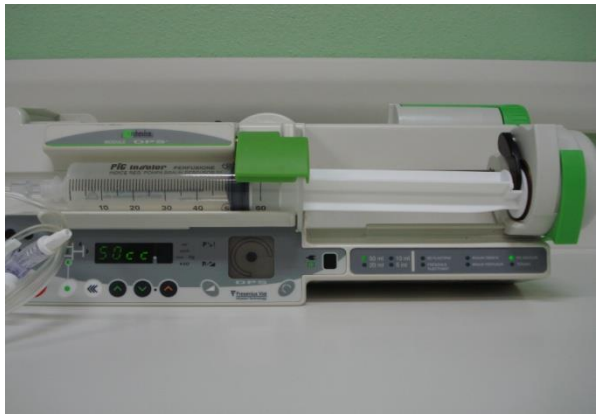
Noradrenalina vs Dopamina

Adverse events	Dopamina	Noradrenalina	
Arrhythmias — no. (%)	207 (24.1)	102 (12.4)	<0.001
Atrial fibrillation	176 (20.5)	90 (11.0)	
Ventricular tachycardia	21 (2.4)	8 (1.0)	
Ventricular fibrillation	10 (1.2)	4 (0.5)	

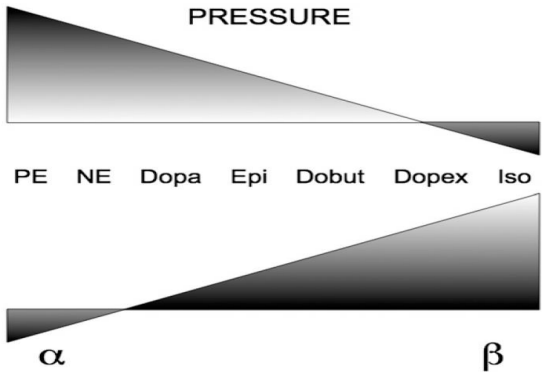
In summary, although the rate of death did not differ significantly between the group of patients treated with dopamine and the group treated with norepinephrine, this study raises serious concerns about the safety of dopamine therapy, since dopamine, as compared with norepinephrine, was associated with more arrhythmias and with an increased rate of death in the subgroup of patients with cardiogenic shock.

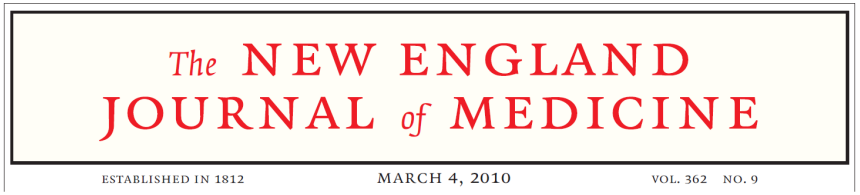
Conclusioni

- Trattamento individualizzato → FISIOPATOLOGIA

- Inotropi vs Vasopressori → NORADRENALINA/DOBUTAMINA





Comparison of Dopamine and Norepinephrine in the Treatment of Shock

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- Supporti meccanici → IABP/LVAD/ECMO

GRAZIE PER L’ATTENZIONE