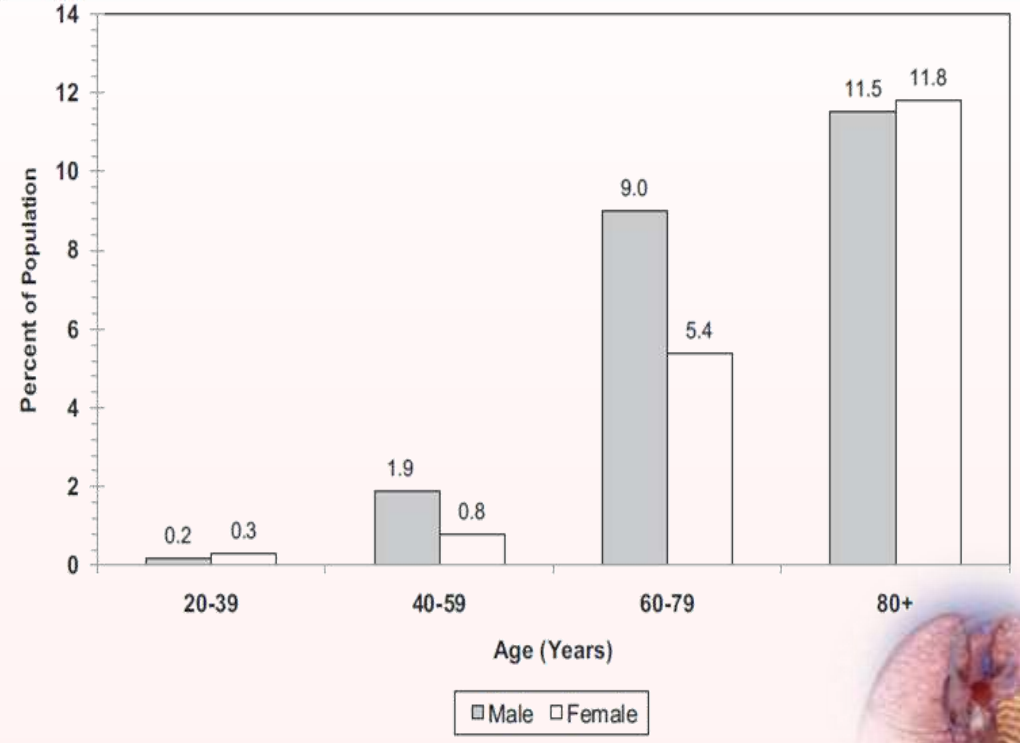
Traitement pharmacologique de l'insuffisance cardiaque aigue

Pr Souheil Elatrous
E.P.S. Taher Sfar Mahdia

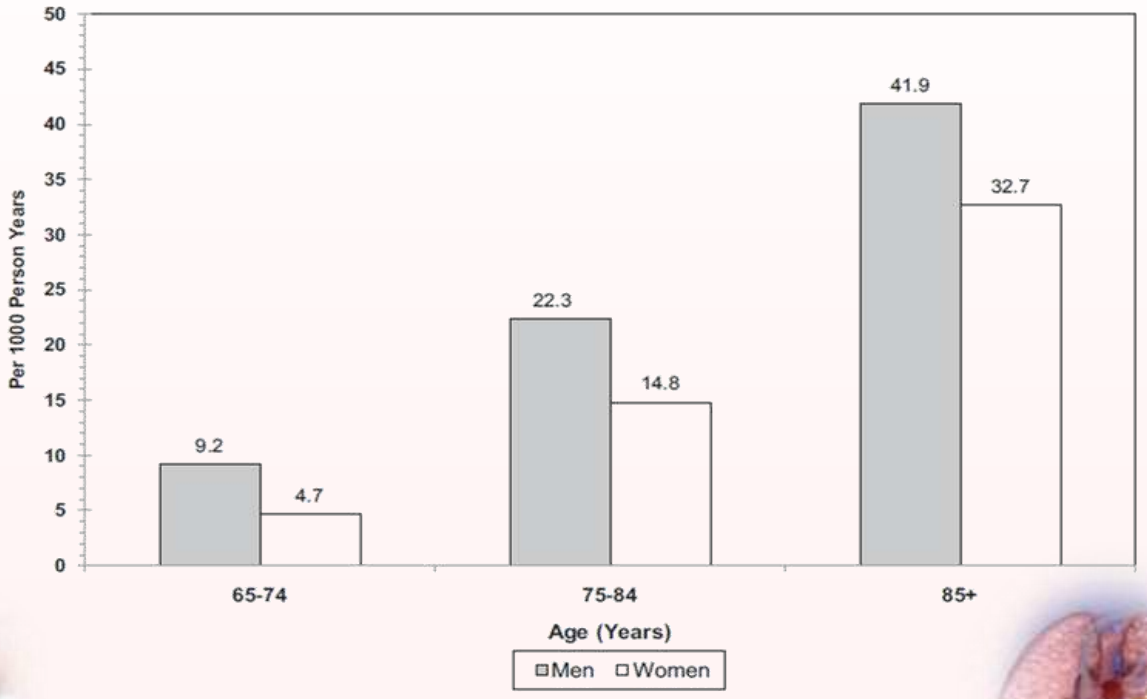
Prévalence

- **2005-2008 : 5700000 Américains ≥ 20 ans Ice cardiaque (2.4%)**
- **2010 : prévalence 6.6 Millions US adultes ≥ 18 ans (2.8%)**
- **2030 : 3 Millions de plus et augmentation prévalence 25%**



Incidence

- Incidence 10 / 1000 après 65 ans
- 75% ont un antécédent d'HTA
- Risque de IC 20% après 40 ans



Temporal trends in the hospitalization and outcomes of patients with decompensated heart failure
Multicenter study

Novack V. International Journal of Cardiology 147 (2011) 265–270

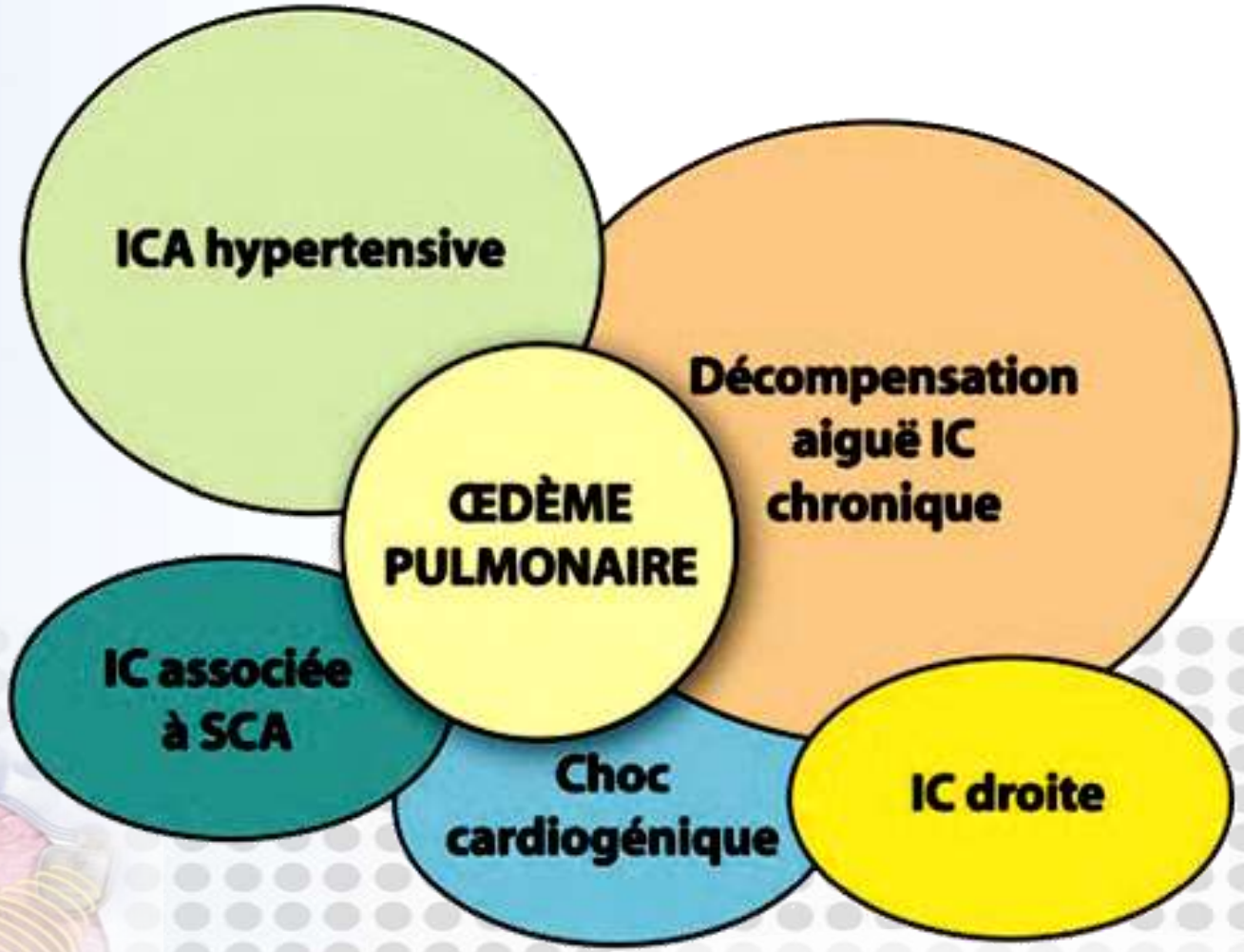
Table 2
Clinical outcomes and in-hospital interventions of the study population stratified by the admission year.

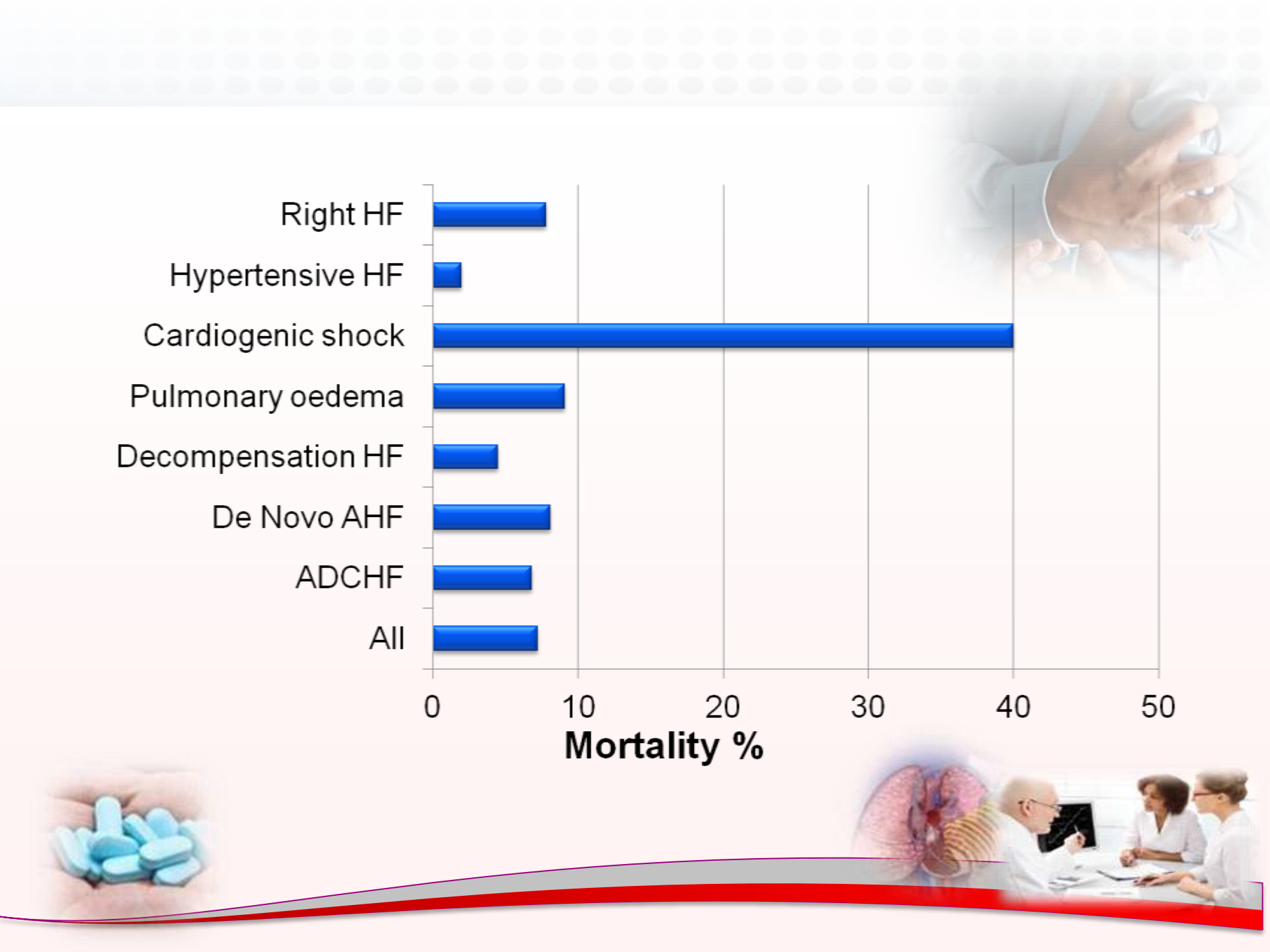
	2000	2001	2002	2003	2004	*p*-value for trend
ICU admission, (%)	8.3	7.6	8.0	9.5	10.4	0.002
ICU Length of stay, days Median (IQR)	4.8 (2.0–8.9)	4.5 (1.7–8.5)	5.0 (1.6–8.0)	4.0 (2.0–7.7)	4.6 (2.5–8.5)	0.98
Total length of stay, days	4.2 (2.6–7.1)	4.2 (2.6–7.1)	4.3 (2.8–7.3)	4.2 (2.8–7.2)	4.4 (2.8–7.3)	0.03
In-hospital mortality, (%)	6.0	5.8	6.4	5.8	5.8	0.45
30 day mortality, (%)	9.2	8.9	9.2	8.7	8.3	0.31
1-year mortality, (%)	32.0	30.1	29.7	30.3	28.0	0.01
18 month mortality, (%)	38.9	36.9	36.5	36.3	33.9	<0.001
1-year mortality, (%)	32.0	30.1	29.7	30.3	28.0	0.01
18 month mortality, (%)	38.9	36.9	36.5	36.3	33.9	<0.001

50% de décès après 5 ans

Europe & France

- Prévalence en Europe : 0.4-2%
- France 1% de la population
- 10% des sujets de plus de 70 ans
- 1ere cause de dyspnée aux urgences
- 80% des sujets suspect = hospitalisation
- Mortalité des épisodes aigues : 15-20%


ICA hypertensive
Décompensation aiguë IC chronique
ŒDÈME PULMONAIRE
IC associée à SCA
Choc cardiogénique
IC droite


Right HF
Hypertensive HF
Cardiogenic shock
Pulmonary oedema
Decompensation HF
De Novo AHF
ADCHF
All
0
10
20
30
40
50
Mortality %

Traitement de l'insuffisance cardiaque

oxygène

Diurétiques

Vasodilatateurs

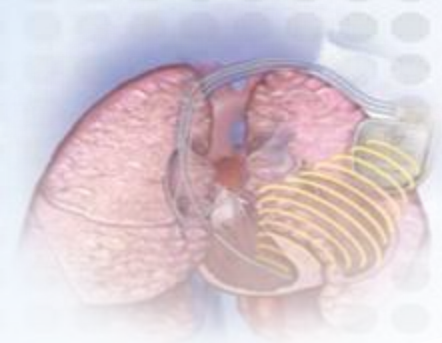
Inotropes

Scénario clinique

Scénarios	Fréquence	Profils cliniques	Physiopathologie
1. PAS > 140 mmHg	~50%	• Apparition brutale • Œdème pulmonaire diffus	• HTA d'origine vasculaire • ↓ compliance VG • FEVG souvent préservée
2. PAS 100-140 mmHg	~40%	• Apparition progressive • Œdèmes systémiques prédominants	• Rétention hydrosodée progressive • Insuffisance cardiaque chronique
3. PAS < 100 mmHg	< 10%	• Apparition brutale ou progressive • Congestion souvent peu marquée • Détecter hypoperfusion	• IC chronique avancée • ↓ souvent sévère de la FEVG • Bas débit cardiaque
4. Syndrome coronarien aigu	~20%	• Apparition brutale • DRS/signes ECG d'ischémie • Elévation significative troponine	• Ischémie myocardique • Altération de la fonction systolique et diastolique du VG
5. Insuffisance ventriculaire droite isolée	~3%	• Apparition brutale ou progressive • Signes de congestion veineuse systémique • Symptômes gastro-intestinaux	• Dysfonction ventriculaire droite • Hypertension artérielle pulmonaire • Bas débit cardiaque

Oxygène

Patient hypoxémique SaO2 < 90%



Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary edema (Review)

Analysis 1.1. Comparison 1 NONINVASIVE POSITIVE PRESSURE VENTILATION (CPAP and BILEVEL), Outcome 1 HOSPITAL MORTALITY.

Review: Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary edema

Comparison: 1 NONINVASIVE POSITIVE PRESSURE VENTILATION (CPAP and BILEVEL)

Outcome: 1 HOSPITAL MORTALITY

Study or subgroup	NPPV n/N	SMC n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bersten 1991	2/20	4/20		4.0 %	0.50 [0.10, 2.43]
Crane 2004	5/40	6/20		8.9 %	0.42 [0.14, 1.20]
Delclaux 2000	7/22	7/20		13.7 %	0.91 [0.39, 2.14]
Kelly 2002	1/27	7/31		2.4 %	0.16 [0.02, 1.25]
L'Her 2004	12/43	14/46		23.7 %	0.92 [0.48, 1.76]
Masip 2000	0/20	2/20		1.1 %	0.20 [0.01, 3.92]
Nava 2003	6/65	9/65		10.5 %	0.67 [0.25, 1.77]
Park 2001	1/16	0/10		1.0 %	1.94 [0.09, 43.50]
Park 2004	3/56	6/27		5.8 %	0.24 [0.07, 0.89]
Rsnen 1985	3/20	6/20		6.5 %	0.50 [0.14, 1.73]
Sharon 2000	2/20	0/20		1.1 %	5.00 [0.26, 98.00]
Takeda 1997	1/15	3/15		2.2 %	0.33 [0.04, 2.85]
Total (95% CI)	**489**	**441**		**100.0 %**	**0.62 [0.45, 0.84]**

Total events: 53 (NPPV), 85 (SMC)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 12.74$, df = 16 (P = 0.69); $I^2 = 0.0\%$

Test for overall effect: Z = 3.01 (P = 0.0026)

0.01 0.1 1 10 100

Favours NPPV Favours SMC

The NEW ENGLAND JOURNAL of MEDICINE

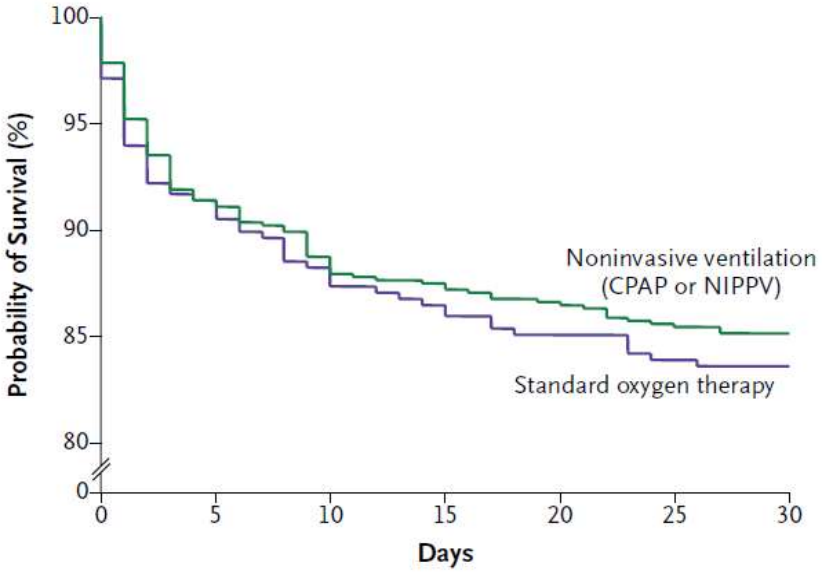
ORIGINAL ARTICLE

Noninvasive Ventilation in Acute Cardiogenic Pulmonary Edema

Alasdair Gray, M.D., Steve Goodacre, Ph.D., David E. Newby, M.D., Moyra Masson, M.Sc., Fiona Sampson, M.Sc., and Jon Nicholl, M.Sc., for the 3CPO Trialists*

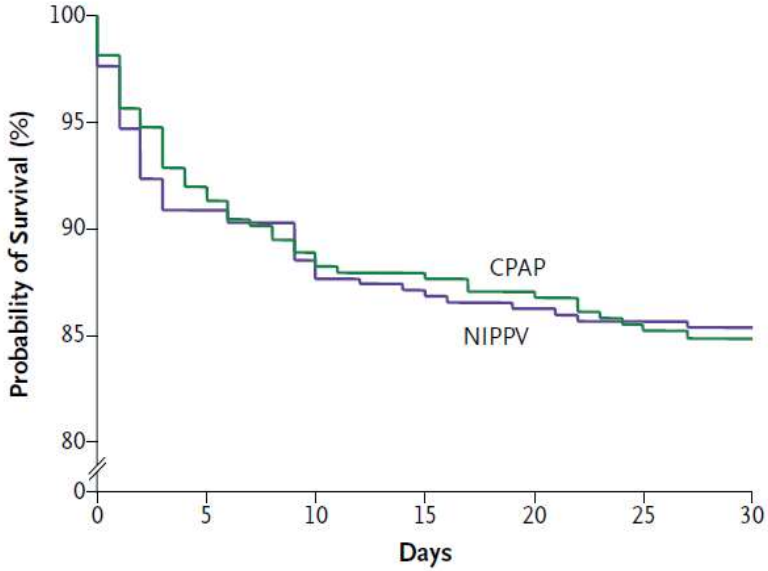
N Engl J Med 2008;359:142-51.

A



No. at Risk							
CPAP or NIPPV	667	609	591	583	577	570	567
Standard therapy	348	318	307	301	296	292	291

B



No. at Risk							
CPAP	325	298	288	285	282	277	275
NIPPV	342	311	303	298	295	293	292

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

High-flow oxygen is recommended in patients with a capillary oxygen saturation <90% or PaO_2 <60 mmHg (8.0 kPa) to correct hypoxaemia.	I	C
Non-invasive ventilation (e.g. CPAP) should be considered in dyspnoeic patients with pulmonary oedema and a respiratory rate >20 breaths/min to improve breathlessness and reduce hypercapnia and acidosis. Non-invasive ventilation can reduce blood pressure and should not generally be used in patients with a systolic blood pressure <85 mmHg (and blood pressure should be monitored regularly when this treatment is used).	IIa	B

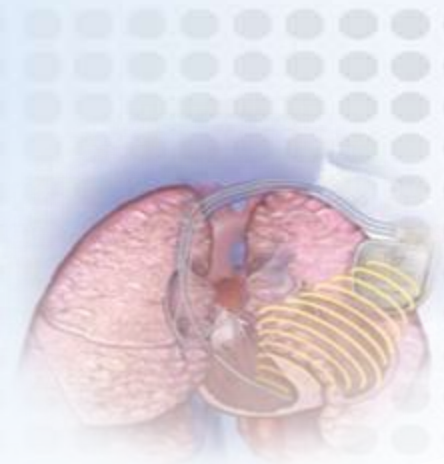


Table A Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Table B Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Diurétique & vasodilatateurs

- Pour quels patients : profils hémodynamiques?
  - → Niveau de pression de remplissage (sec ou congestif)
  - → Perfusion tissulaire : chaud ou froid

Hypoperfusion au repos	Congestion au repos : NON	Congestion au repos : OUI
NON	B : chaud sec	A : chaud congestif
OUI	D : froid sec	C : froid congestif

Signes de congestion :

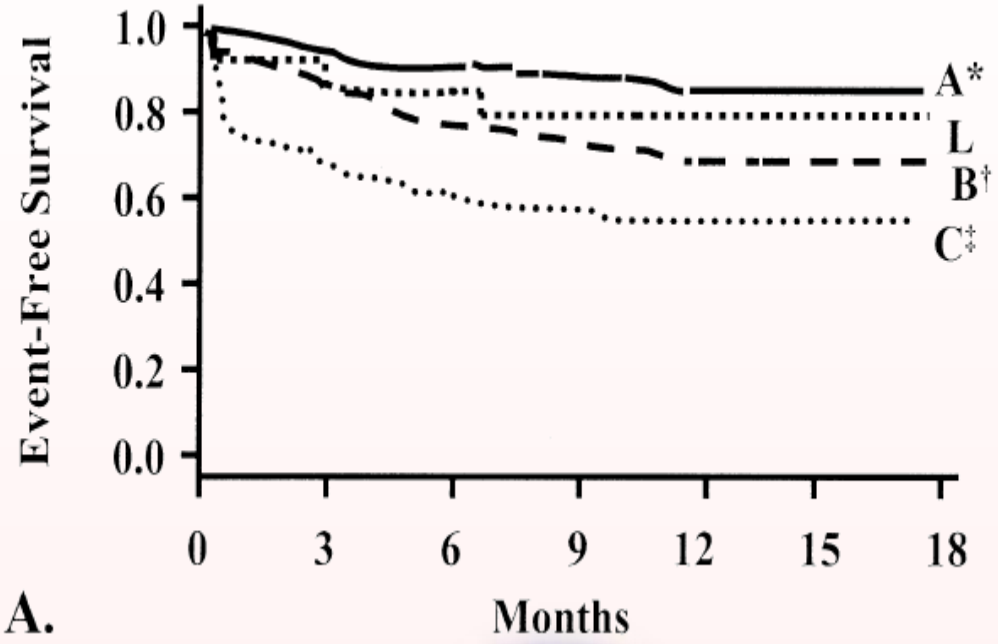
Orthopnée, dyspnée paroxystique nocturne
Turgescence ou reflux jugulaire
Hépatomégalie
Œdèmes déclives
Crépitants pulmonaires
PA élevée

Signes en faveur d'une hypoperfusion :

Pression pulsée basse
Somnolence, obnubilation
Hyponatrémie
Extrémités froides
Hypotension sous IEC
Insuffisance rénale

Clinical Assessment Identifies Hemodynamic Profiles That Predict Outcomes in Patients Admitted With Heart Failure

ADEQUATE PERFUSION	CONGESTION --	CONGESTION +
+	**A** *dry-warm (N=123)*	**B** *wet-warm (N=222)*
-	**L** *dry-cold (N=16)*	**C** *wet-cold (N=91)*



A.

Anju Nohria J Am Coll Cardiol 2003;41:1797– 804

Diurétiques de l'anse

- En présence de congestion et a fortiori œdèmes périphériques
- Voie intraveineuse : Furosémide (lasilix®) bumétamide (Burinex ®)
- Inhibent l'échangeur Na-K-2Cl sur son site tubulaire au niveau de l'anse ascendante de Henlé
- **Bolus**
  - effet veinodilatateur rapide, modeste
  - effet diurétique après 30 min avec un pic 1 à 2 h après l'injection
- Nécessité de plusieurs injections ou **perfusion continue**

Diuretic Efficacy of High Dose Furosemide in Severe Heart Failure: Bolus Injection Versus Continuous Infusion

TOM P. J. DORMANS, MD, JOSEPH J. M. VAN MEYEL, MD, PHD,*
PAUL G. G. GERLAG, MD, PHD,† YUEN TAN, FRANS G. M. RUSSEL, PHD,
PAUL SMITS, MD, PHD
Nijmegen, Amsterdam and Veldhoven, The Netherlands

Table 3. Urinary Volume, Electrolyte and Furosemide Excretion (mean ± SEM) 8 and 24 h After Administration of Furosemide as Oral Dosage (day 2), Intravenous Bolus Injection or Continuous Infusion in Patients With Heart Failure

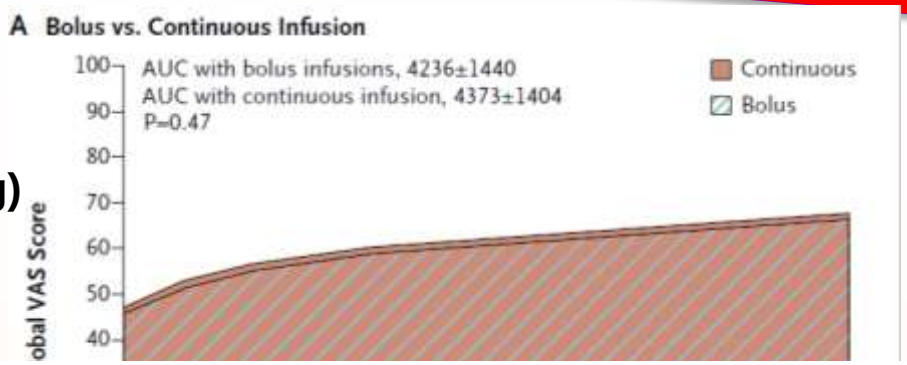
		Bolus		Infusion		Bolus Versus Infusion (p value)	
	Oral, 0–26 h	0–8 h	0–24 h	0–8 h	0–24 h	0–8 h	0–24 h
U_v (ml)	2,200 ± 160	1,350 ± 90	2,260 ± 150	1,700 ± 120	2,860 ± 240	0.0002	0.0005
U_{Na} (mmol)	130 ± 30	110 ± 10	150 ± 20	140 ± 20	210 ± 40	0.0010	0.0045
U_K (mmol)	70 ± 6	30 ± 5	70 ± 5	40 ± 4	80 ± 5	0.0006	< 0.0001
U_{Cl} (mmol)	130 ± 20	120 ± 10	150 ± 20	150 ± 20	220 ± 35	0.0006	0.0018
$U_{furosemide}$ (mg)	140 ± 30	290 ± 50	330 ± 60	220 ± 40	310 ± 60	< 0.0001	0.0195
Recovery (%)	21 ± 2	44 ± 2	50 ± 2	33 ± 2	44 ± 2	< 0.0001	0.0195
Efficiency (mmol/mg)	2.9 ± 1.5	0.7 ± 0.2	0.9 ± 0.3	1.1 ± 0.3	1.3 ± 0.4	0.0005	0.0019

Statistical analyses were made using the Student *t* test for paired data. U_{Cl} = urinary chloride excretion; $U_{furosemide}$ = urinary furosemide excretion; U_K = urinary potassium excretion; U_{Na} = urinary sodium excretion; U_v = urinary volume.

JACC Vol. 28, No. 2
August 1996:376–82

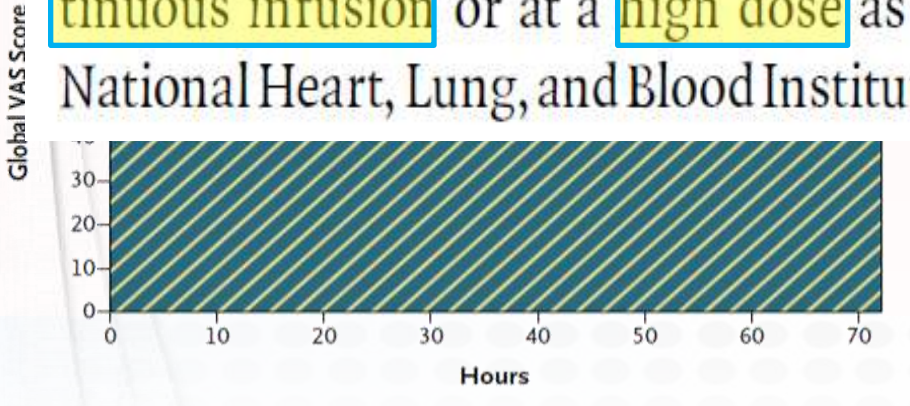
Diuretic Strategies in Patients with Acute Decompensated Heart Failure

308 patients
Faible dose = dose habituelle PO (130 mg)
Forte dose = 2.5 dose habituelle
Bolus /12h vs continue



CONCLUSIONS

Among patients with acute decompensated heart failure, there were no significant differences in patients' global assessment of symptoms or in the change in renal function when diuretic therapy was administered by bolus as compared with continuous infusion or at a high dose as compared with a low dose. (Funded by the National Heart, Lung, and Blood Institute; ClinicalTrials.gov number, NCT00577135.)



G. Michael Felker NEJM 2011; 364: 797-805

European Heart Journal (2012) **33**, 1787–1847
doi:10.1093/eurheartj/ehs104

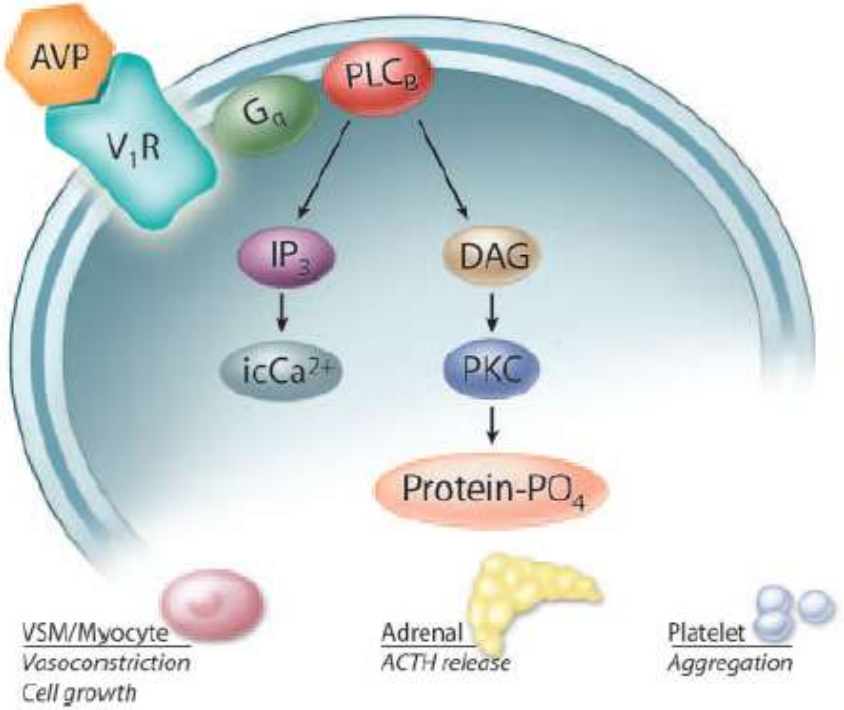
ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

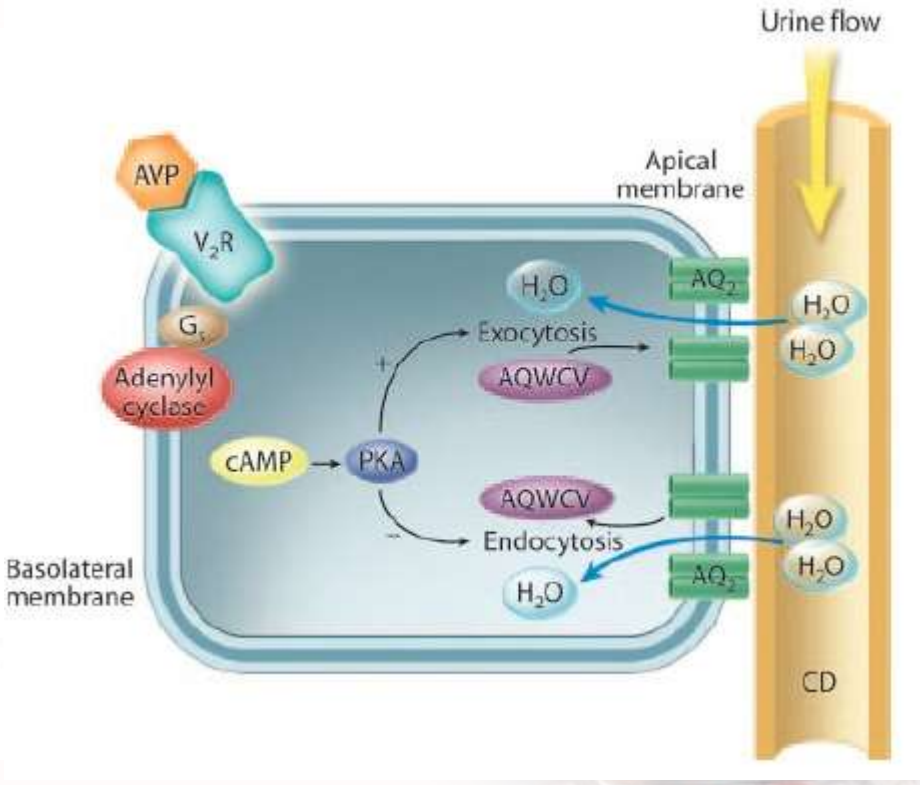
Recommendations for the treatment of patients with acute heart failure

Recommendations	Class[a]	Level[b]
Patients with pulmonary congestion/oedema without shock		
An i.v. loop diuretic is recommended to improve breathlessness and relieve congestion. Symptoms, urine output, renal function, and electrolytes should be monitored regularly during use of i.v. diuretic.	I	B

Perspectives

Antagonistes des récepteurs à la vasopressine





John J. Finley Circulation. 2008;118:410-421

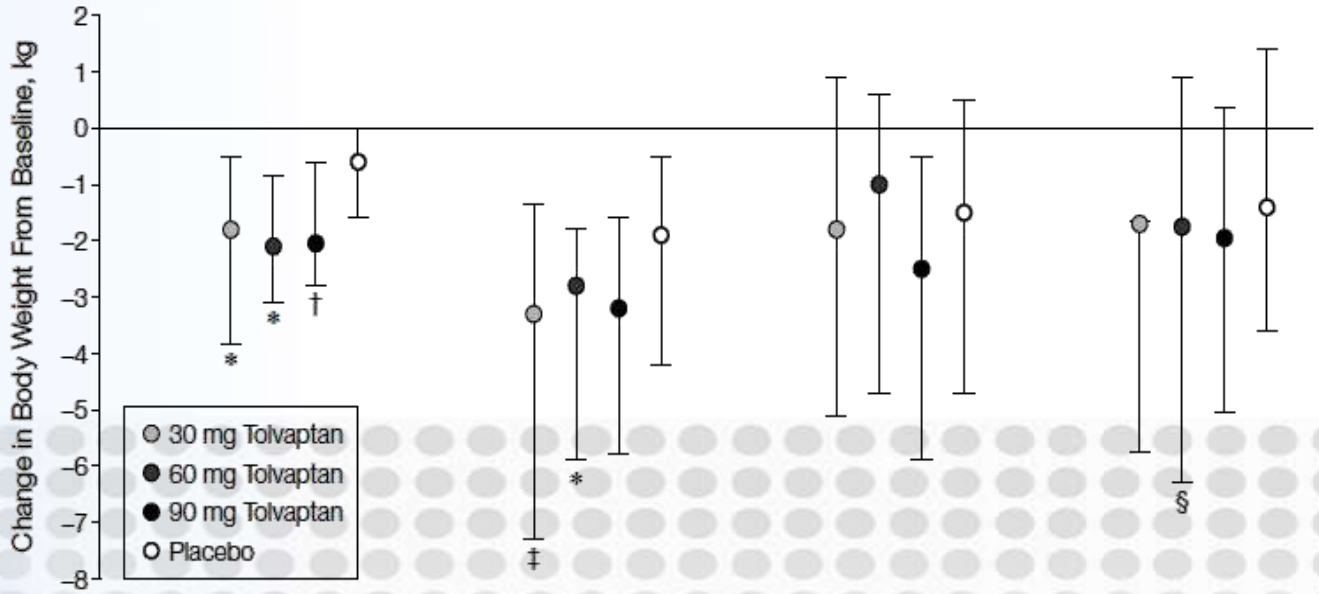
Effects of Tolvaptan, a Vasopressin Antagonist, in Patients Hospitalized With Worsening Heart Failure

A Randomized Controlled Trial

ACTIV in CHF

319 patients

Figure 2. Median Changes in Body Weight Over Time



*Indicates $P=.002$; †, $P=.009$; ‡, $P=.006$; and §, $P=.008$ for comparisons with placebo group. Error bars indicate interquartile range.

Mihai GheorghiadeJ AMA. 2004;291:1963-1971

Effects of Tolvaptan, a Vasopressin Antagonist, in Patients Hospitalized With Worsening Heart Failure

A Randomized Controlled Trial

ACTIV in CHF

Mihai Gheorghiade *JAMA. 2004;291:1963-1971*

Figure 3. Mean 24-Hour Urine Volumes at Day 1 and at Hospital Discharge

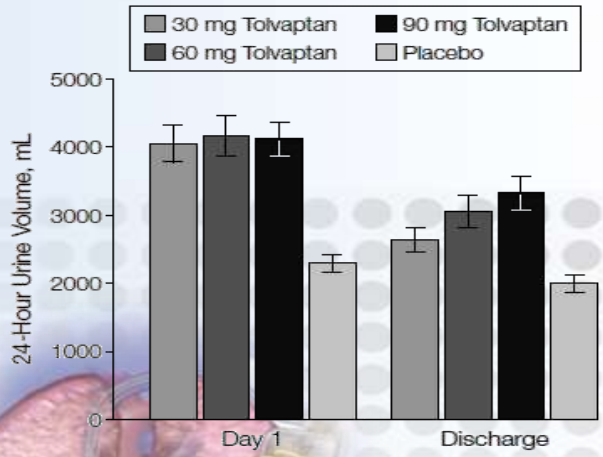
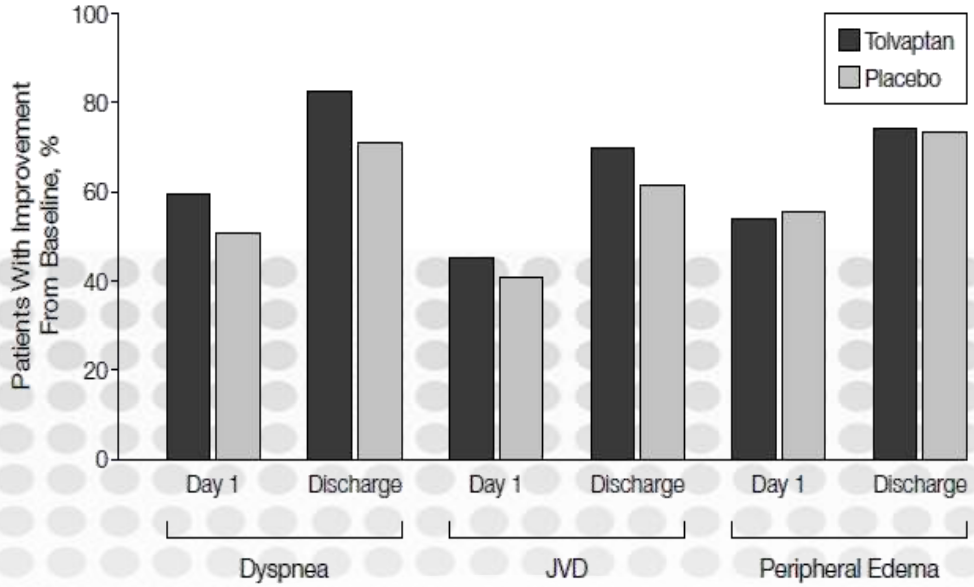


Figure 4. Signs and Symptoms of Heart Failure at Day 1 and at Hospital Discharge

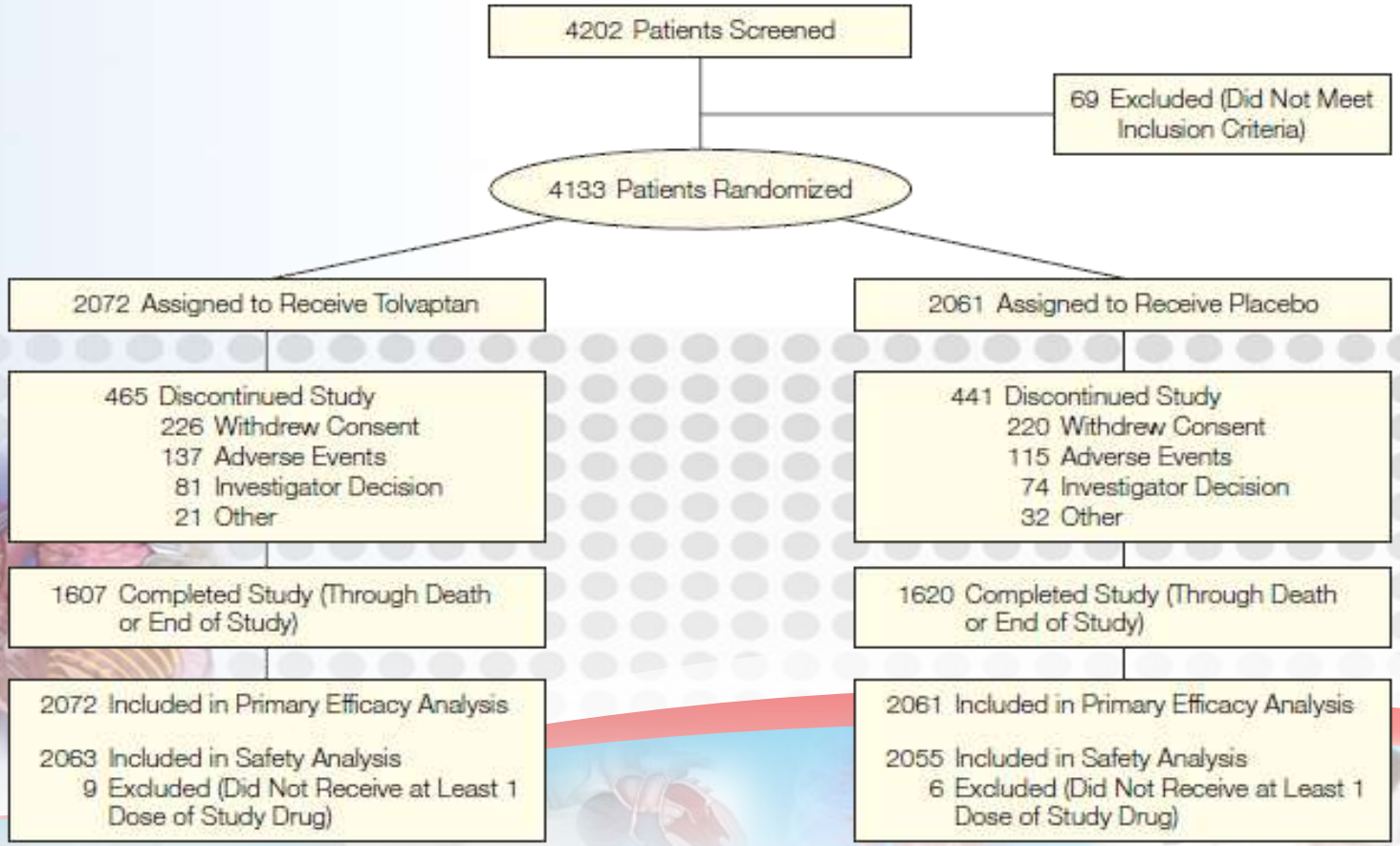


Effects of Oral Tolvaptan in Patients Hospitalized for Worsening Heart Failure

The EVEREST Outcome Trial

Marvin A. Konstam, JAMA. 2007;297:1319-1331

Figure 1. Flow of Participants Through the Trial

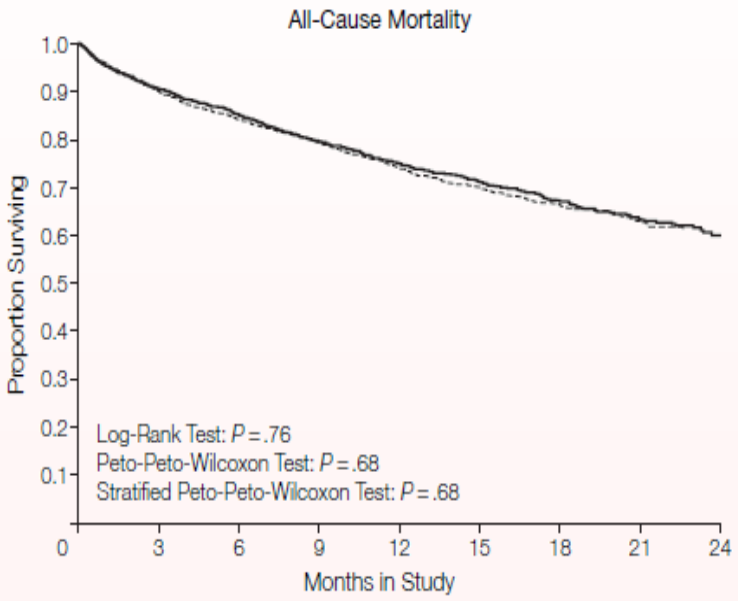


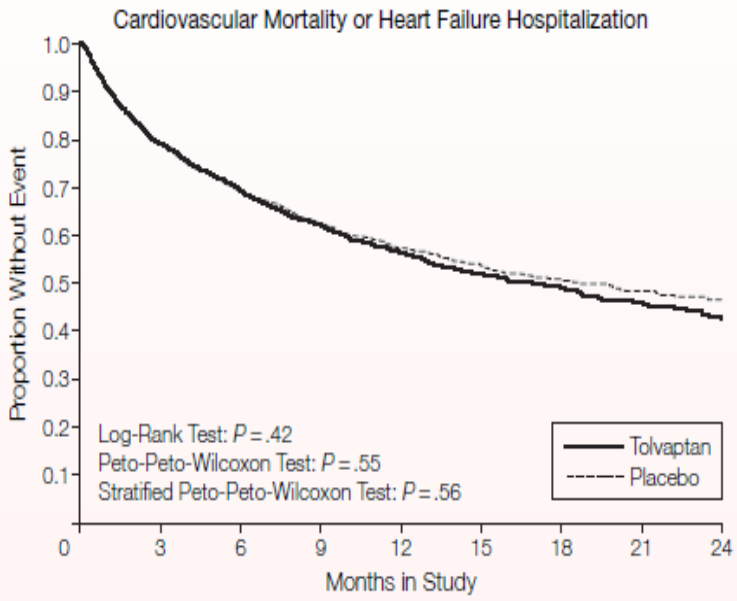
Effects of Oral Tolvaptan in Patients Hospitalized for Worsening Heart Failure

The EVEREST Outcome Trial

Marvin A. Konstam, JAMA. 2007;297:1319-1331

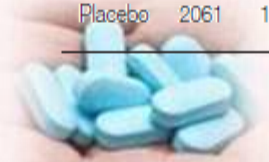
Figure 2. Kaplan-Meier Analyses of All-Cause Mortality and Cardiovascular Mortality or Hospitalization for Heart Failure





No. at Risk									
Tolvaptan	2072	1812	1446	1112	859	589	404	239	97
Placebo	2061	1781	1440	1109	840	580	400	233	95

2072	1562	1446	834	607	396	271	149	58
2061	1532	1137	819	597	385	255	143	55



Effects of Oral Tolvaptan in Patients Hospitalized for Worsening Heart Failure

The EVEREST Outcome Trial

Table 3. Effects of Tolvaptan on Change From Baseline in Secondary End Points: Body Weight, Patient-Assessed Dyspnea, Serum Sodium Concentration, Edema, and KCCQ Overall Summary Score

	Tolvaptan	Placebo	*P* Value
Change in body weight at 1 day, mean (SD), kg	−1.76 (1.91) [n = 1999]	−0.97 (1.84) [n = 1999]	<.001*
Change in dyspnea at 1 day, % showing improvement in dyspnea score†	74.3 [n = 1835]	68.0 [n = 1829]	<.001‡
Change in serum sodium at 7 days (or discharge if earlier), mean (SD), mEq/L§	5.49 (5.77) [n = 162]	1.85 (5.10) [n = 161]	<.001*
Change in edema at 7 days (or discharge), % showing at least a 2-grade improvement†	73.8 [n = 1600]	70.5 [n = 1595]	.003‡
Change in KCCQ overall summary score at postdischarge week 1, mean (SD)	19.90 (18.71) [n = 872]	18.52 (18.83) [n = 856]	.39*

Abbreviation: KCCQ, Kansas City Cardiomyopathy Questionnaire.
*Based on analysis of covariance model.
†Among patients with symptoms at baseline.
‡Based on van Elteren test.[28]
§Among participants with baseline sodium levels of less than 134 mEq/L.

Marvin A. Konstam, JAMA. 2007;297:1319-1331

Les vasodilatateurs

Dérivés nitrés

- **Action** : agissent sur l'endothélium, induisant la **libération de NO** et en aval la production de (GMPc) responsable d'une vaso-relaxation dite **«endothélium dépendante»**
- **A FAIBLE DOSE**
  - ***Action prédomine sur le secteur veineux*** capacitif avec réduction du retour veineux, des volumes ventriculaires droit et gauche et donc des pressions intraventriculaires diastoliques
  - **Action sur le système artériel** → coronaire et gros troncs artériels : une baisse de l'impédance aortique et baisse de la post charge → augmentation VES
- **A FORTE DOSE**
  - ***Action sur le système résistif*** → baisse des RVS et de la PA

Dérivés nitrés

- Voie intraveineuse +++
- Sublinguale ou en spray : a domicile en cas d'OAP
- Utilisation en bolus

Articles

Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema

Gad Cotter, Einat Metzkor, Edo Kaluski, Zwi Faigenberg, Rami Miller, Avi Simovitz, Ori Shaham, Doron Marghitay, Maya Koren, Alex Blatt, Yaron Moshkovitz, Ronit Zaidenstein, Ahuva Golik

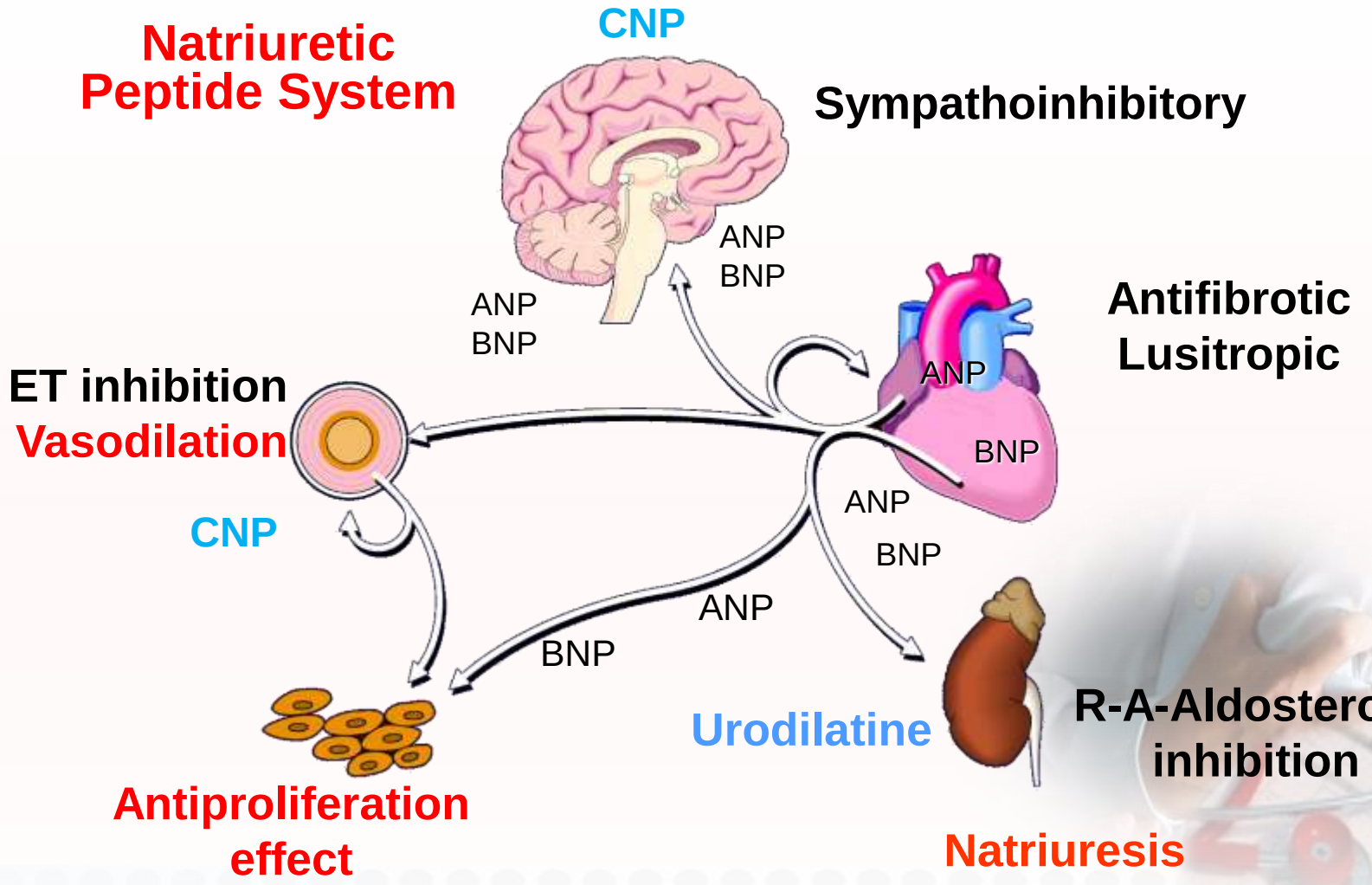
Primary outcome	Group A (n=52)	Group B (n=52)	P
Died	1 (2%)	3 (6%)	0.61
Required mechanical ventilation	**7 (13%)**	**21 (40%)**	**0.0041**
Myocardial infarction	9 (17%)	19 (37%)	0.047
Any adverse event	13 (25%)	24 (46%)	0.041

THE LANCET • Vol 351 • February 7, 1998

Nitroprussiate de sodium

- **Ganglioplégique**
- **Vasodilatateur mixte**
  - Diminution de la précharge et la post charge → augmentation du volume systolique et débit cardiaque sans stimulation sympathique réactionnelle
  - Baisse des résistances vasculaires proximales → diminution de la post charge → ↑↑ VES
- Seringue électrique et tubulure opaque 0.2 à 0.4 µg/Kg/min

Peptides natriurétiques



Niseritide

- Produit par recombinaison génétique
- Sa demi-vie est de 15 minutes.
- **Propriétés:**
  - ***Vasodilatatrices*** sans stimulation hormonale réflexe
  - ***diurétiques***

Sustained Hemodynamic Effects of an Infusion of Nesiritide (Human b-Type Natriuretic Peptide) in Heart Failure

A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

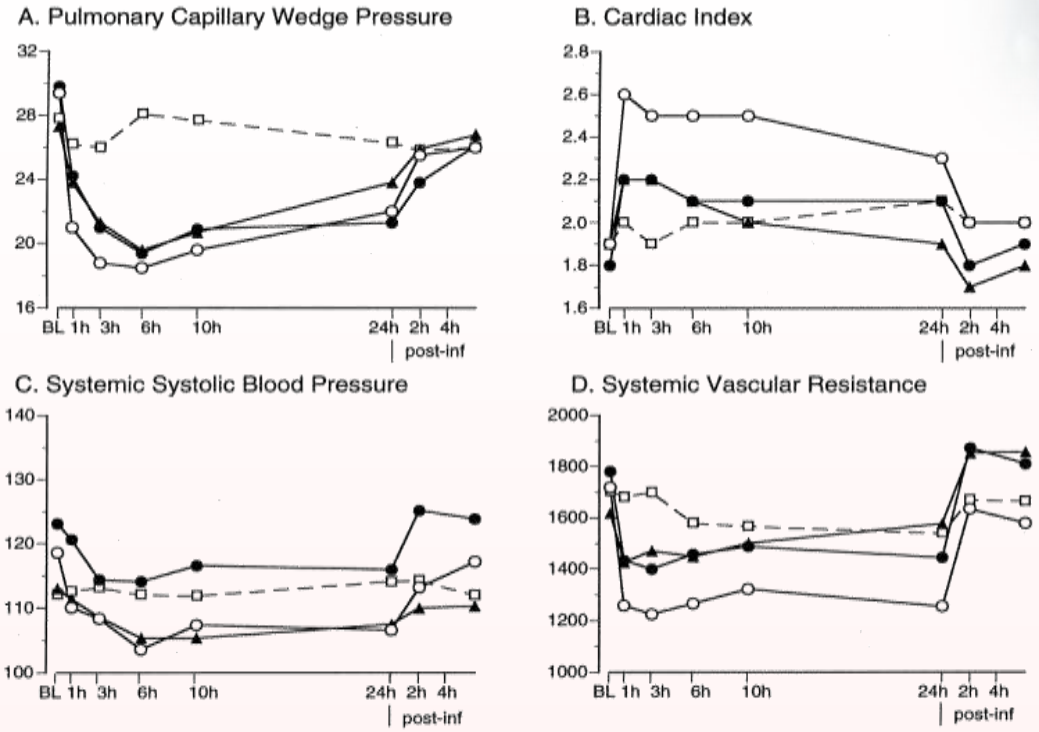


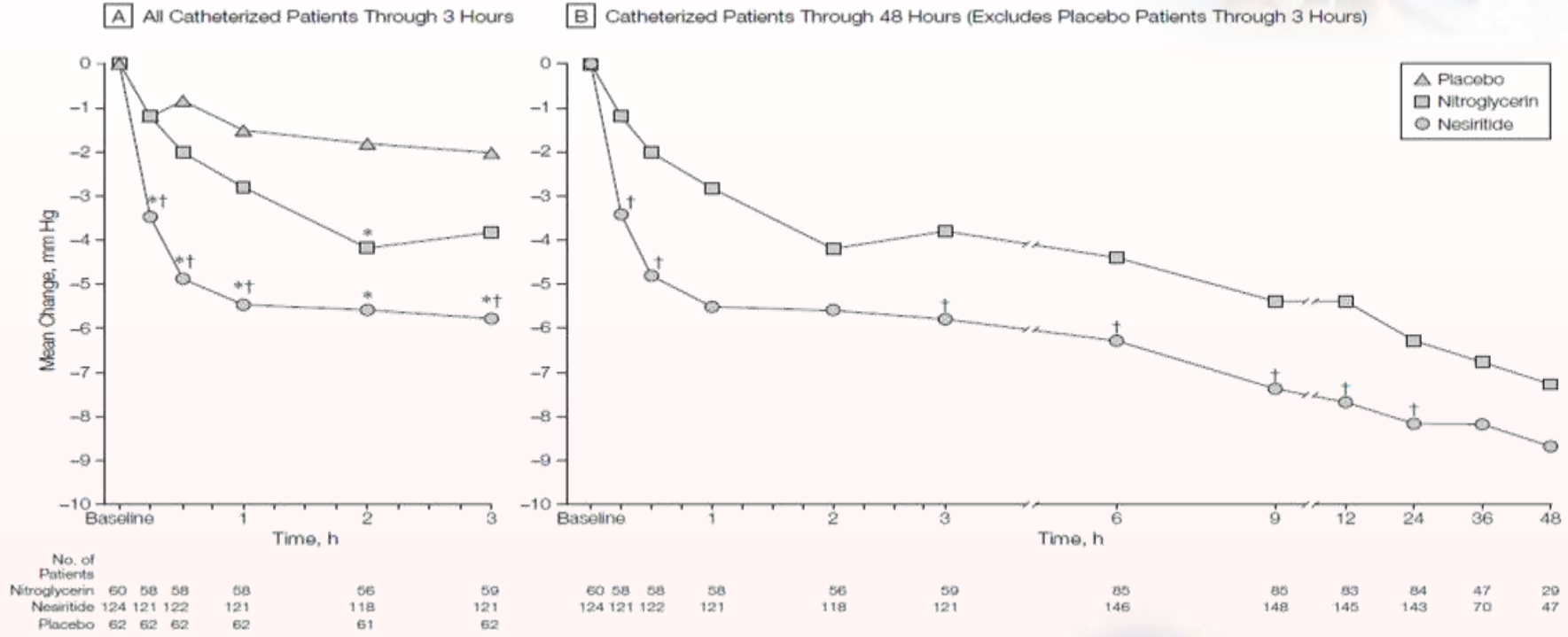
Figure 2. Mean observed hemodynamic values: results from baseline (BL) through 24 h of infusion (inf) and 4 h postinfusion. **(A)** Pulmonary capillary wedge pressure units are mm Hg. **(B)** Cardiac index units are liters/min/m^2. **(C)** Systemic systolic blood pressure units are mm Hg. **(D)** Systemic vascular resistance units are dyn/s/cm^{-5}. **Open squares:** placebo; **closed circles:** 0.015 μg/kg/min; **closed triangles:** 0.03 μg/kg/min; **open circles:** 0.06 μg/kg/min.

Roger M. Mills J Am Coll Cardiol 1999;34:155– 62

Intravenous Nesiritide vs Nitroglycerin for Treatment of Decompensated Congestive Heart Failure

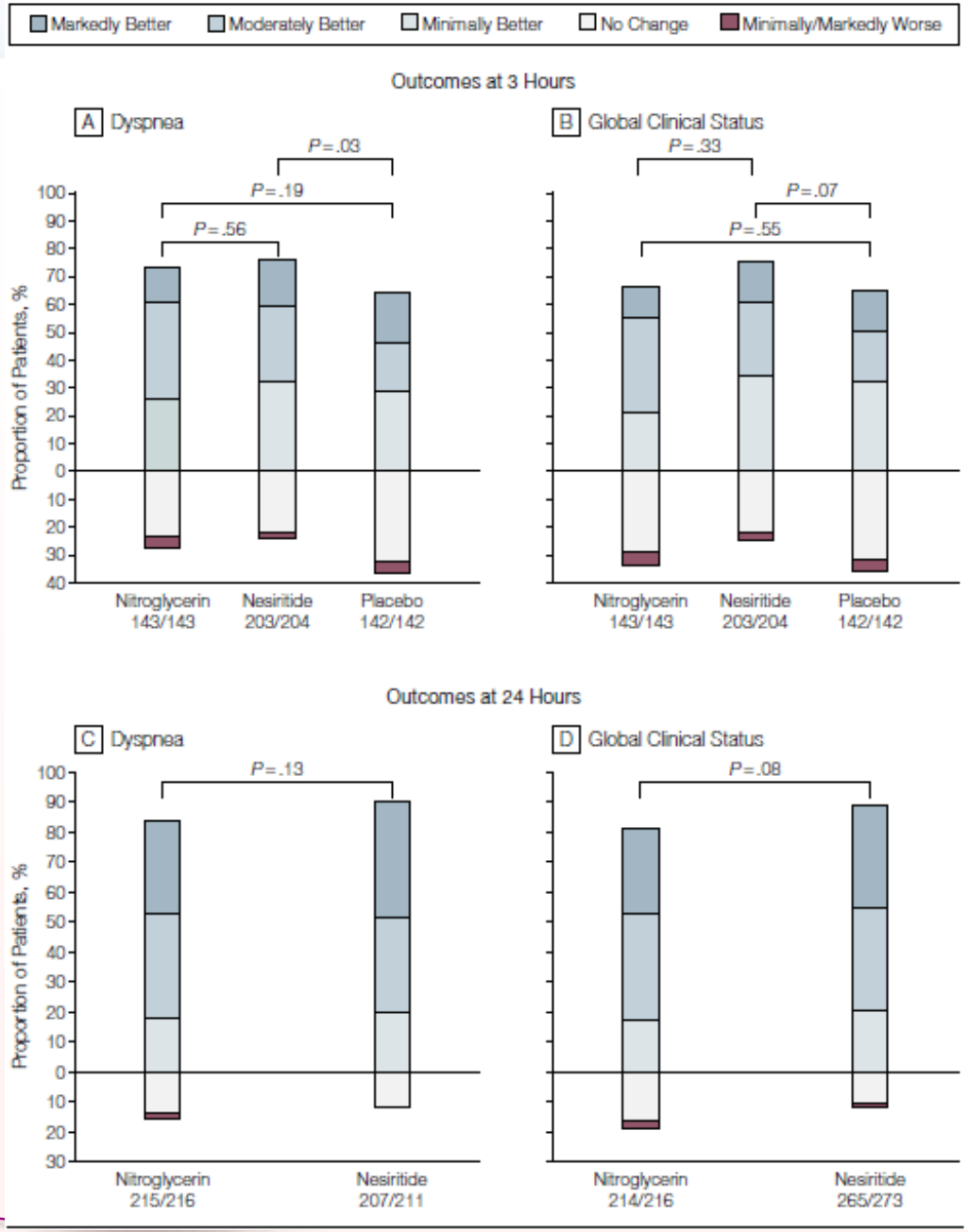
A Randomized Controlled Trial

Figure 2. Changes From Baseline in Pulmonary Capillary Wedge Pressure



VMAC Investigator JAMA. 2002; 287 : 1531-40

Figure 3. Outcomes at 3 and 24 Hours for All Treated Patients by Randomization Group



Intravenous Nesiritide vs Nitroglycerin for Treatment of Decompensated Congestive Heart Failure

A Randomized Controlled Trial

Table 4. Adverse Events During First 24 Hours After Start of Study Drug

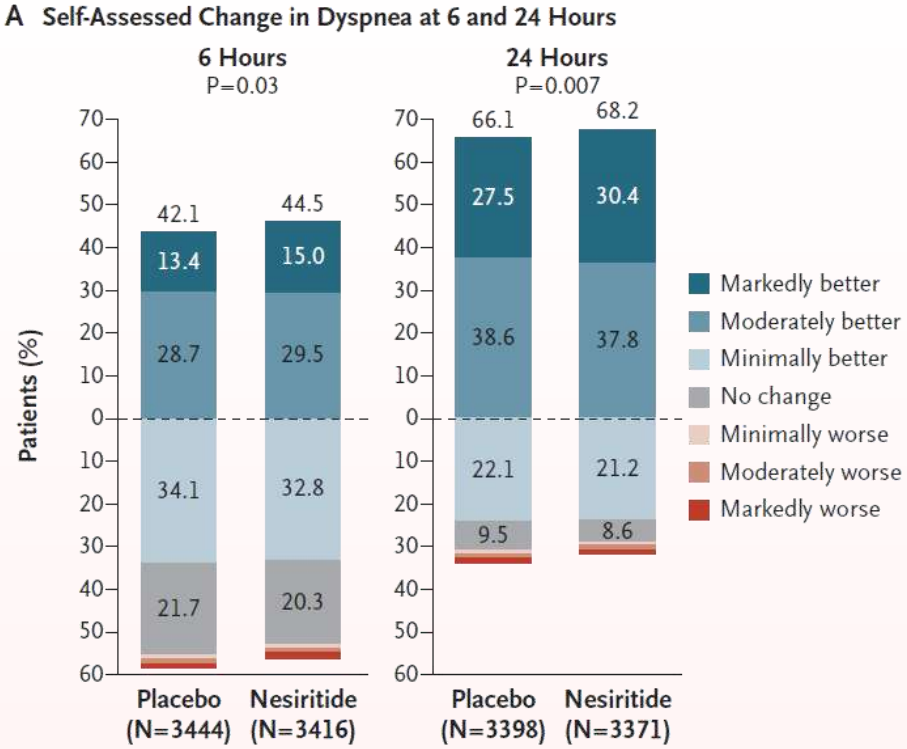
Adverse Event	Nitroglycerin (n = 216)	Nesiritide (n = 273)	*P* Value*
Any adverse event	146 (68)	140 (51)	<.001
General headache	44 (20)	21 (8)	<.001
Pain			
General	11 (5)	11 (4)	.66
Abdominal	11 (5)	4 (1)	.03
Catheter	11 (5)	4 (1)	.03
Nausea	13 (6)	10 (4)	.28
Cardiovascular			
Hypotension			
Asymptomatic	17 (8)	23 (8)	.87
Symptomatic	10 (5)	12 (4)	>.99
Nonsustained tidal volume	11 (5)	9 (3)	.36
Angina pectoris	5 (2)	5 (2)	.76

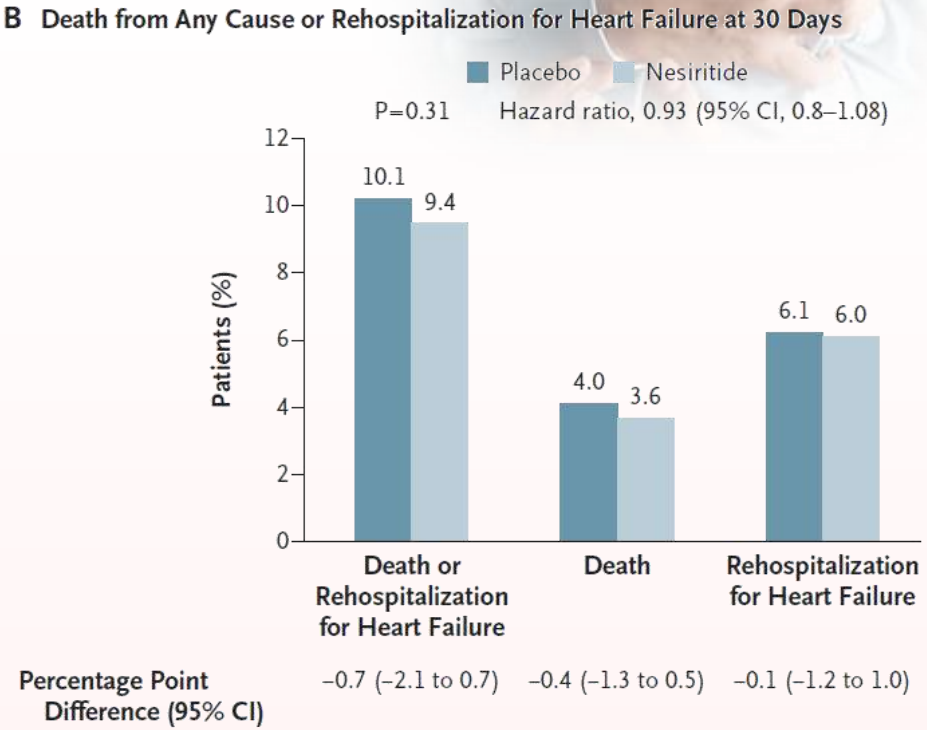
*Calculated using the Fisher exact test.

VMAC Investigator JAMA. 287 : 1531-40

Effect of Nesiritide in Patients with Acute Decompensated Heart Failure

ASCEND-HF





C.M. O'Connor N Engl J Med 2011;365:32-43.

Carpertine

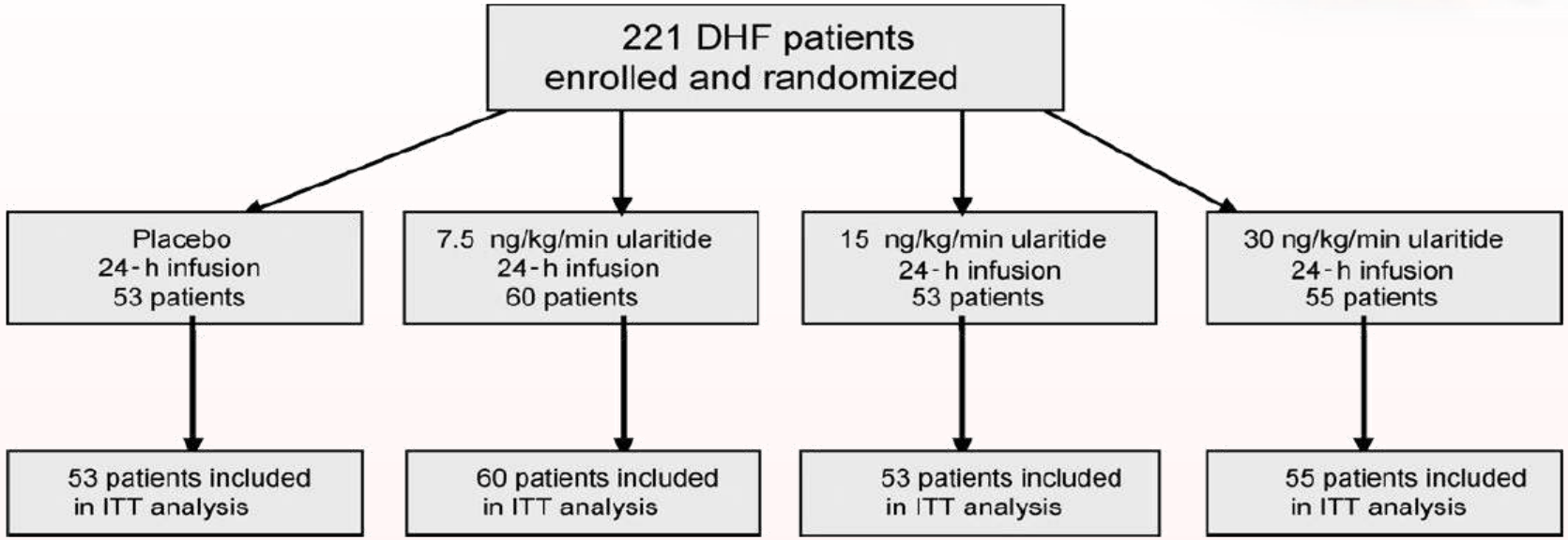
- Analogue synthétique de l'ANP humain
- Vasodilatation essentiellement veineuse
  - diminue les pressions de remplissage cardiaques mais aussi le débit cardiaque
- Amélioration clinique et leur insuffisance rénale
  - ***Suwa M et al Circ J 2005;69:283-90.*** ***(3777 patients)***
  - ***Nomura F, Circ J 2008;72:1777-86***

Ularitide

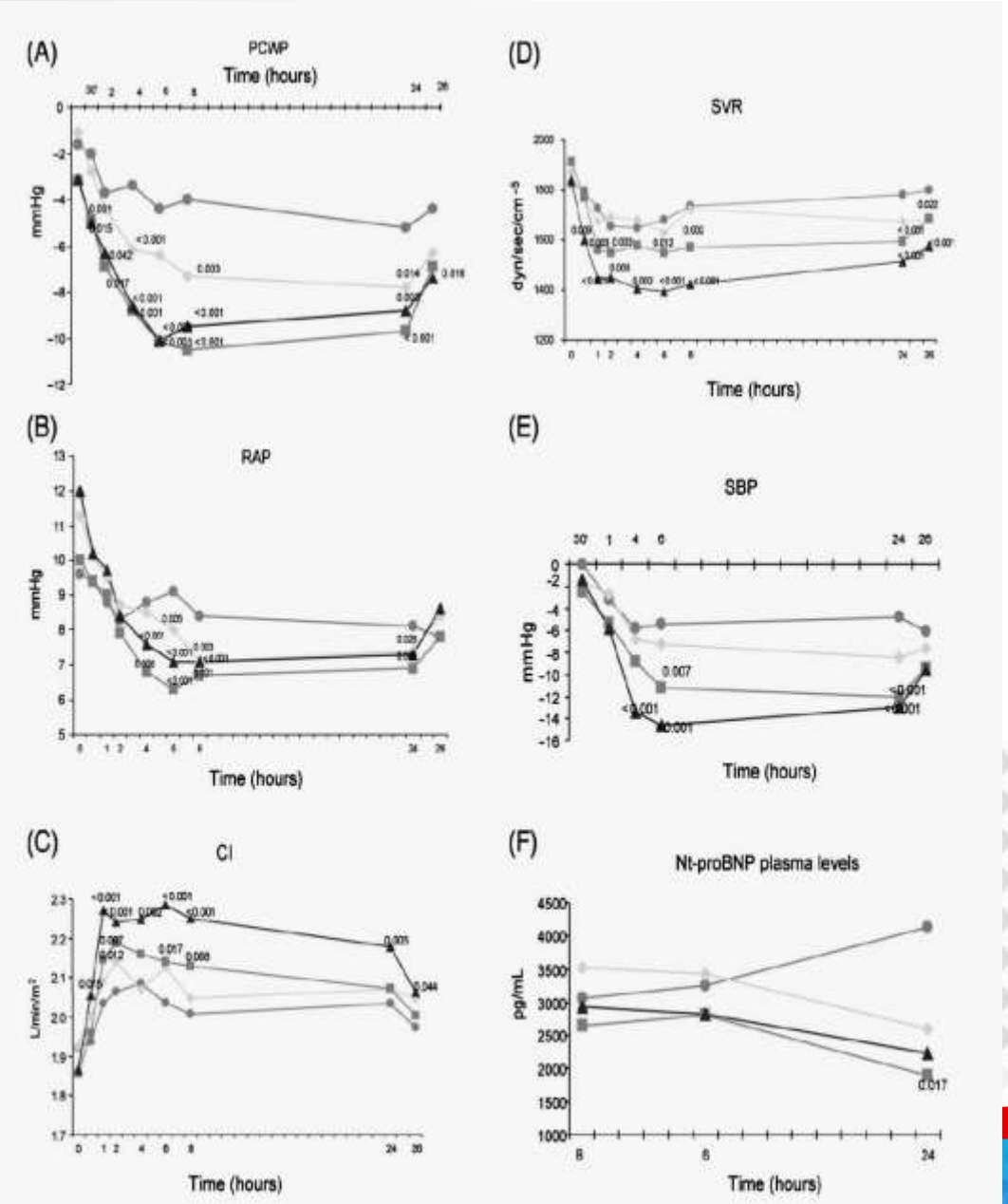
- Analogue synthétique de l'**urodilatine**
- Il entraîne:
  - une vasodilatation artérielle et veineuse puissante
  - une inhibition de la réabsorption tubulaire rénale de sodium : **un effet diurétique et natriurétique**

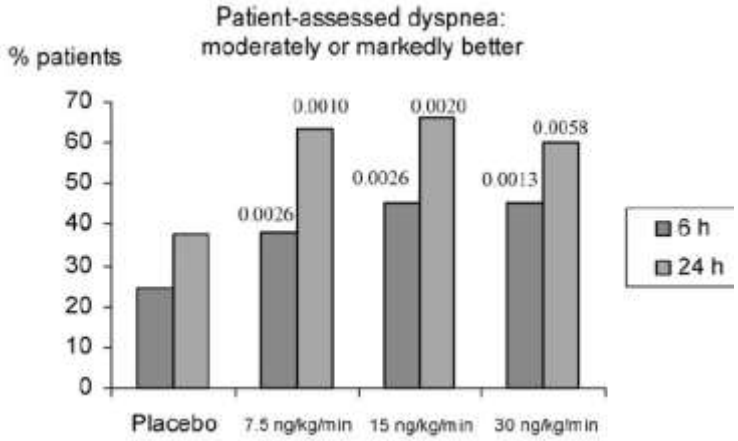
European Heart Journal (2006) 27, 2823–2832
doi:10.1093/eurheartj/ehl337

Haemodynamic and clinical effects of ularitide in decompensated heart failure



Veselin Mitrovic European heart journal 2007;27:2823-32





Veselin Mitrovic European heart journal 2007;27:2823-32

Effects of Tezosentan on Symptoms and Clinical Outcomes in Patients With Acute Heart Failure

The VERITAS Randomized Controlled Trials

John J. V. McMurray *JAMA. 2007;298(17):2009-2019*

- Antagoniste des récepteurs de l'**ENDOTHELINE**
- Endothéline :
  - synthétisée par les tissus cardiaques et vasculaires
  - Vasoconstriction artérielle et veineuse
  - Taux plasmatique élevé dans l'insuffisance cardiaque

Effects of Tezosentan on Symptoms and Clinical Outcomes in Patients With Acute Heart Failure

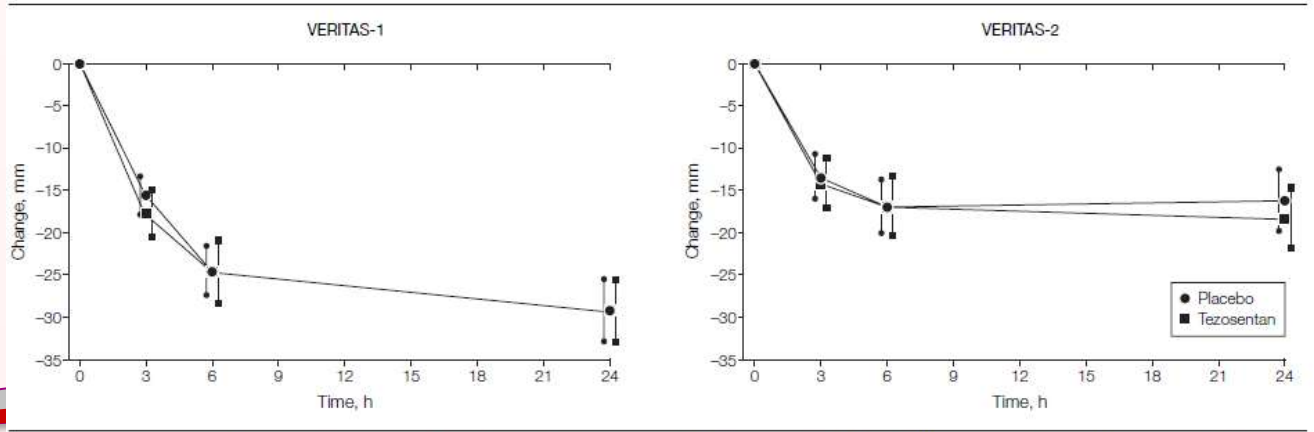
The VERITAS Randomized Controlled Trials

Table 3. Hemodynamic Changes From Baseline at 3, 6, and 24 Hours in Patients Who Underwent Pulmonary Artery Catheterization

Measure	Baseline, Mean (95% CI)	Change From Baseline					
		3 h		6 h		24 h	
		Mean (95% CI)	*P* Value[a]	Mean (95% CI)	*P* Value[a]	Mean (95% CI)	*P* Value[a]
Cardiac index[b]							
Placebo (n = 41)	2.01 (1.86 to 2.15)	0.18 (0.00 to 0.36)	.07	0.18 (−0.02 to 0.39)	.19	0.15 (−0.08 to 0.39)	.39
Tezosentan (n = 43)	2.14 (1.98 to 2.30)	0.31 (0.17 to 0.45)		0.25 (0.11 to 0.40)		0.15 (−0.01 to 0.31)	
PCWP, mm Hg							
Placebo (n = 41)	25.6 (23.9 to 27.3)	−1.5 (−3.0 to 0.0)	.02	−1.9 (−4.0 to 0.1)	.01	−2.9 (−5.6 to −0.1)	.24
Tezosentan (n = 43)	26.3 (24.5 to 28.1)	−4.6 (−6.3 to −2.9)		−5.2 (−7.1 to −3.2)		−4.1 (−6.8 to −1.4)	
mPAP, mm Hg							
Placebo (n = 40)	35.4 (32.3 to 38.5)	−0.7 (−3.1 to 1.6)	.003	−0.9 (−3.5 to 1.7)	.005	−0.8 (−4.4 to 2.7)	.07
Tezosentan (n = 42)	36.7 (34.1 to 39.3)	−5.0 (−7.2 to −2.8)		−5.6 (−8.1 to −3.0)		−4.4 (−8.0 to −0.7)	
SVR, dyne·s/cm^5							
Placebo (n = 41)	1813 (1590 to 2037)	−157 (−361 to 47)	.02	−54 (−253 to 145)	.02	137 (−148 to 421)	.04
Tezosentan (n = 41)	1742 (1538 to 1946)	−371 (−524 to −218)		−306 (−475 to −137)		−101 (−365 to 163)	
PVR, dyne·s/cm^5							
Placebo (n = 40)	243 (174 to 313)	9 (−44 to 61)	.06	−21 (−32 to 75)	.03	127 (27 to 228)	.07
Tezosentan (n = 41)	232 (190 to 273)	−39 (−79 to 1)		−38 (−82 to 6)		53 (−36 to 142)	
RAP, mm Hg							
Placebo (n = 41)	15.9 (13.5 to 18.3)	0.8 (−0.6 to 2.2)	.02	−0.2 (−2.1 to 1.6)	.27	0.7 (−1.9 to 3.3)	.33
Tezosentan (n = 42)	14.6 (12.8 to 16.5)	−2.0 (−3.2 to −0.7)		−1.0 (−2.7 to 0.7)		0.0 (−2.4 to 2.4)	

John J. V. McMurray *JAMA.* *2007;298(17):2009-2019*

Figure 2. Change in Dyspnea in VERITAS-1 and VERITAS-2



Change in dyspnea shown as the area under the curve. VERITAS indicates Value of Endothelin Receptor Inhibition With Tezosentan in Acute Heart Failure Studies. Error bars indicate 95% confidence intervals.

Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial

John R Teerlink The Lancet
Novembre 2012

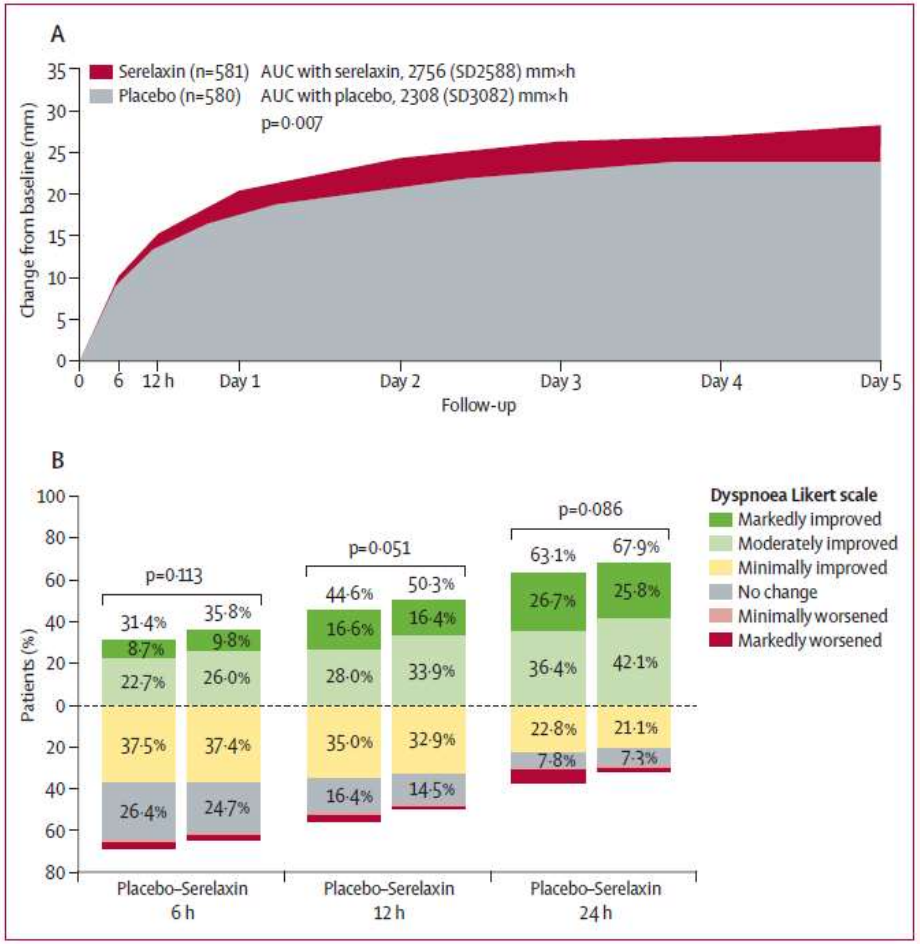
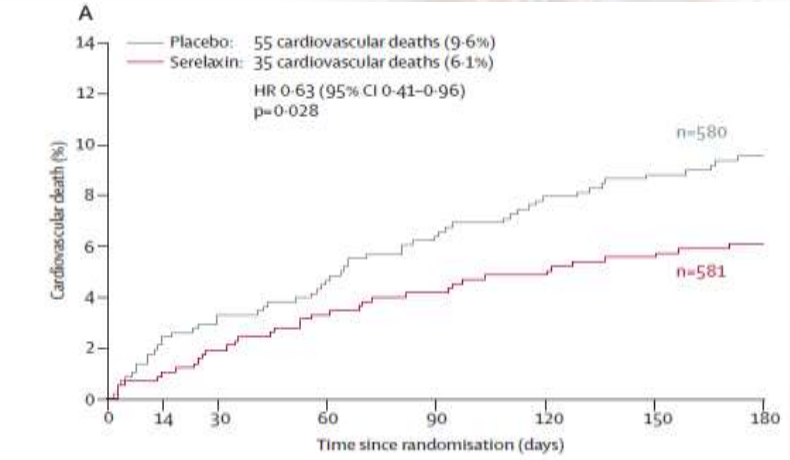
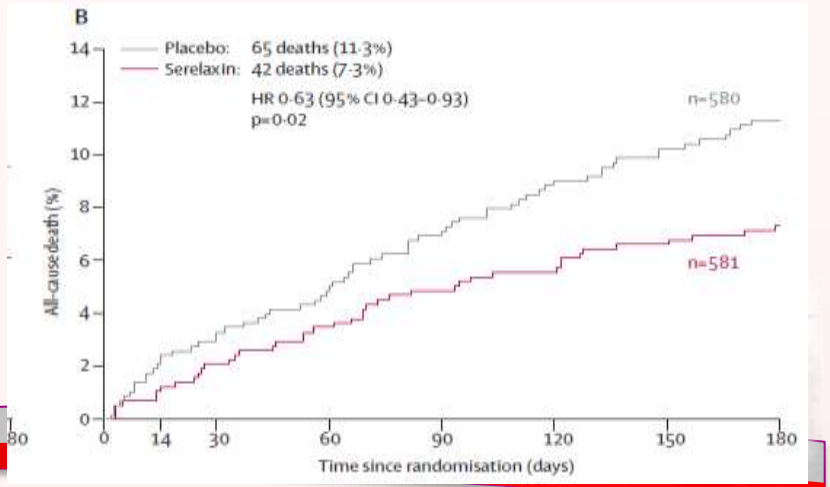


Figure 2: Patient-reported change in dyspnoea





European Heart Journal (2012) **33**, 1787–1847
doi:10.1093/eurheartj/ehs104

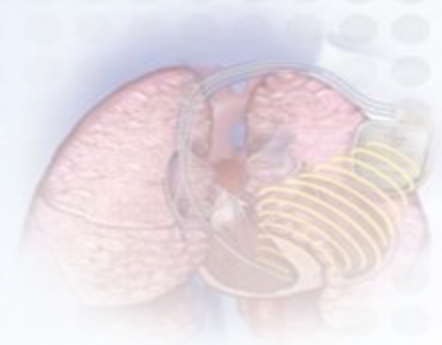
ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

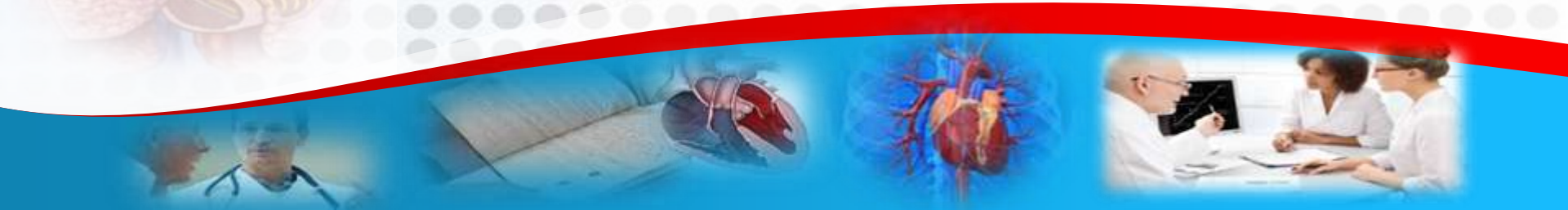
An i.v. infusion of a nitrate should be considered in patients with pulmonary congestion/oedema and a systolic blood pressure >110 mmHg, who do not have severe mitral or aortic stenosis, to reduce pulmonary capillary wedge pressure and systemic vascular resistance. Nitrates may also relieve dyspnoea and congestion. Symptoms and blood pressure should be monitored frequently during administration of i.v. nitrates.	IIa	B
An i.v. infusion of sodium nitroprusside may be considered in patients with pulmonary congestion/oedema and a systolic blood pressure >110 mmHg, who do not have severe mitral or aortic stenosis, to reduce pulmonary capillary wedge pressure and systemic vascular resistance. Caution is recommended in patients with acute myocardial infarction. Nitroprusside may also relieve dyspnoea and congestion. Symptoms and blood pressure should be monitored frequently during administration of i.v. nitroprusside.	IIb	B

Nesiritide

Nesiritide—a human BNP that acts mainly as a vasodilator—was recently shown to reduce dyspnoea by a small but statistically significant amount when added to conventional treatment (mainly diuretic).[228]

Les inotropes et vasopresseurs





Les inotropes et vasopresseurs

L'agent inotrope positif se définit comme une molécule qui augmente la contractilité myocardique le plus souvent gauche et droite.

4 CLASSES

Classe 1

Ce sont les moléules qui augmentent la concentration intracellulaire d'adénosine monophosphate cyclique (AMPc)

- Catécholamines : Dobutamine
- Inhibiteur de la phosphodiestérase

Classe 2

agissent sur les pompes et canaux ioniques de la membrane cellulaire telles que les digitaliques

Classe 3

modulent l'utilisation du Ca ++ par la troponine C, telles que le levosimendan : « sensibiliseurs du calcium »

Classe 4

Ce sont des molécules à mécanisme d'action multiple telles que le primobendan et la vesnarinone

Catherine L. Tacon
John McCaffrey
Anthony Delaney

Dobutamine for patients with severe heart failure: a systematic review and meta-analysis of randomised controlled trials

Intensive Care Med 2011

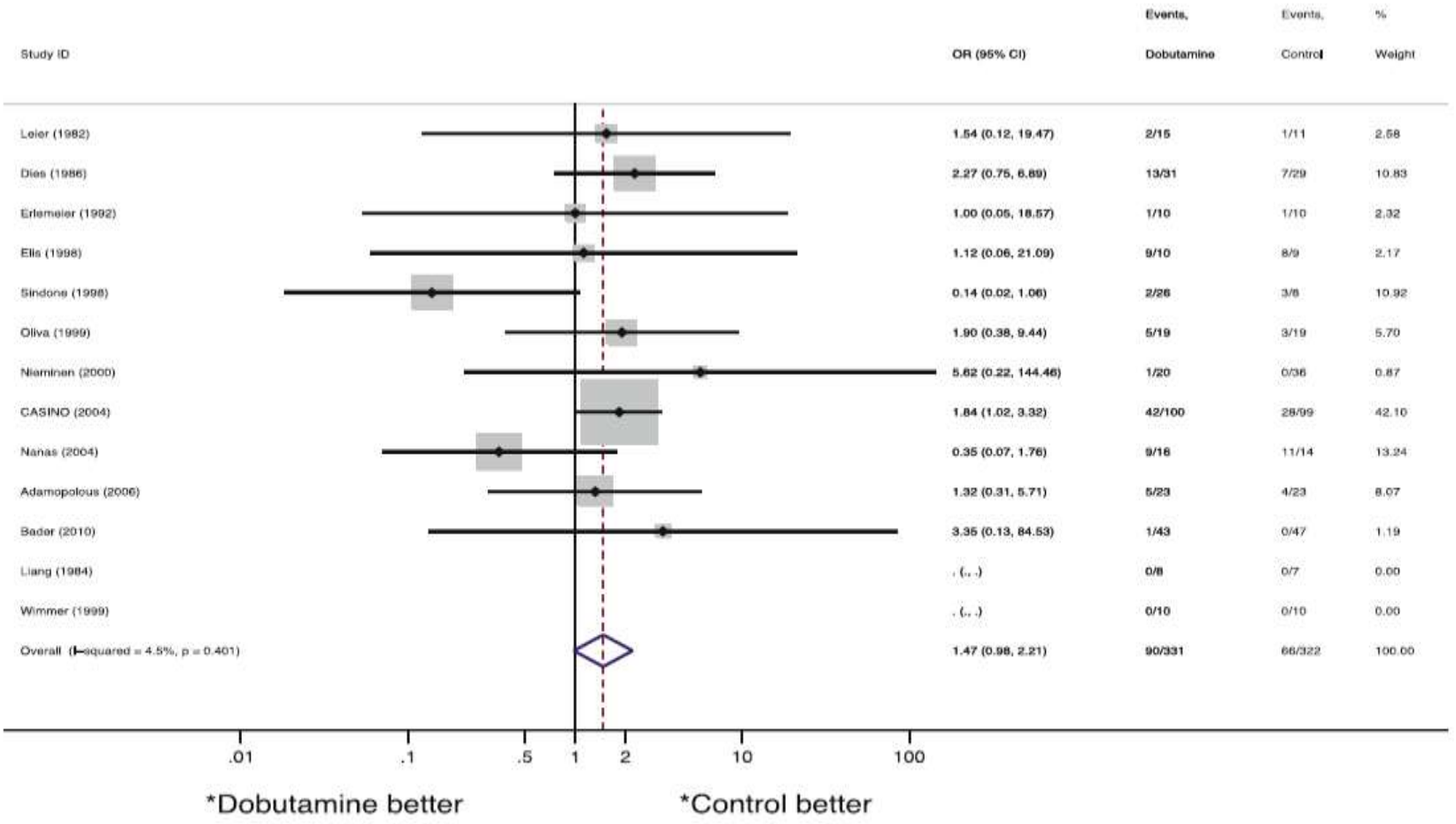


Fig. 2 Forrest plot showing the pooled estimate of the odds ratio for mortality for dobutamine compared with placebo or standard care in patients with severe heart failure

Reassessing treatment of acute heart failure syndromes: the ADHERE Registry

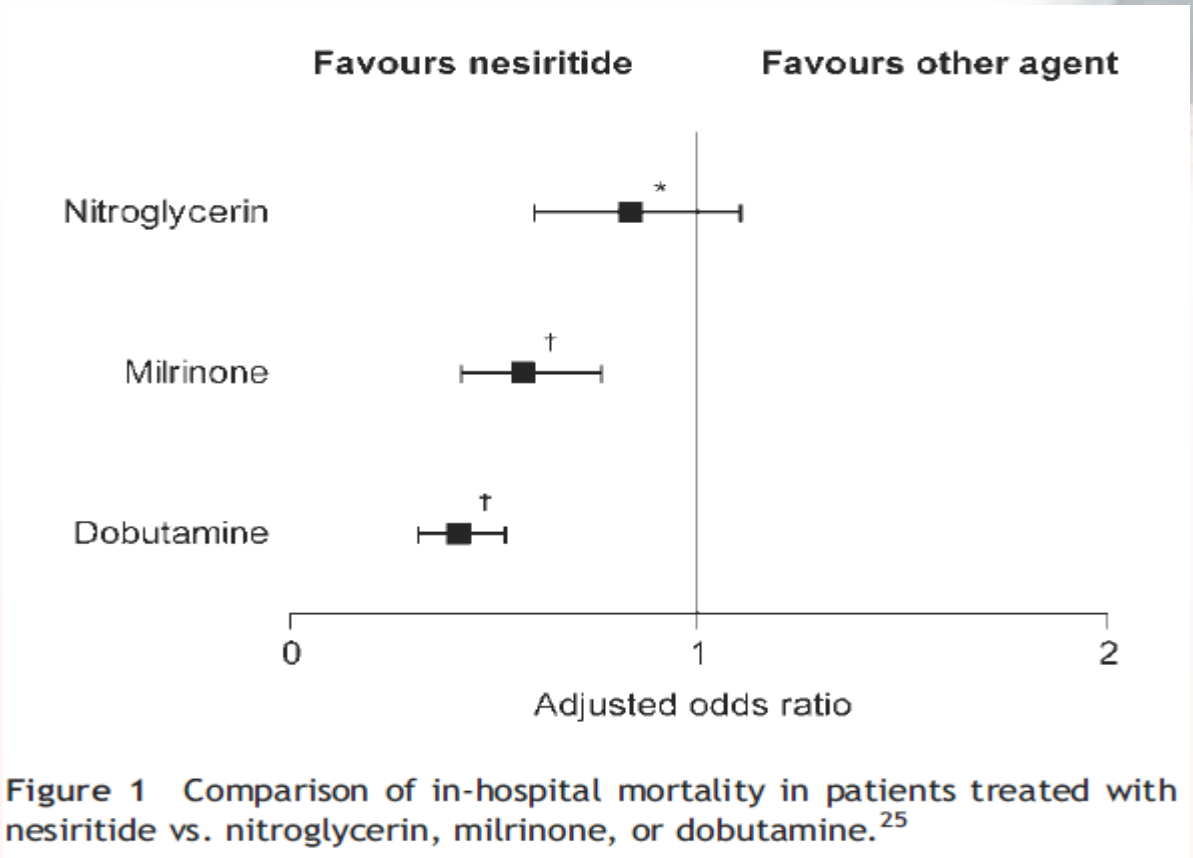


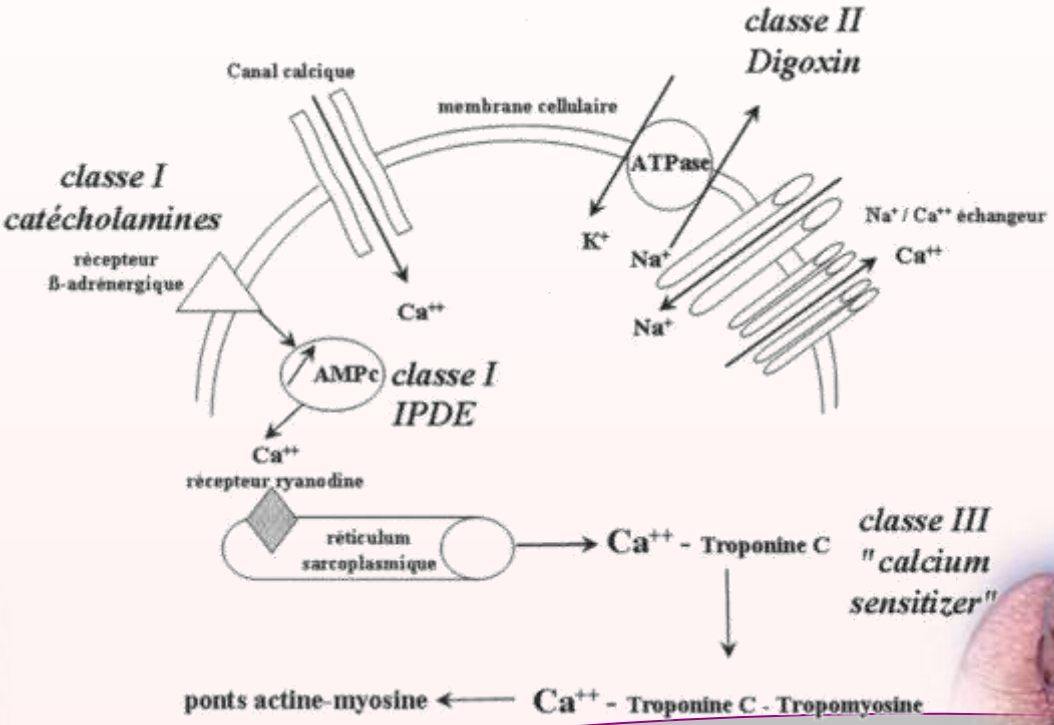
Figure 1 Comparison of in-hospital mortality in patients treated with nesiritide vs. nitroglycerin, milrinone, or dobutamine.[25]

Mihai Gheorghiade European Heart Journal 2005; 7 : B13–B19

INHIBITEURS DE LA PHOSPHO-DIESTÉRASE

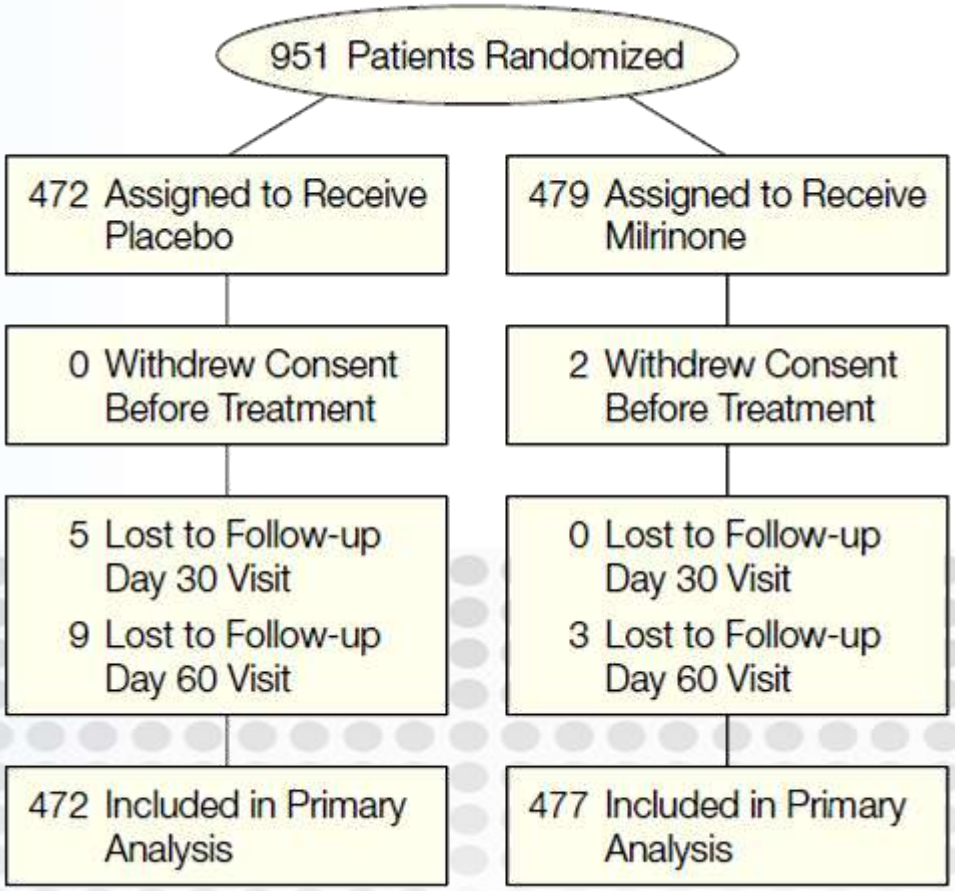
Les effets hémodynamiques:

- une augmentation du débit cardiaque et du volume d'éjection
- une diminution des pressions artérielles pulmonaires, des résistances vasculaires systémiques et pulmonaires.
- Combinent les effets hémodynamiques des vasodilatateurs purs type dérivés nitrés et des inotropes positifs du type dobutamine



Short-term Intravenous Milrinone for Acute Exacerbation of Chronic Heart Failure

A Randomized Controlled Trial



Cuffe MS Optime-CHF JAMA 2002

Short-term Intravenous Milrinone for Acute Exacerbation of Chronic Heart Failure

A Randomized Controlled Trial

Table 4. Primary Outcome and Hospitalization

Outcome	Placebo (n = 472)	Milrinone (n = 477)	*P* Value
Days of hospitalization for cardiovascular causes within 60 days			
Median (IQR)*	7 (4, 14)	6 (4, 13)	.71
Mean (SD)	12.5 (14.0)	12.3 (14.1)	
Days of hospitalization from infusion to initial discharge			
Median (IQR)	5 (4, 8)	5 (4, 7)	.99
Mean (SD)	7.0 (6.6)	7.0 (6.2)	
Days of hospitalization for cardiovascular causes from discharge to 60 days			
Median (IQR)	0 (0, 5)	0 (0, 5)	.59
Mean (SD)	5.9 (12.5)	5.7 (12.6)	
Days of hospitalization for any cause within 60 days			
Median (IQR)	8 (4, 16)	7 (4, 15)	.83
Mean (SD)	13.5 (14.4)	13.4 (14.7)	
Death or readmission within 60 days, No./Total (%)	164/464 (35.3)	166/474 (35.0)	.92

*IQR indicates interquartile range.

Cuffe MS Optime-CHF JAMA 2002

Short-term Intravenous Milrinone for Acute Exacerbation of Chronic Heart Failure

A Randomized Controlled Trial

Table 6. Adverse Events and Mortality*

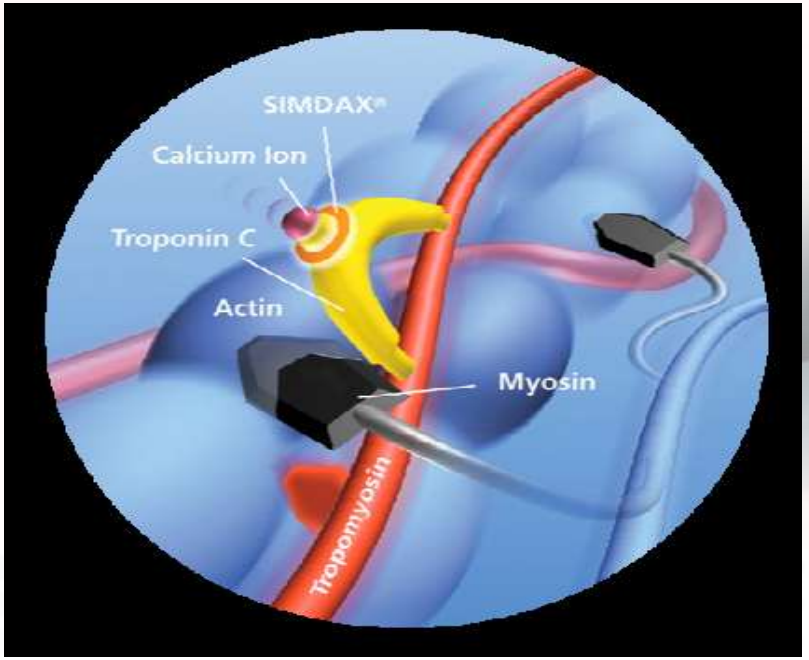
Adverse Event, No. (%)	Placebo (n = 472)	Milrinone (n = 477)	*P* Value
Treatment failure cause at 48 hours	43/466 (9.2)	97/470 (20.6)	<.001
Progression of heart failure	6.8	7.9	.54
Adverse event	2.1	12.6	<.001
Sustained hypotension‡	15 (3.2)	51 (10.7)	<.001
Death	11 (2.3)	18 (3.8)	.19
Events within 60 days			
Myocardial infarction	5/448 (1.1)	10/462 (2.2)	.21
New atrial fibrillation or flutter	16/446 (3.6)	26/462 (5.6)	.14
Ventricular tachycardia or fibrillation	20/446 (4.5)	23/461 (5.0)	.72
Death	41/463 (8.9)	49/474 (10.3)	.41

Pas de preuve scientifique mettant en évidence la supériorité d'un des IPDE par rapport aux autres

Cuffe MS Optime-CHF JAMA 2002

Levosimendan

- C'est un nouvel agent inotrope de la classe III des « calcium sensitizers »
- Il possède deux mécanismes d'action :
  - Il agit en augmentant l'affinité de la **troponine C** **au ca^{++}**→ une contraction myofibrillaire prolongée sans modification de la concentration du Ca $^{++}$ intracellulaire : accroît l'intensité et la durée de la contraction des cardiomyocytes.



Levosimendan

- Le lévosimendan induit aussi une **vasodilatation** coronaire, artérielle et veineuse périphérique en exerçant un effet agoniste des canaux potassiques ATP-dépendants des fibres musculaires lisses → améliore aussi la contractilité myocardique par baisse de la pré- et de la postcharge
- *Demi vie courte*
- Bolus 10 min puis perfusion continue de 24 h
- **Métabolite actif** : activité myocardique aussi importante que le levosimendan mais demi vie longue de 80 heures.

Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction

A randomized, placebo-controlled, double-blind study (RUSSLAN)

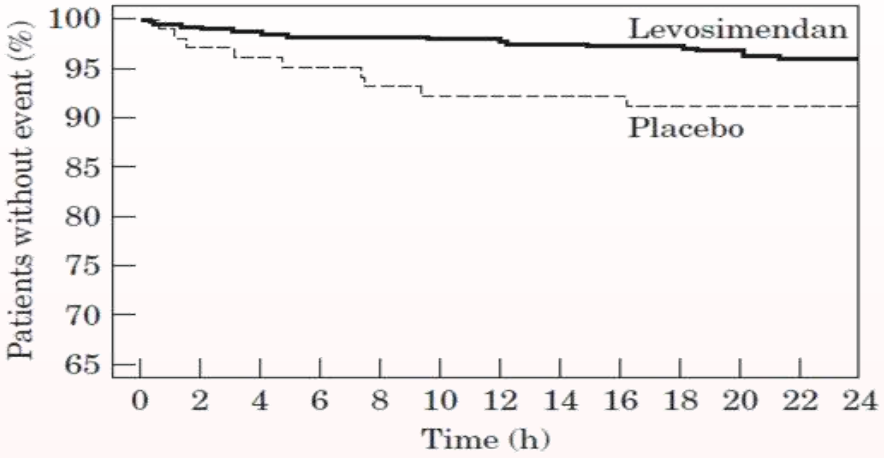


Figure 2 Combined risk of death and worsening heart failure during the first 24 h after start of infusion. The combined risk of death and worsening heart failure was 2·0% in levosimendan group and 5·9% in placebo group during the 6–h infusion period (P=0·033, log-rank) and 4·0% in levosimendan group and 8·8% in placebo group (P=0·044) during the first 24 h after start of infusion.

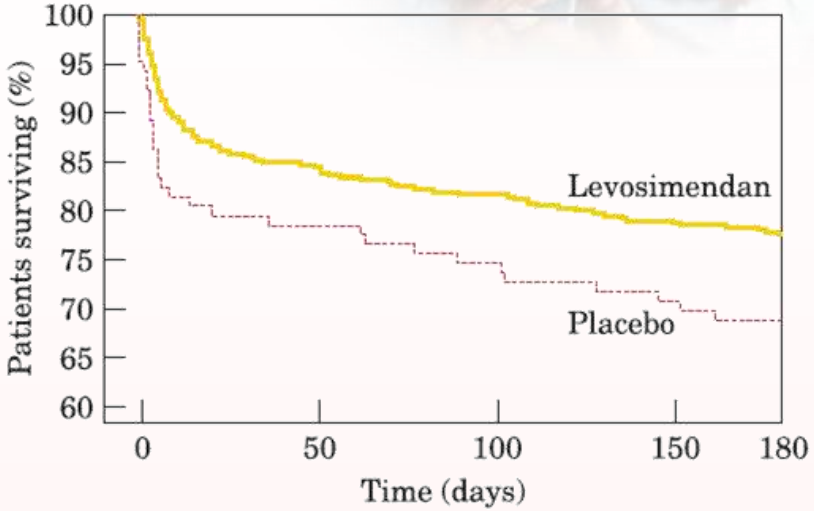
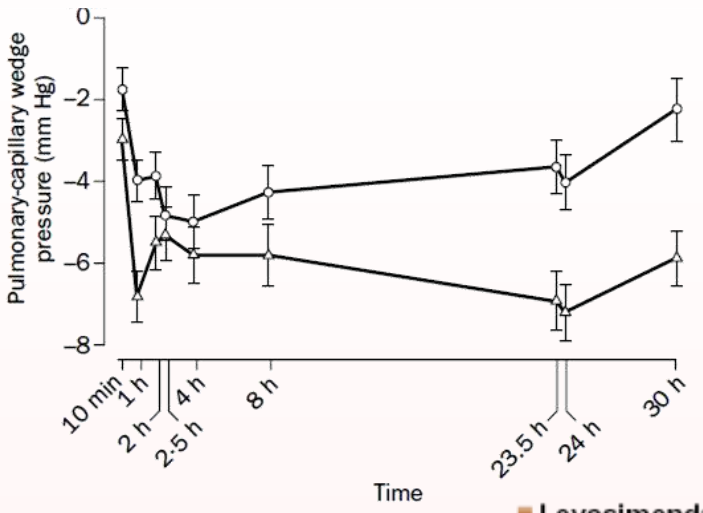


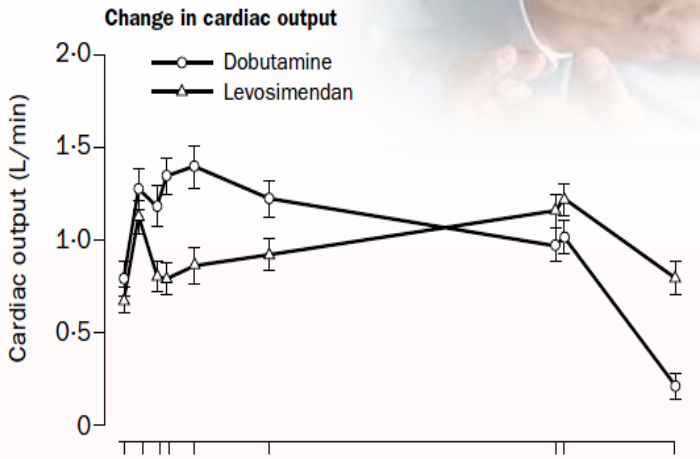
Figure 3 Overall survival in 180 days after start of infusion. The mortality rates at 14 days were 11·7% in the levosimendan group and 19·6% in the placebo group (P=0·031, Cox Proportional Hazards); at 180 days the rates were 22·6% and 31·4%, respectively (P=0·053).

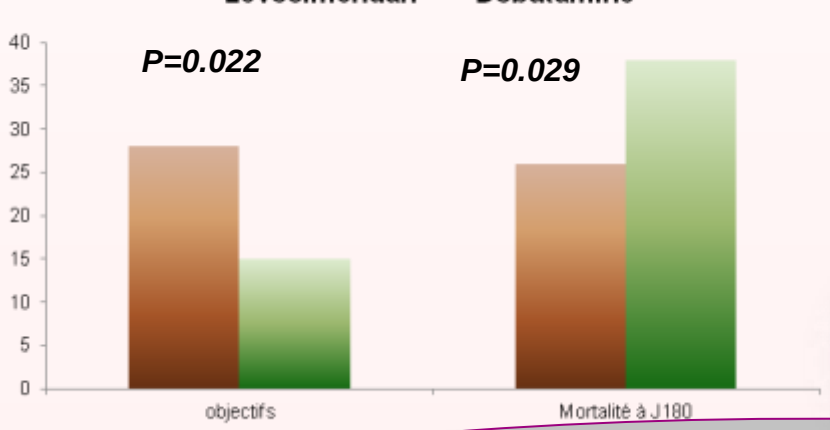
V. S. Moiseyev European Heart Journal (2002) 23, 1422–1432

Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial

103 patients were assigned levosimendan and 100 dobutamine.





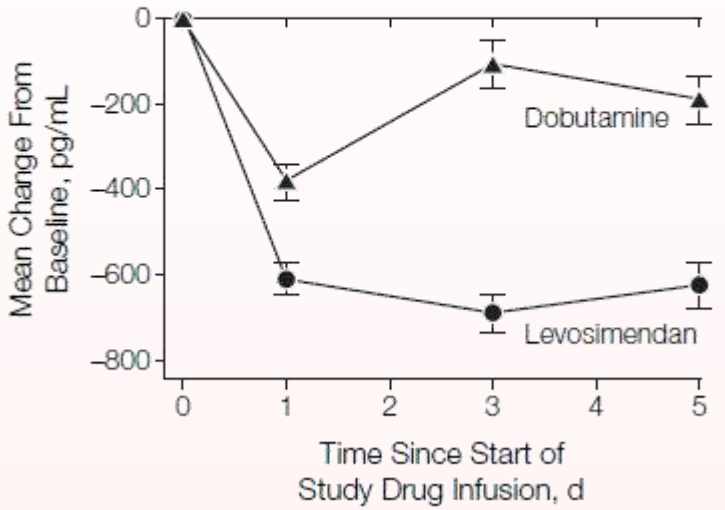


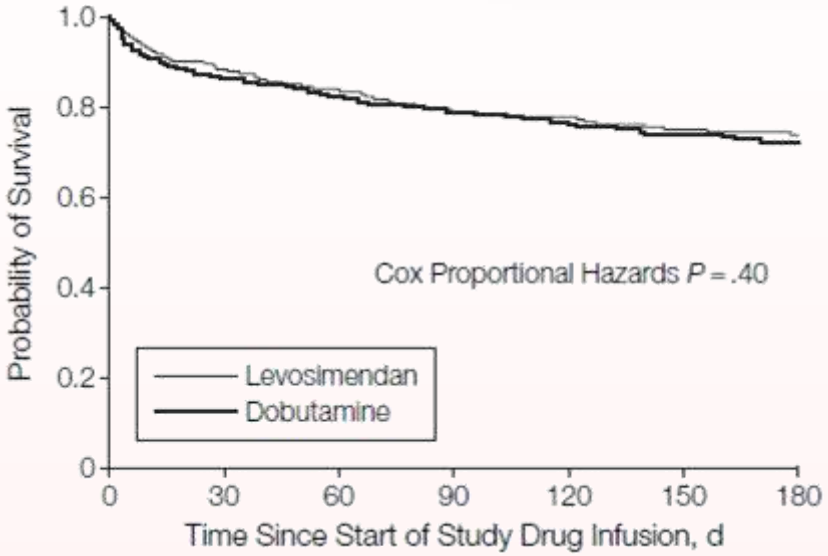
F Follath, Lancet 2002; 360: 196–202

Levosimendan vs Dobutamine for Patients With Acute Decompensated Heart Failure

The SURVIVE Randomized Trial

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

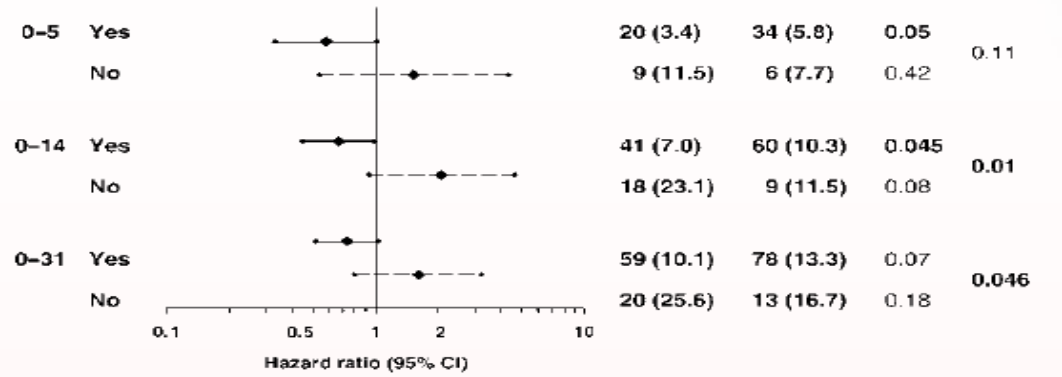




Alexandre Mebazaa *JAMA. 2007;297:1883-1891*

Levosimendan vs. dobutamine: outcomes for acute heart failure patients on β-blockers in SURVIVE†

B



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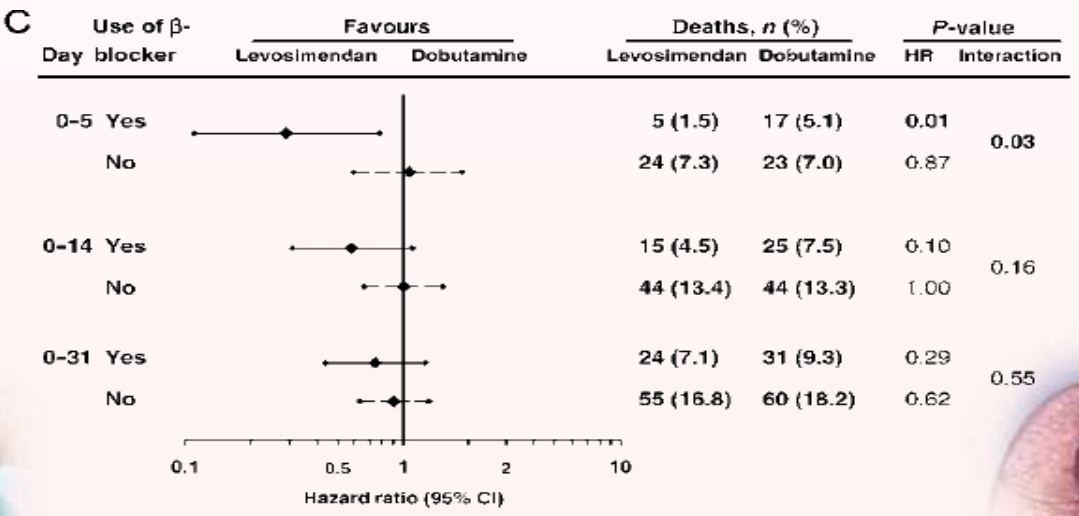


Alexandre Mebazaa
European Journal of Heart Failure (2009) 11, 304–311

Levosimendan for the treatment of acute severe heart failure: A meta-analysis of randomised controlled trials

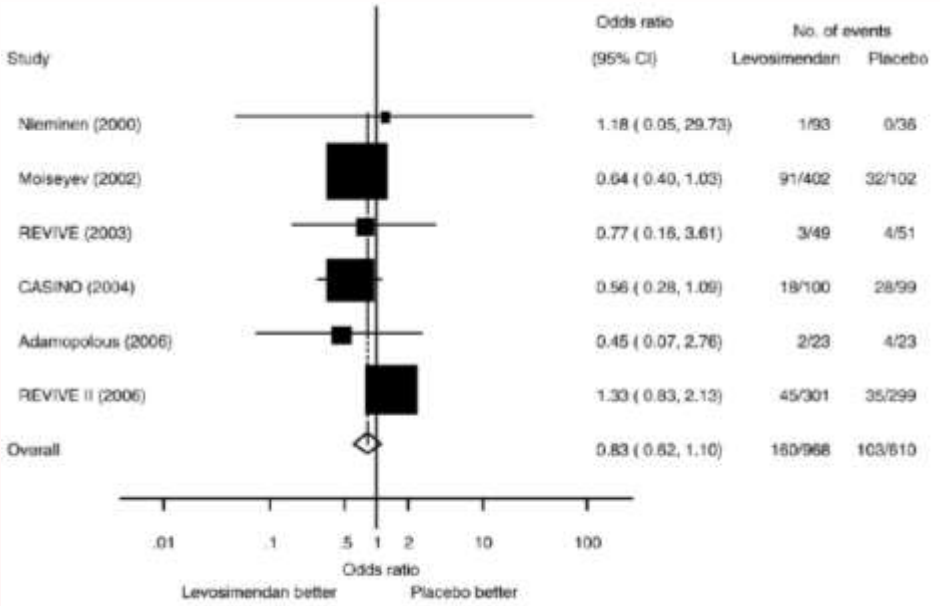


Fig. 2. The effect of levosimendan compared to placebo on mortality.

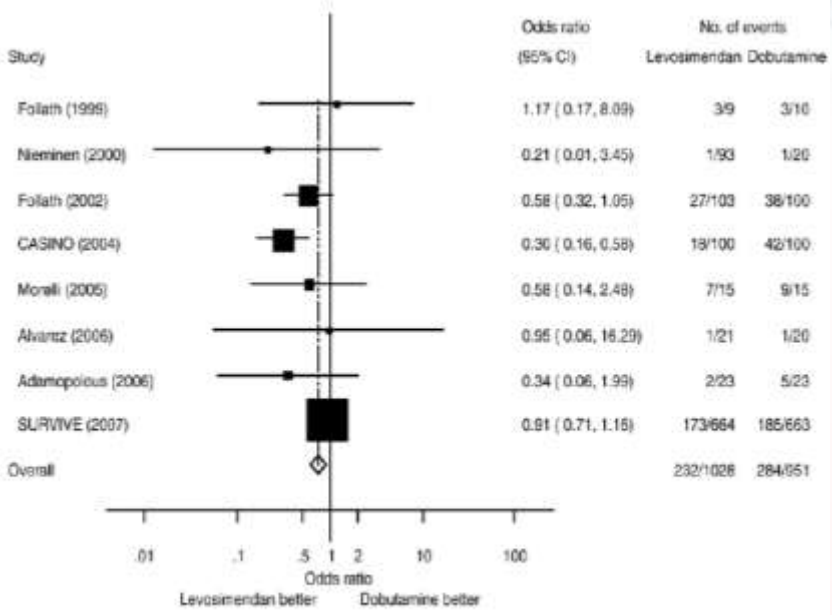


Fig. 3. The effect of levosimendan compared to dobutamine on mortality.

Anthony Delaney International Journal of Cardiology 138 (2010) 281–289

Levosimendan for the treatment of acute severe heart failure: A meta-analysis of randomised controlled trials

Summary of the haemodynamic effects of levosimendan compared to control.

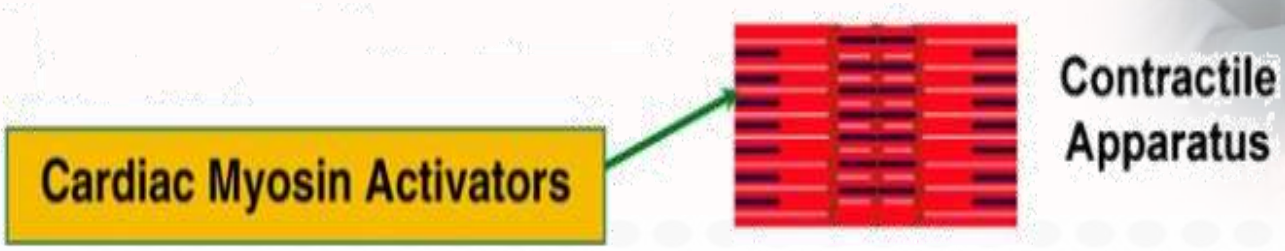
Control group	Haemodynamic parameter	Number of studies	WMD	95%CI	*p* value
Placebo	EF (%)	3	3.2	0.3 to 6.0	0.03
	Cardiac index (l/min/m^2)	2	0.15	−0.1 to 0.4	0.26
	PAOP (mm Hg)	2	−3.8	−6.3 to −1.3	0.003
	BNP (pg/ml)	2	−329	−617 to −42	0.025
Dobutamine	EF (%)	1	3.0	−1.4 to 7.4	0.18
	Cardiac index (l/min/m^2)	3	0.33	0.24 to 0.43	<0.0005
	PAOP (mm Hg)	3	−2.91	−3.3 to −2.5	<0.0005
	BNP (pg/ml)	2	−595	−1000 to −180	0.005
Milrinone	Cardiac index (l/min/m^2)	1	0.1	−0.48 to 0.68	0.73
	PAOP (mm Hg	1	−2.0	−4.5 to 0.5	0.12
PGE1	PAOP (mm Hg)	1	−1.0	−3.4 to 1.4	0.41
	BNP (pg/ml)	1	−210	−611 to 191	0.31

WMD = weighted mean difference, CI = confidence interval, EF = ejection fraction, PAOP = pulmonary artery occlusion pressure, BNP = B-type natureitic peptide.

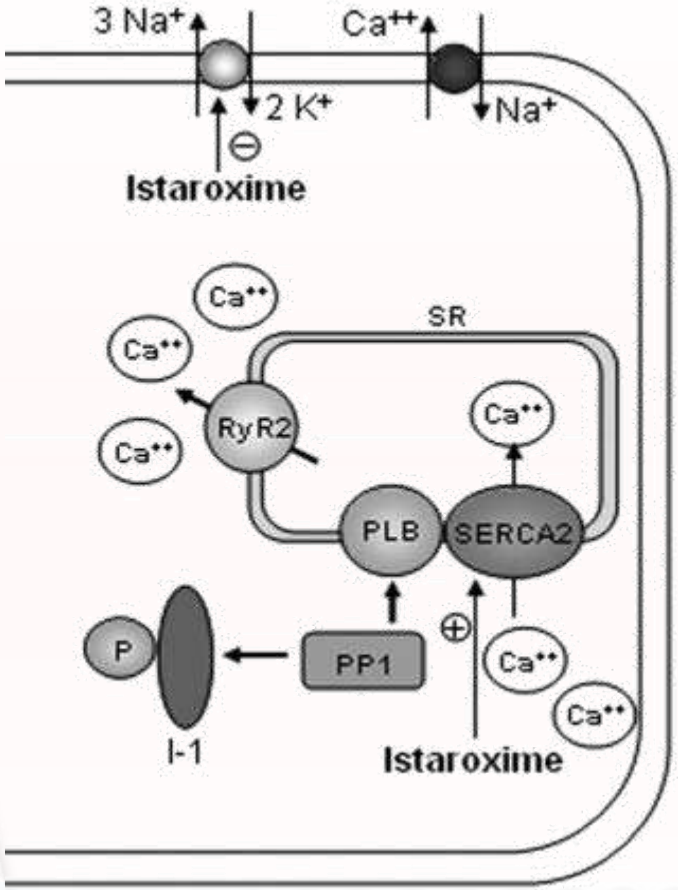
Anthony Delaney International Journal of Cardiology 138 (2010) 281–289

Activateur de la myosine cardiaque

- **Les activateurs de la myosine cardiaque :**
  - augmentent l'activité de l'ATPase myofibrillaire → accroît la force contractile des cardiomyocytes sans augmenter le nombre de molécules d'ATP consommées,
  - ces substances augmentent la force contractile du myocarde sans élever la concentration intracytoplasmique en calcium
- CK-1827452 études animales positives
- Etudes phase 1 en cours



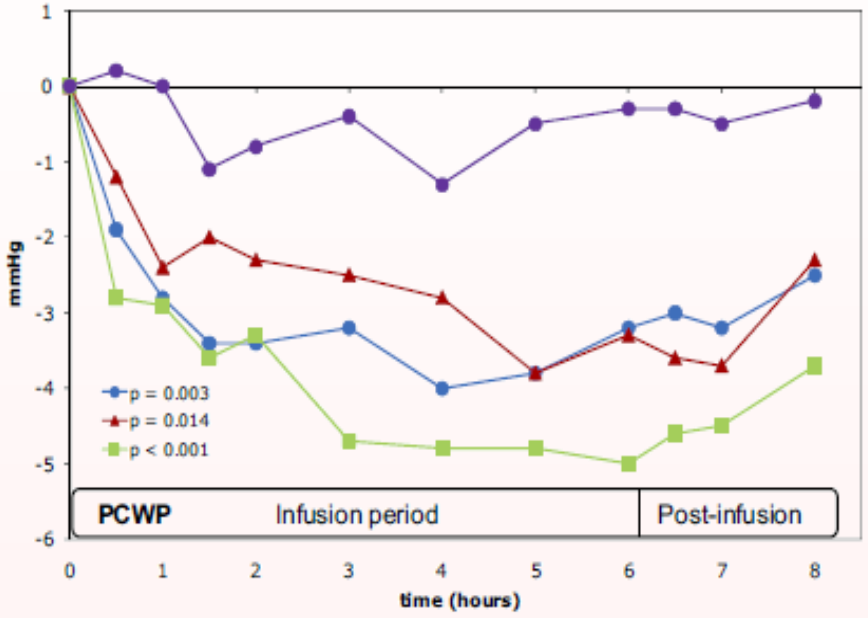
ISTAROXIME

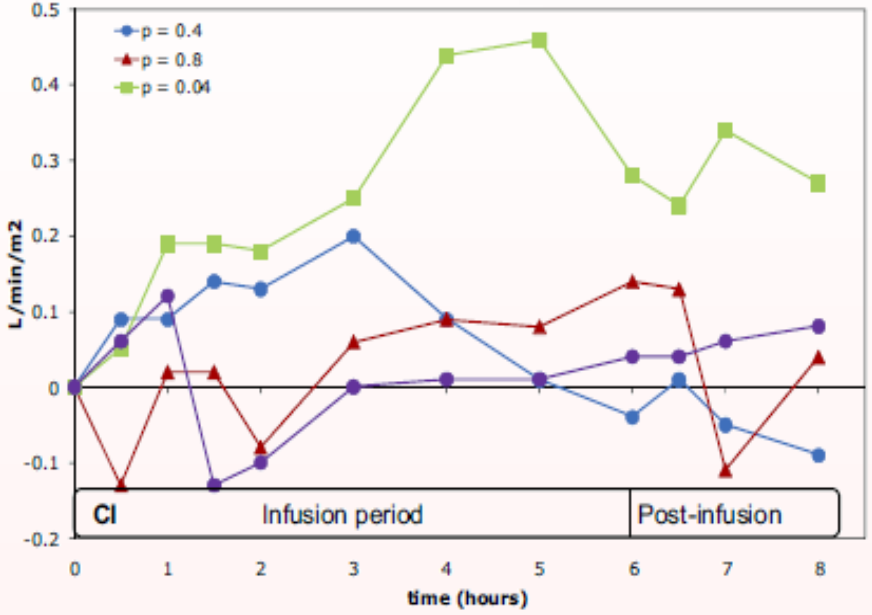


- un inhibiteur de la pompe Na/K ATPase qui augmente l'activité de la pompe «Sarco-Endoplasmic Reticulum Ca2+-ATPase (SERCA)»

Hemodynamic, Echocardiographic, and Neurohormonal Effects of Istaroxime, a Novel Intravenous Inotropic and Lusitropic Agent

A Randomized Controlled Trial in Patients Hospitalized With Heart Failure





Mihai Gheorghiade J am Coll Cardiol 2008;51:2276–85

Effects of istaroxime on diastolic stiffness in acute heart failure syndromes: Results from the *Hemodynamic, Echocardiographic, and Neurohormonal Effects of Istaroxime, a Novel Intravenous Inotropic and Lusitropic Agent: a Randomized Controlled Trial in Patients Hospitalized with Heart Failure (HORIZON-HF) trial*

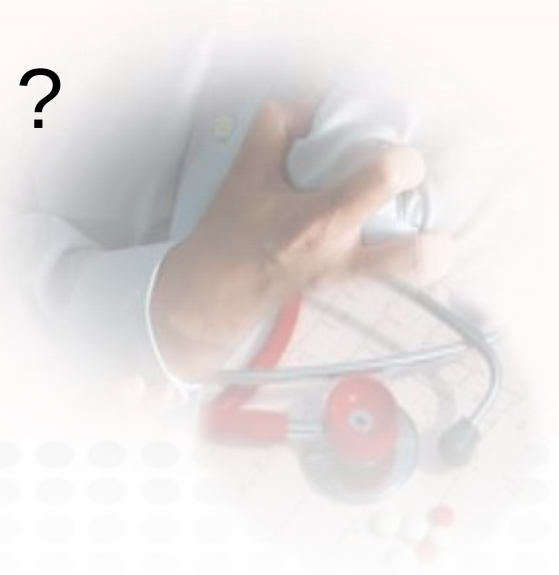
Table III. Changes in hemodynamic and echocardiographic parameters with drug infusion

	Istaroxime (n = 89)		Placebo (n = 31)		
	Change from baseline	*P* (within group)	Change from baseline	*P* (within group)	*P* (between groups)
Hemodynamic parameters					
Heart rate (beat/min)	−2.1 ± 10.3	.06	0.3 ± 6.0	.78	.24
Systolic blood pressure (mm Hg)	9.2 ± 12.9	<.0001	2.1 ± 11.0	.31	.008
Diastolic blood pressure (mm Hg)	1.4 ± 9.4	.17	0.4 ± 6.4	.71	.61
Mean arterial pressure (mm Hg)	4.0 ± 8.9	.0001	1.0 ± 6.9	.44	.10
Right atrial pressure (mm Hg)	−1.3 ± 3.2	.0006	−0.3 ± 2.2	.53	.13
PCWP (mm Hg)	−3.7 ± 6.0	<.0001	−0.2 ± 3.1	.97	.001
Cardiac index (L min^{-1} m^{-2})	0.12 ± 0.76	.16	0.03 ± 0.65	.83	.57
Stroke volume index (mL/m^2)	2.7 ± 12.7	.051	0.5 ± 10.2	.80	.39
Systemic vascular resistance index (dynes s^{-1} cm^{-5} m^{-2})	30 ± 799	.73	−47 ± 583	.67	.64
Stroke work index (g · m/m^2 per beat)	6.4 ± 13.3	<.0001	1.8 ± 9.9	.35	.09
Echocardiographic parameters					
LV end-diastolic volume (mL)	−4.6 ± 18.1	.02	4.4 ± 33.0	.49	.07
LV end-systolic volume (mL)	−8.8 ± 13.7	<.0001	−2.2 ± 25.9	.66	.08
LVEF (%)	3.0 ± 3.9	<.0001	3.4 ± 4.0	.0001	.65
E velocity (cm/s)	−3.2 ± 16.0	.07	−3.1 ± 11.2	.15	.99
A velocity (cm/s)	6.3 ± 16.1	.0005	2.6 ± 16.6	.41	.30
E/A ratio	−0.43 ± 0.83	<.0001	−0.28 ± 0.87	.10	.42
E-wave deceleration time (ms)	22.1 ± 49.6	.0001	3.9 ± 51.2	.69	.10

Sanjiv J. Shah Am Heart J 2009;157:1035-41

Inhibiteurs de la No synthase

- NO
  - produit en grande quantité lors de l'insuffisance cardiaque
  - Effets délétères sur la fonction cardiaque et diminue les RVS
- Effets des de la NO synthase ?



LINCS: L-NAME (a NO synthase inhibitor) In the treatment of refractory Cardiogenic Shock

A prospective randomized study

Table 3 Secondary Outcome measures in the 2 groups

	No Treatment	L-NAME	*P* value
No of Patients	15	15	
Unaugmented MAP at 24 h (mmHg)	66±13	86±20	0.004*
Unaugmented MAP Increase (mmHg)	+3.6±9.3	+24.8±18	<0.001*
Urine Output at 24 h (cc/h)	110±87	210±86	0.009*
Urine Output Change (cc/h)	−12±87	+135±78	0.001*
Time on IABP (h)	103±60	59±58	0.043*
Time on Mechanical Ventilation (h)	140±55	77±60	0.028*
4-Month Survival	33%	73%	0.028*

*$P<0.05$

Gad Cotter European Heart Journal (2003) 24, 1287–1295

LINCS: L-NAME (a NO synthase inhibitor) In the treatment of refractory Cardiogenic Shock

A prospective randomized study

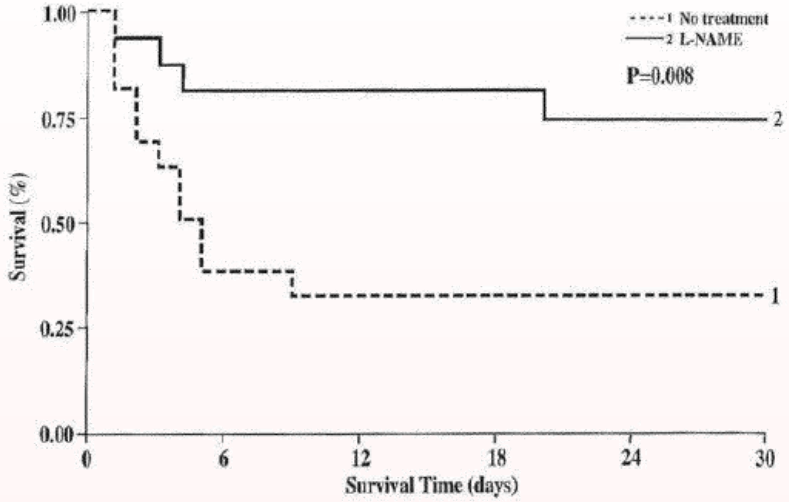


Fig. 1 One-month survival in the two treatment arms.

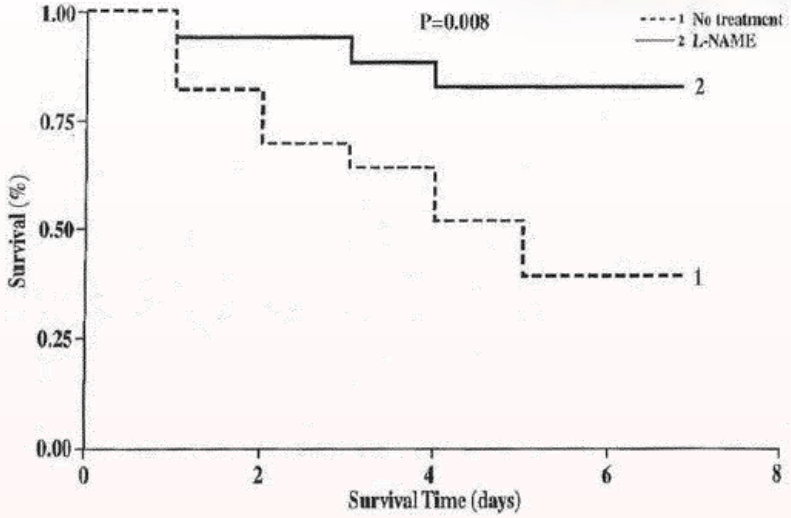
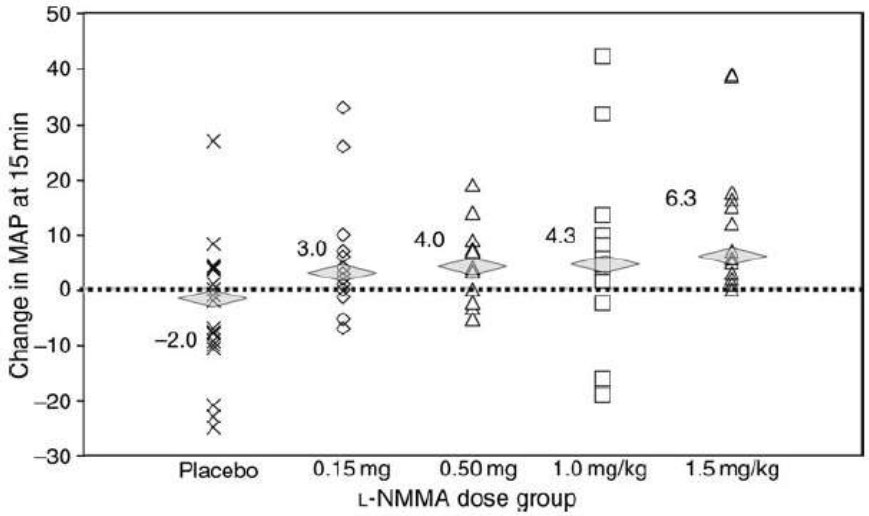


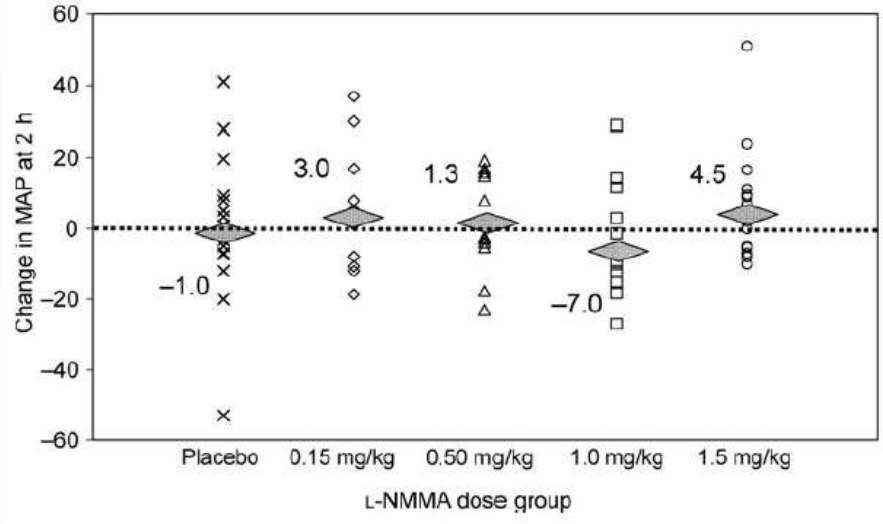
Fig. 2 One-week survival in the two treatment arms.

Gad Cotter European Heart Journal (2003) 24, 1287–1295

Effect of nitric oxide synthase inhibition on haemodynamics and outcome of patients with persistent cardiogenic shock complicating acute myocardial infarction: a phase II dose-ranging study

(SHOCK-2) Investigators

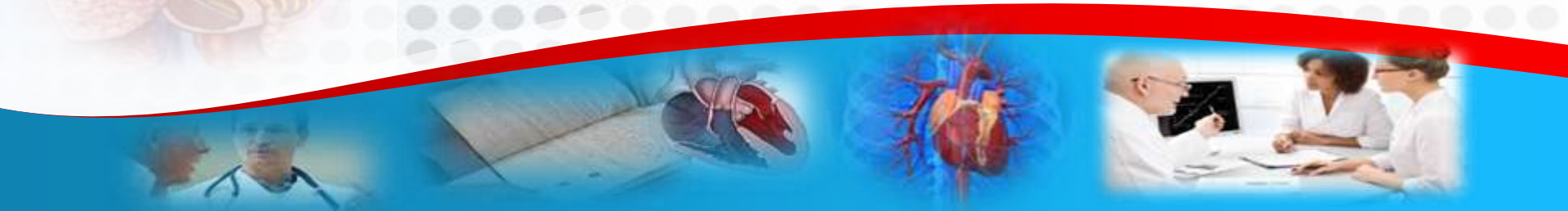




Vladimir Dzavık **European Heart Journal (2007) 28, 1109–1116**

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

Inotropic agents are NOT recommended unless the patient is hypotensive (systolic blood pressure <85 mmHg), hypoperfused, or shocked because of safety concerns (atrial and ventricular arrhythmias, myocardial ischaemia, and death).	III	C
An i.v. infusion of an inotrope (e.g. dobutamine) should be considered in patients with hypotension (systolic blood pressure <85 mmHg) and/or hypoperfusion to increase cardiac output, increase blood pressure, and improve peripheral perfusion. The ECG should be monitored continuously because inotropic agents can cause arrhythmias and myocardial ischaemia.	IIa	C
A vasopressor (e.g. dopamine or norepinephrine) may be considered in patients who have cardiogenic shock, despite treatment with an inotrope, to increase blood pressure and vital organ perfusion. The ECG should be monitored as these agents can cause arrhythmias and/or myocardial ischaemia. Intra-arterial blood pressure measurement should be considered.	IIb	C
An i.v. infusion of levosimendan (or a phosphodiesterase inhibitor) may be considered to reverse the effect of beta-blockade if beta-blockade is thought to be contributing to hypoperfusion. The ECG should be monitored continuously because inotropic agents can cause arrhythmias and myocardial ischaemia, and, as these agents are also vasodilators, blood pressure should be monitored carefully.	IIb	C



Conclusions

- ICA regroupent des patients aux profils cliniques multiples
- O2, VNI, Diurétiques et vasodilatateurs
- Inotropes si Hypotension
- Traitement selon les scénarios cliniques
- Nombreuses innovations thérapeutiques
- plusieurs n’ont pu monter de bénéfices sur la mortalité ou les taux de réadmission hospitalière en ICA