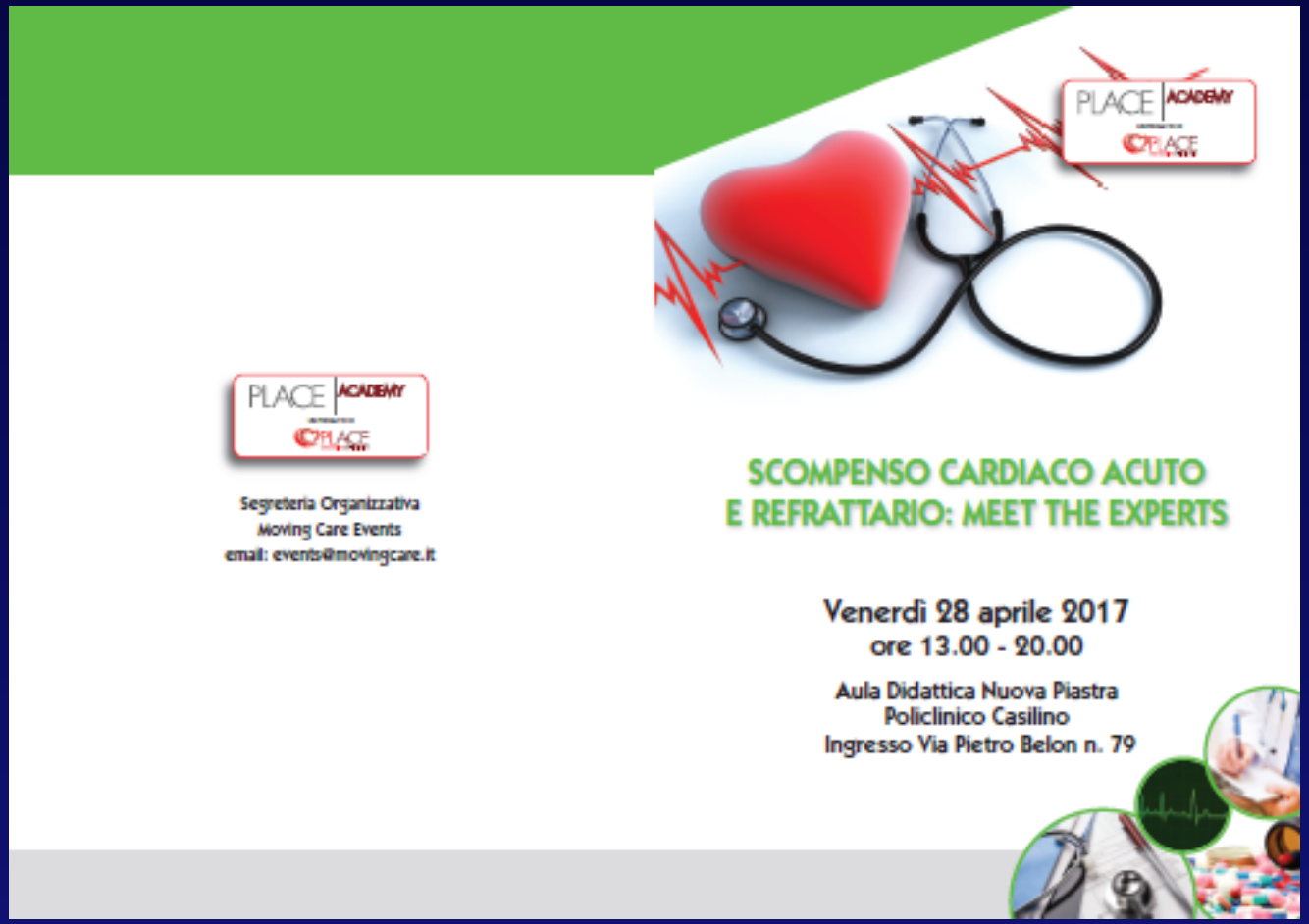
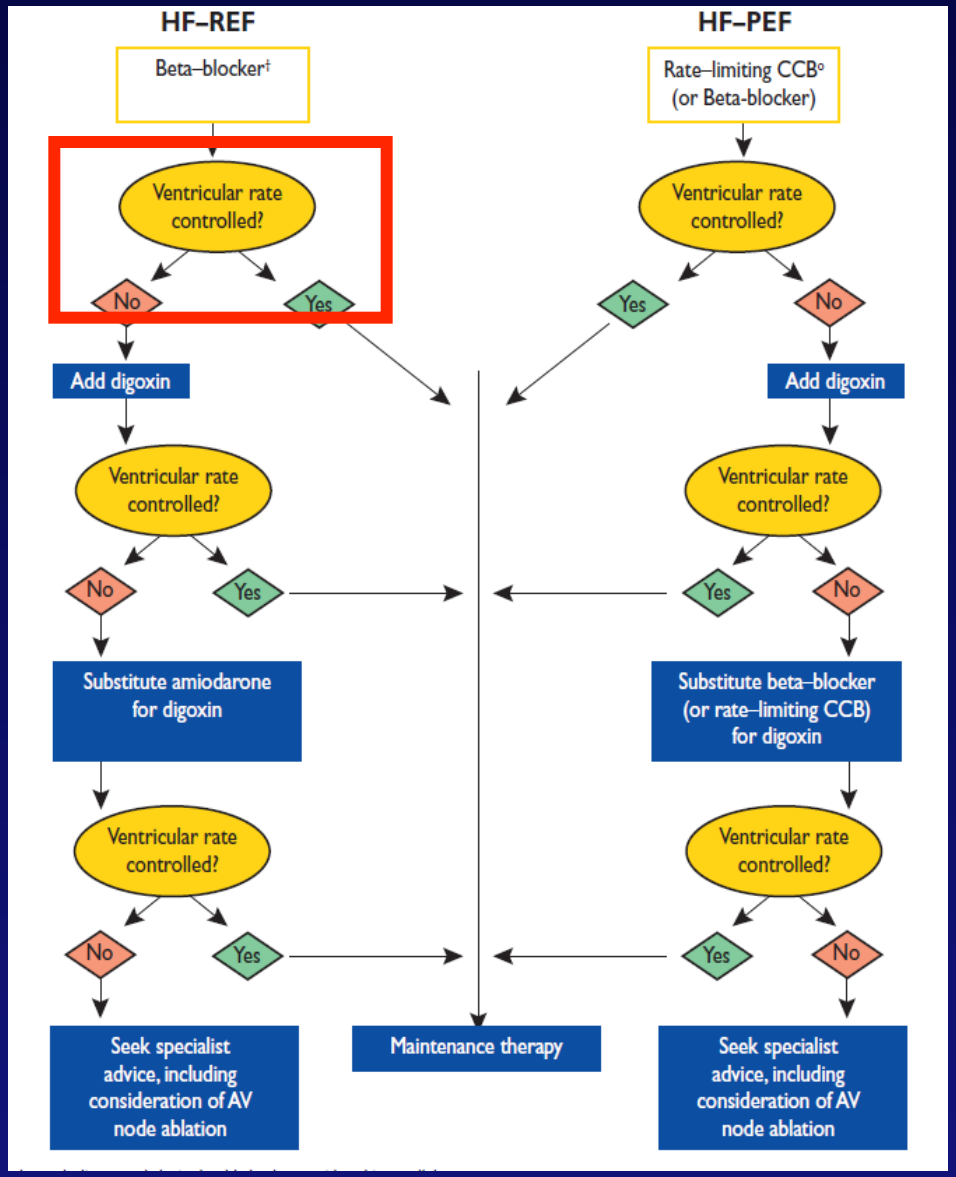


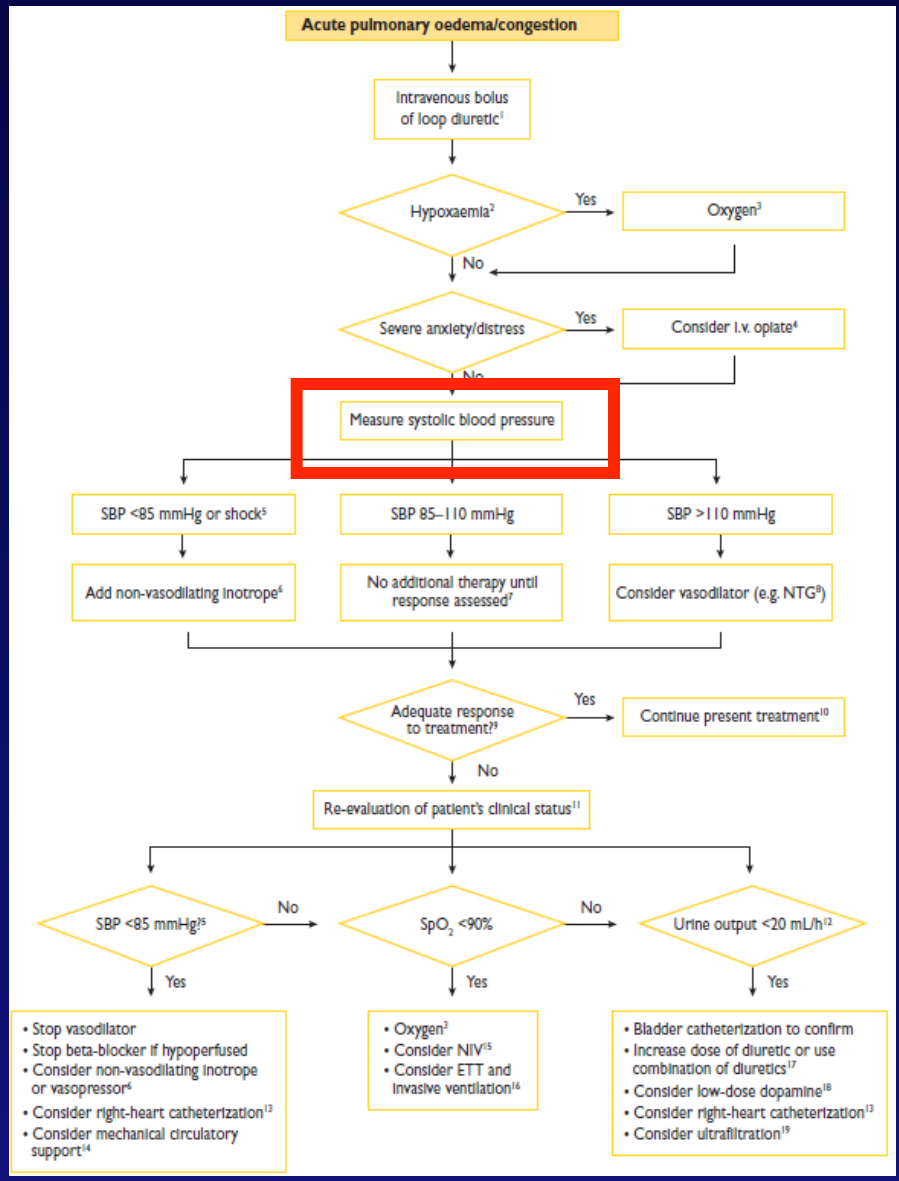

**Inotropi in acuto e nello scompenso refrattario cronico: quando, quali farmaci e in quali pazienti**

**Vito Piazza**

**1 Cardiologia**

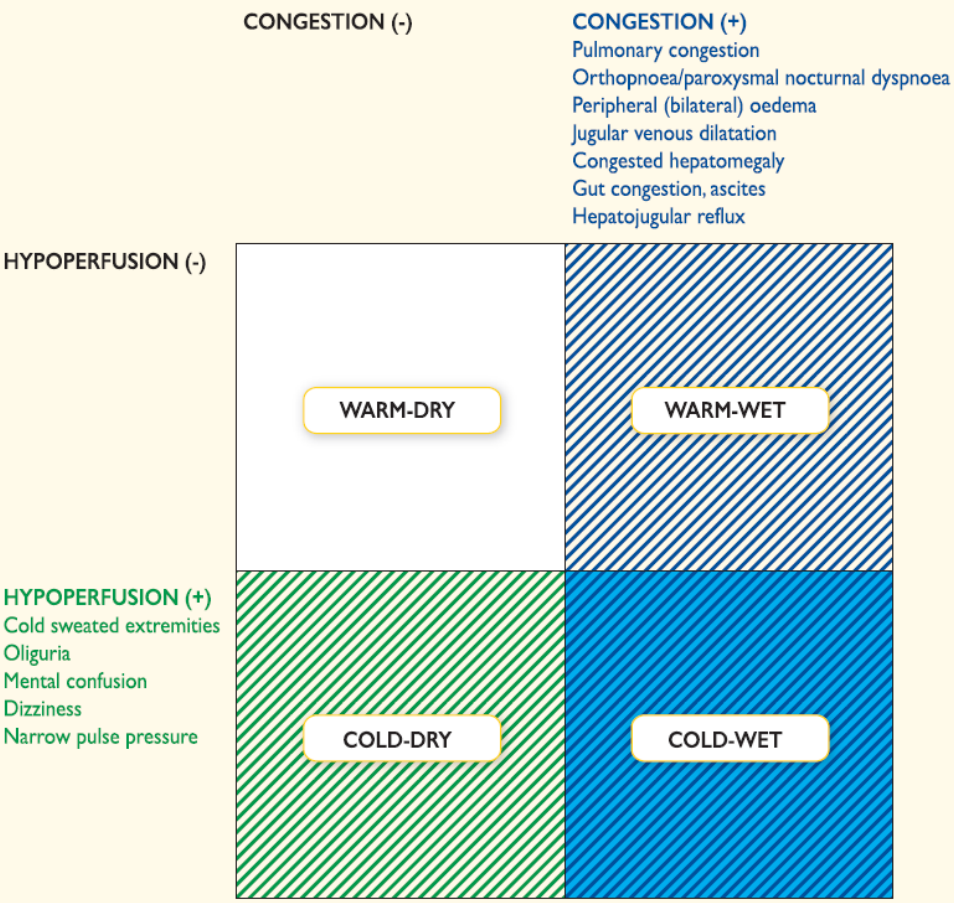
**Ospedale San Camillo Roma**


HF–REF
HF–PEF
Beta–blocker†
Rate–limiting CCB°
(or Beta-blocker)
Ventricular rate controlled?
No
Yes
Add digoxin
Substitute amiodarone for digoxin
Substitute beta–blocker (or rate–limiting CCB) for digoxin
Seek specialist advice, including consideration of AV node ablation
Maintenance therapy

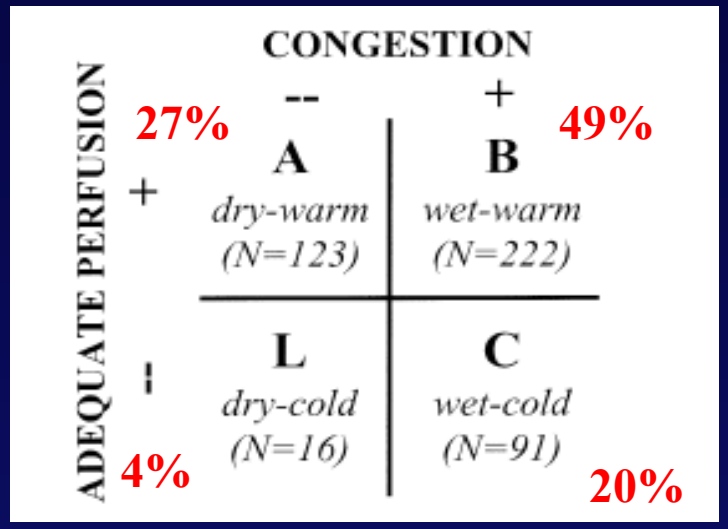

Acute pulmonary oedema/congestion
Intravenous bolus of loop diuretic[1]
Hypoxaemia[2]
Yes
Oxygen[3]
No
Severe anxiety/distress
Consider i.v. opiate[4]
Measure systolic blood pressure
SBP <85 mmHg or shock[5]
SBP 85–110 mmHg
SBP >110 mmHg
Add non-vasodilating inotrope[6]
No additional therapy until response assessed[7]
Consider vasodilator (e.g. NTG[8])
Adequate response to treatment?[9]
Continue present treatment[10]
Re-evaluation of patient's clinical status[11]
SBP <85 mmHg?[5]
SpO2 <90%
Urine output <20 mL/h[12]
• Stop vasodilator
• Stop beta-blocker if hypoperfused
• Consider non-vasodilating inotrope or vasopressor[6]
• Consider right-heart catheterization[13]
• Consider mechanical circulatory support[14]
• Oxygen[3]
• Consider NIV[15]
• Consider ETT and invasive ventilation[16]
• Bladder catheterization to confirm
• Increase dose of diuretic or use combination of diuretics[17]
• Consider low-dose dopamine[18]
• Consider right-heart catheterization[13]
• Consider ultrafiltration[19]

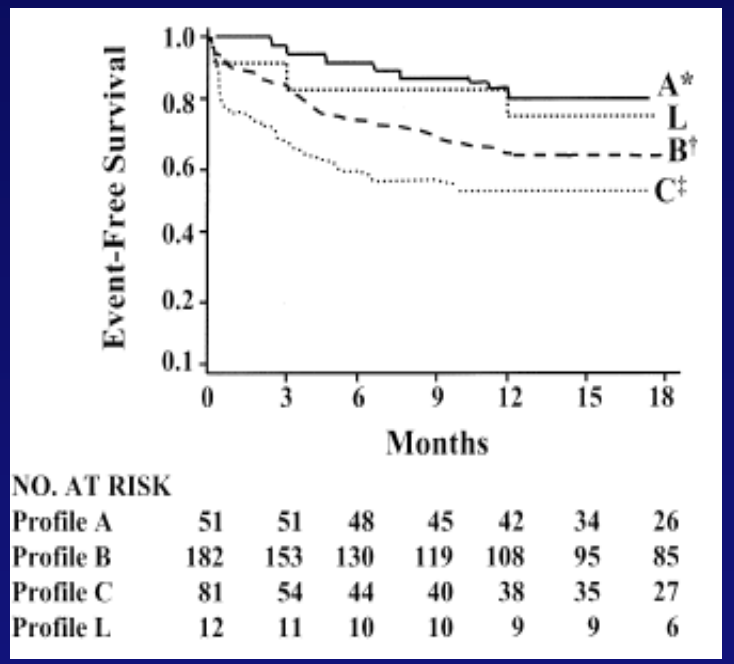
**ESC 2012**

# Frequenza e significato dei profili emodinamici




Hypoperfusion is not synonymous with hypotension, but often hypoperfusion is accompanied by hypotension.



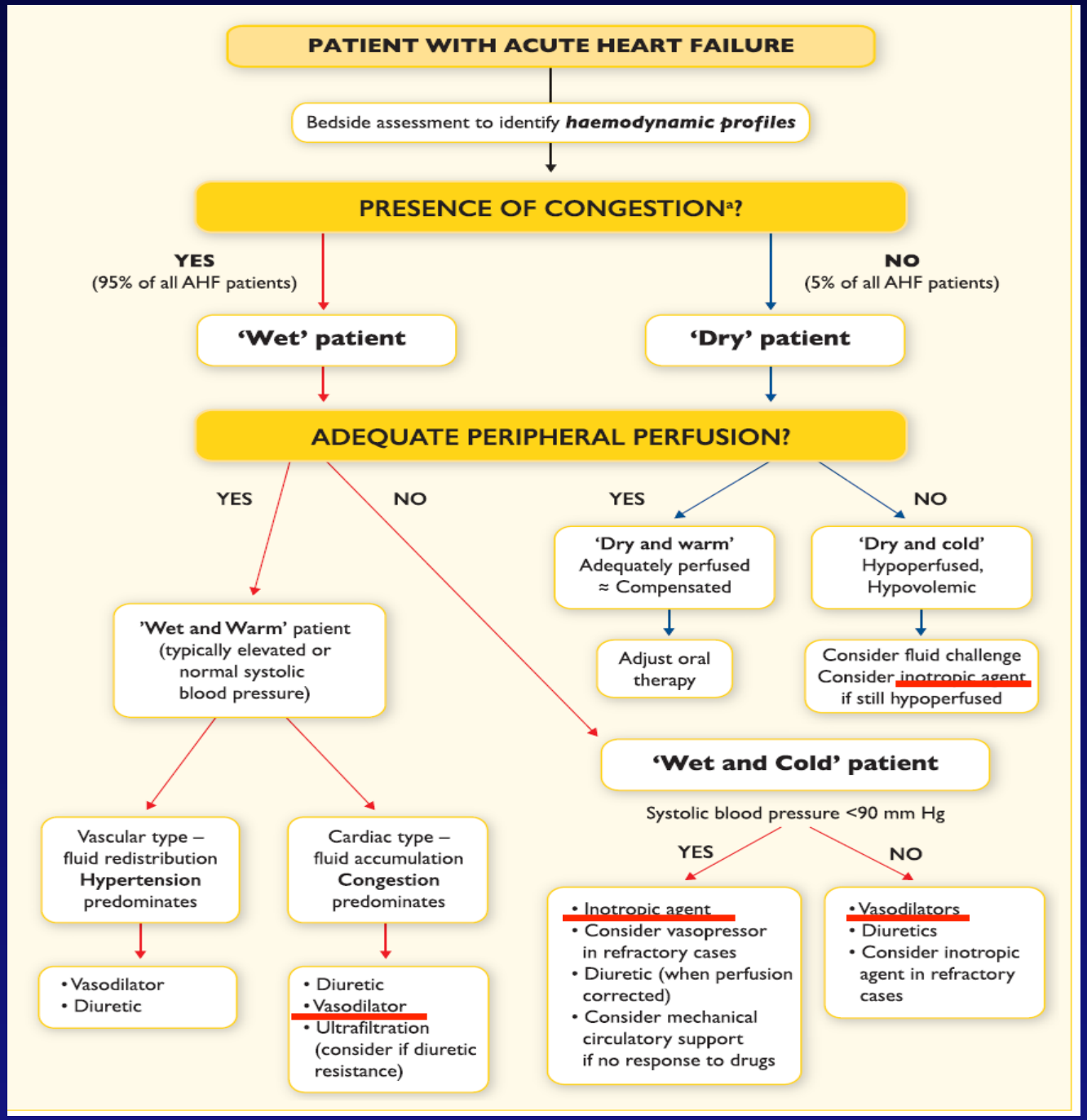




NO. AT RISK

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Profile A | 51 | 51 | 48 | 45 | 42 | 34 | 26 |
| Profile B | 182 | 153 | 130 | 119 | 108 | 95 | 85 |
| Profile C | 81 | 54 | 44 | 40 | 38 | 35 | 27 |
| Profile L | 12 | 11 | 10 | 10 | 9 | 9 | 6 |

ESC 2016

JACC 2003;41:1797


PATIENT WITH ACUTE HEART FAILURE
Bedside assessment to identify haemodynamic profiles
PRESENCE OF CONGESTION[a]?
YES
(95% of all AHF patients)
NO
(5% of all AHF patients)
'Wet' patient
'Dry' patient
ADEQUATE PERIPHERAL PERFUSION?
YES
NO
YES
NO
'Dry and warm'
Adequately perfused
≈ Compensated
'Dry and cold'
Hypoperfused,
Hypovolemic
Adjust oral therapy
Consider fluid challenge
Consider inotropic agent
if still hypoperfused
'Wet and Warm' patient
(typically elevated or normal systolic blood pressure)
'Wet and Cold' patient
Systolic blood pressure <90 mm Hg
YES
NO
Vascular type – fluid redistribution
Hypertension predominates
Cardiac type – fluid accumulation
Congestion predominates
• Vasodilator
• Diuretic
• Diuretic
• Vasodilator
• Ultrafiltration (consider if diuretic resistance)
• Inotropic agent
• Consider vasopressor in refractory cases
• Diuretic (when perfusion corrected)
• Consider mechanical circulatory support if no response to drugs
• Vasodilators
• Diuretics
• Consider inotropic agent in refractory cases

ESC 2016

# Inotropi : usi e abusi

**Table 5 Patient characteristics in previous AHF registries and in IN-HF Outcome**

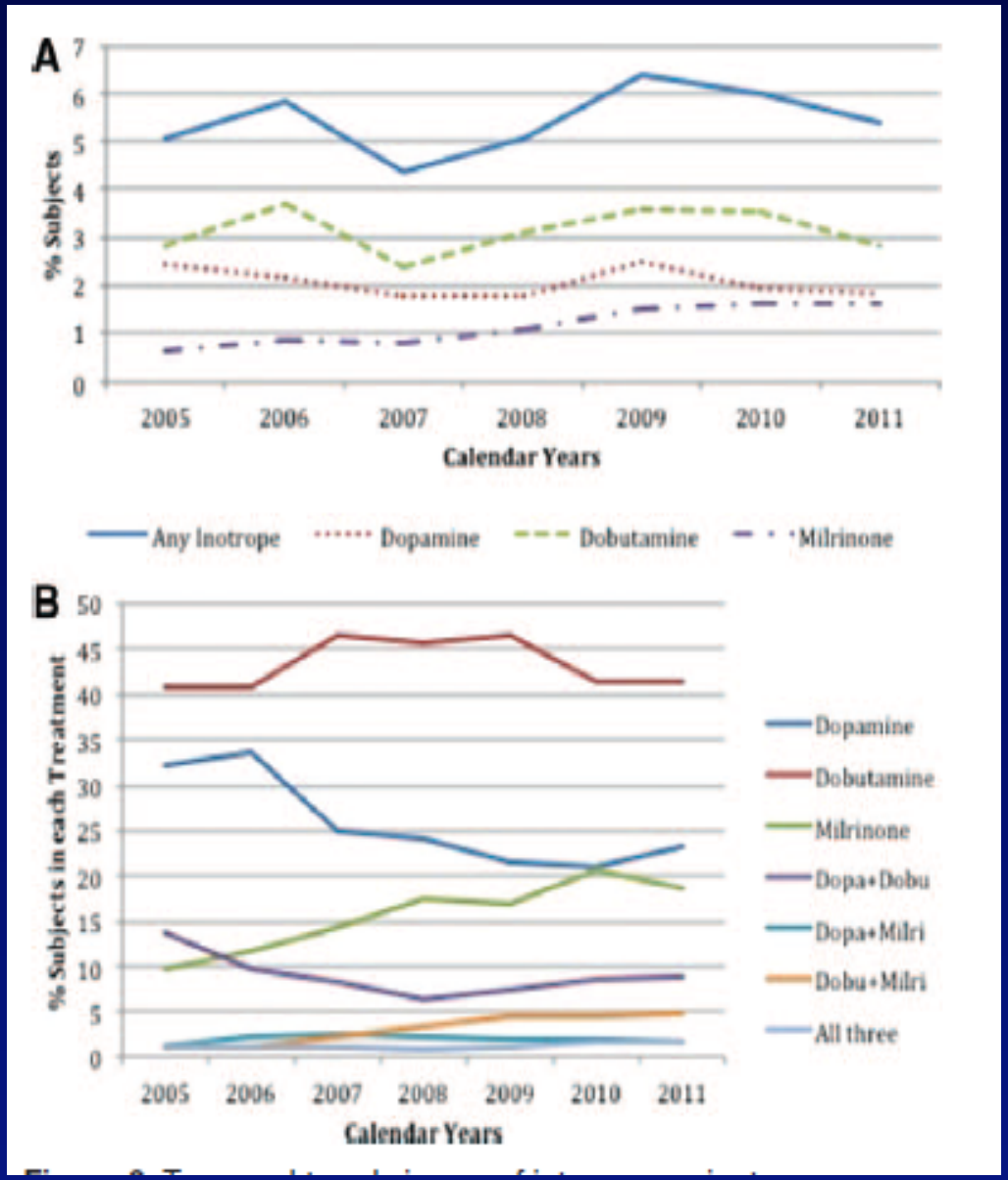
| | Adhere[4] (*n* = 105 388) | EHFS II[10] (*n* = 3580) | Italian S[14] (*n* = 2807) | OPTIMIZED-HF[5] (*n* = 48 612) | ESC HF Pilot[16] (*n* = 1892) | IN HF Outcome (*n* = 1855) |
|---|---|---|---|---|---|---|
| ***Denovo HF (%)*** | 35 | 37.1 | 44 | 11.7 | NA | 43 |
| ***Cardiogenic shock at entry (%)*** | NA | 3.9 | 7.7 | NA | 2.3 | 2.3 |
| ***Hypertensive AHF at entry (%)*** | NA | 11.4 | NA | NA | 4.7 | 5.1 |
| **I.v. therapy and intervention** | | | | | | |
| Diuretic (%) | NA | 84.4 | 95.3 | NA | 84.6 | 99.0 |
| Vasodilators (%) | 21 | 38.7 | 51.3 | 14.3 | 18.5 | 29.9 |
| Inotropes (%) | 15 | 29.8 | 24.6 | 10.9 | 10.5 | 19.4 |
| **Outcome** | | | | | | |
| ICU admission (%) | 18.7 | 50 | 69 | NA | 48 | 51.9 |
| Length of stay (days) | 4.3 | 9.0 | 9.0 | 5.7 | NA | 10 |
| In-hospital mortality (%) | 4.0 | 9.0 | 7.3 | 3.8 | 3.8 | 6.4 |

| Signs/symptoms at presentation | | WHF | de novo HF | |
|---|---|---|---|---|
| Pulmonary congestion, % | 78.2 | 75.8 | 81.4 | 0.004 |
| Peripheral congestion, % | 56.1 | 61.3 | 49.1 | <0.0001 |
| Pulmonary and/or peripheral congestion, % | 88.4 | 87.8 | 89.1 | 0.40 |
| Peripheral hypoperfusion, % | 12.0 | 12.4 | 11.4 | 0.53 |
| Cold, % | 10.8 | 11.1 | 10.4 | 0.66 |
| Somnolent, confused, sedated, % | 11.5 | 9.6 | 14.1 | 0.003 |

**Mortalità 6,4 %, WHF 6,4%, de novo 6%**

EJHF 2012;14:1208 IN-CHF

# Inotropi




**Uso di inotropi nel 6,1% dei pz**

**Relativamente costante nel tempo**

**Somministrati ai pazienti più compromessi**

**Consuetudini locali spiegano il 21% della variabilità**

**Mortalità e durata ricoveri non diverse tra ospedali "ad alto" o "basso uso" di inotropi**

**Circ Heart Fail 2014;7:251**

# Prognosi: vasodilatatori vs inotropi (ADHERE)

**Table 4.** Mortality Odds Ratios in Pair-Wise Treatment Comparisons

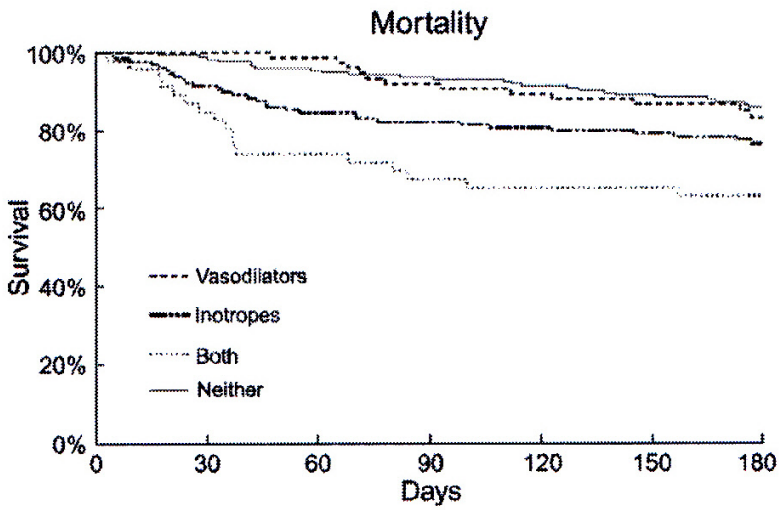
| Analysis* | NTG (n = 6,055) vs. MIL (n = 1,660) | NTG (n = 5,713) vs. DOB (n = 3,478) | NES (n = 4,663) vs. MIL (n = 1,534) | NES (n = 4,270) vs. DOB (n = 3,301) | NES (n = 4,402) vs. NTG (n = 5,668) | DOB (n = 3,656) vs. MIL (n = 1,496) |
|---|---|---|---|---|---|---|
| Unadjusted | 0.34 (0.28–0.41)† | 0.24 (0.20–0.28)† | 0.53 (0.44–0.64)† | 0.37 (0.32–0.44)† | 1.64 (1.38–1.94)† | 1.39 (1.15–1.68)† |
| Adjusted for covariates‖ | 0.69 (0.54–0.88)† | 0.46 (0.38–0.57)† | 0.59 (0.48–0.73)† | 0.47 (0.39–0.56)† | 0.95 (0.78–1.16)‡ | 1.27 (1.04–1.56)§ |
| Adjusted for covariates and propensity score¶ | 0.69 (0.53–0.89)† | 0.46 (0.37–0.57)† | 0.59 (0.48–0.73)† | 0.47 (0.39–0.56)† | 0.94 (0.77–1.16)‡ | 1.24 (1.03–1.55)§ |

Hosmer-Lemeshow goodness-of-fit test not significant at 5% levels for the models adjusted for risk factors and/or

JACC 2005; 46:57

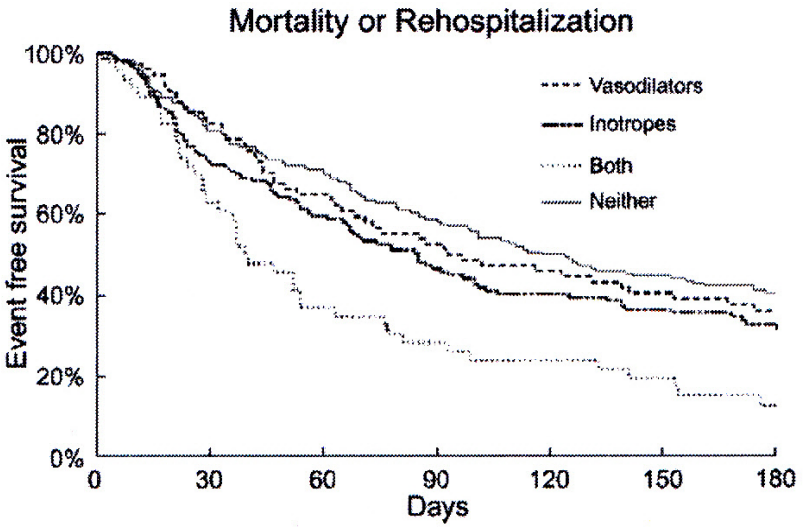
# ESCAPE Trial: vasodilatatori vs inotropi nello scompenso avanzato

**Figure 1**




Kaplan-Meier survival curve for all-cause mortality by intravenous vasoactive medication use.

**Figure 2**




Kaplan-Meier survival curve for freedom from death or rehospitalization by intravenous vasoactive medication use.

**ESCAPE, 433 pazienti, FE 19 %, mortalità 6-mesi 19%:**

**Vasodilatatori** **28 % (nesiritide 15%, nitroprussiato 11%)**

**Inotropi** **42 % ( dobutamina 86%, milrinone 40%)** **Am Heart J 2007; 153:98**

# Variazioni dinamiche della troponina e prognosi

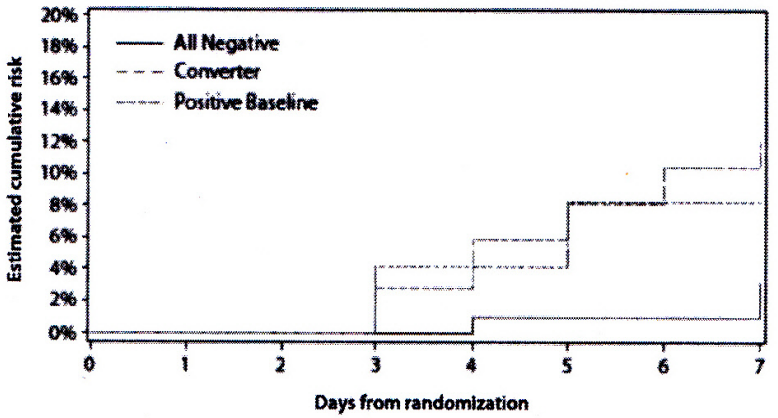



**Figure 2.** In-hospital (up to day 7) worsening heart failure (HF) or death.

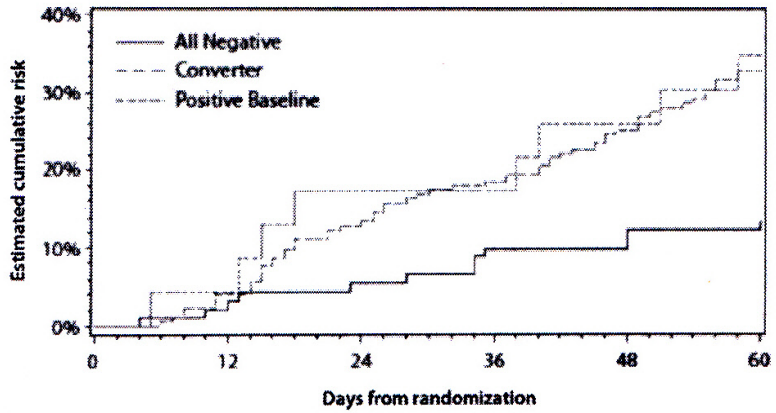



**Figure 1.** Day 60 cardiovascular (CV)/renal hospitalization or death.

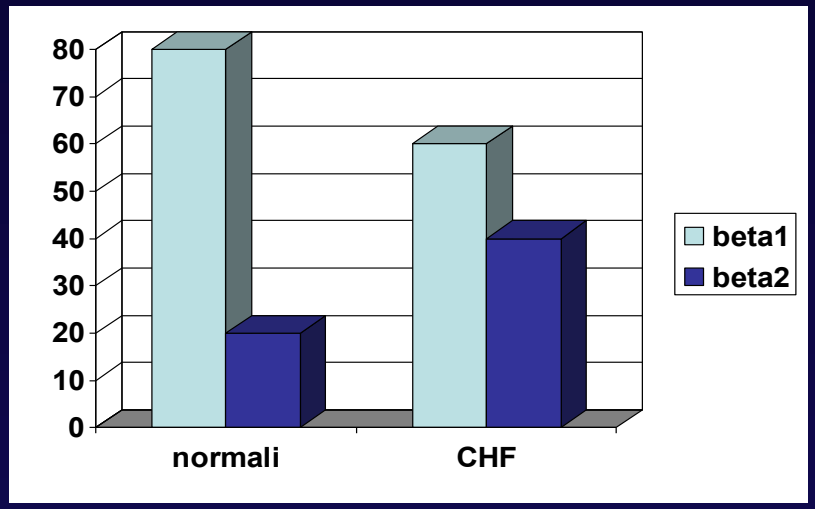
**Una percentuale variabile ( 10 – 40%) di pazienti hanno troponina elevata durante ricovero**

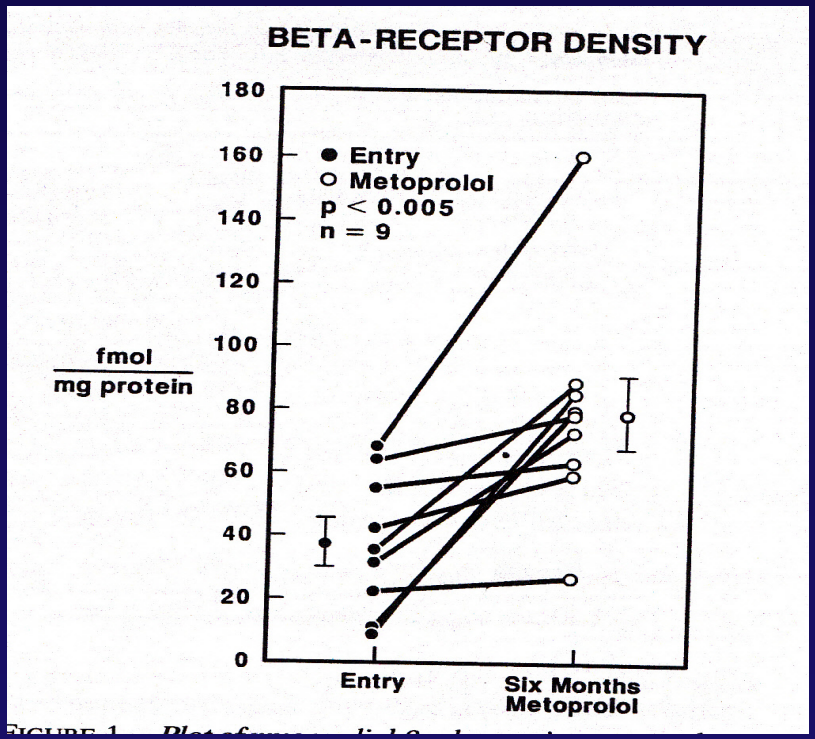
**Nello studio PROTECT:**

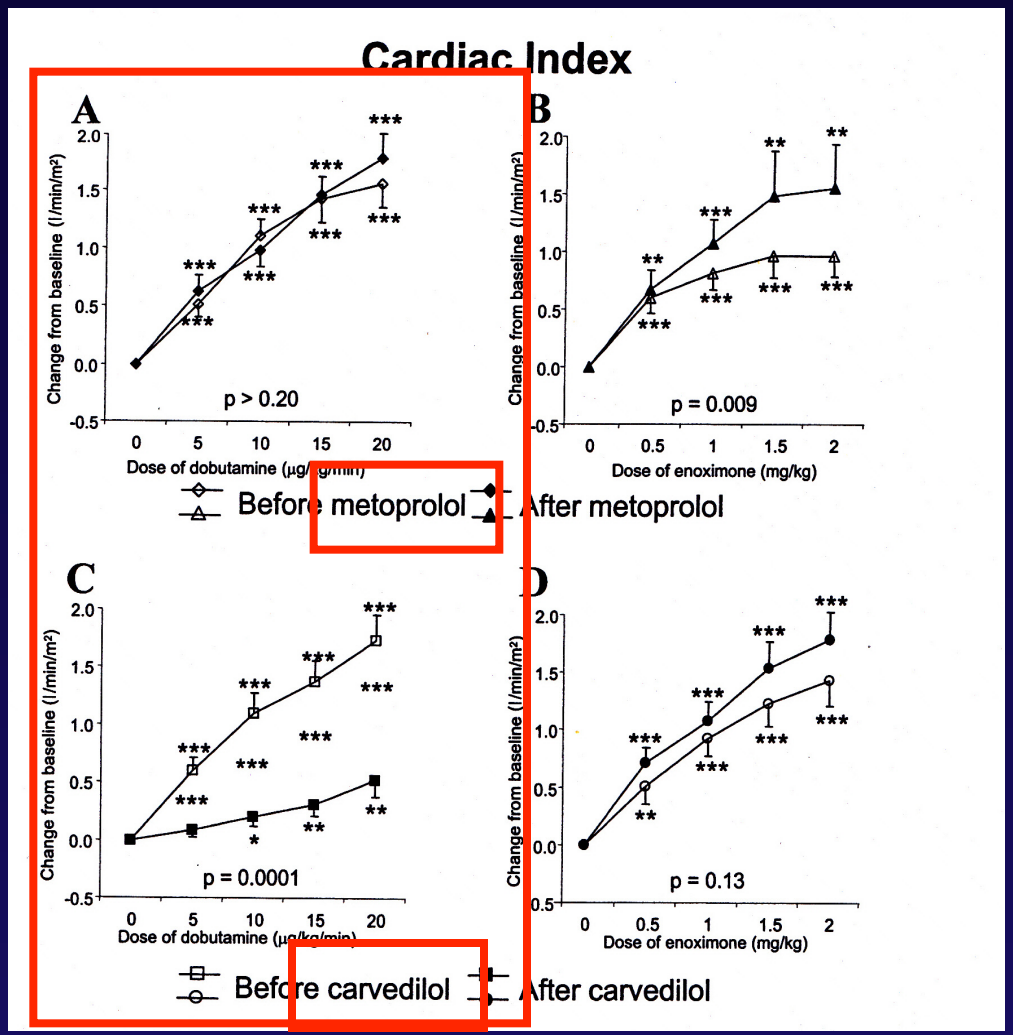
1. **60% hanno Tn > 0,01 ng/ml, 34% hanno Tn < 0,03 ng/ml**
2. **Nessuno dei pazienti con Tn > 0,03 ng/ml si negativizza**
3. **Il 21 % dei negativi all' ingresso si positivizza durante il ricovero**

**O' Connor CM. Circ Heart Fail 2011;4:724**

# Scompenso, recettori adrenergici e beta bloccanti

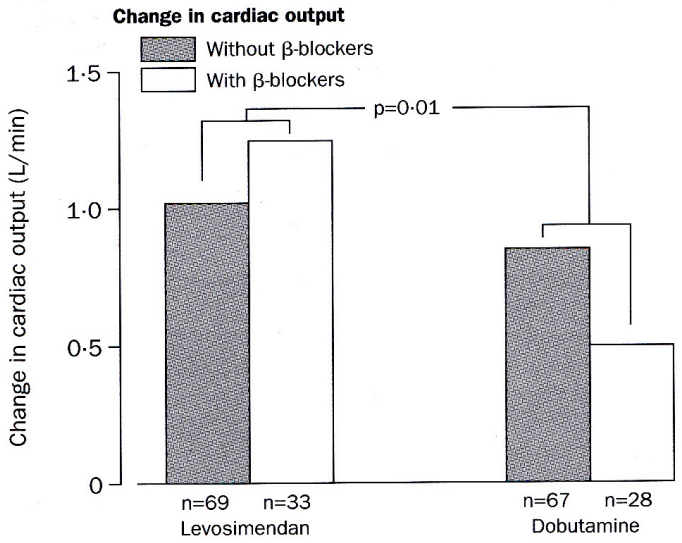



1) lo scompenso riduce i beta recettori
2) i beta bloccanti ripristinano i beta recettori
3) i beta bloccanti (e i pazienti) sono diversi

# Inotropi nei pazienti trattati con beta blocco



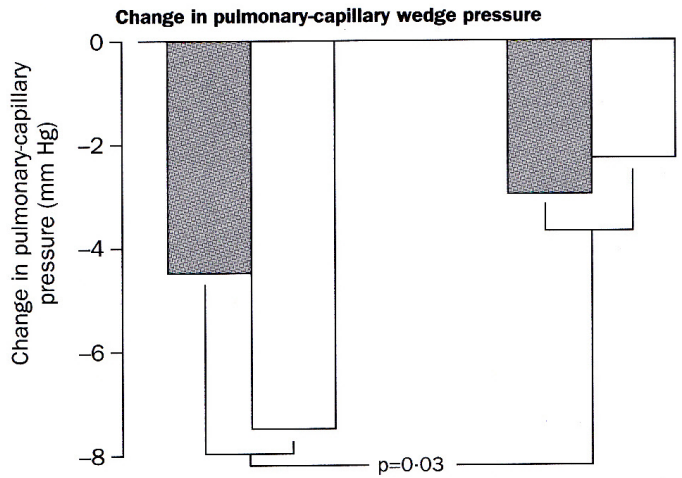
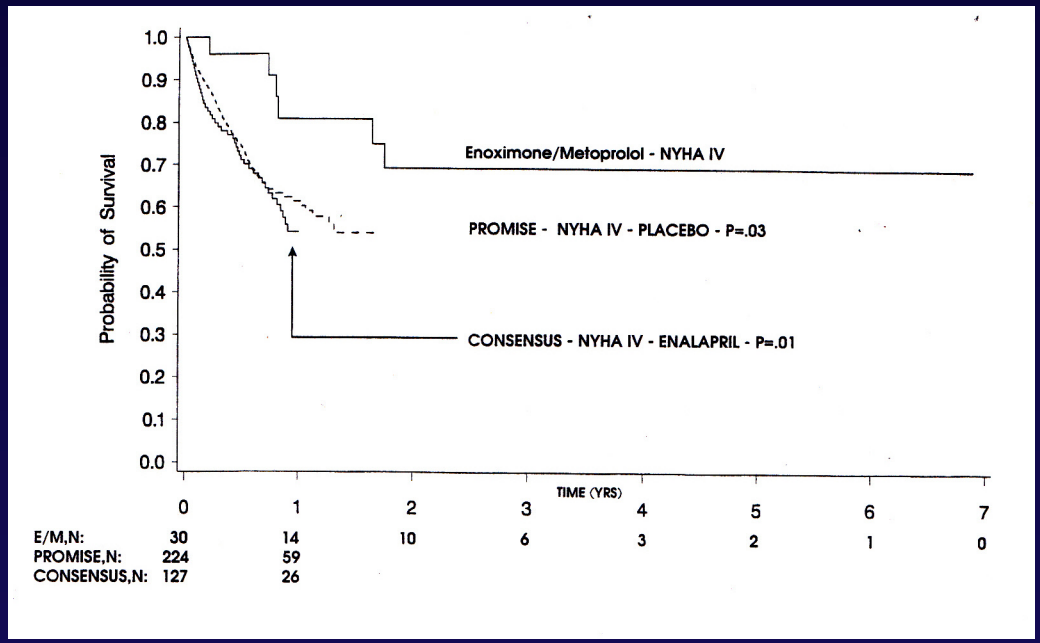



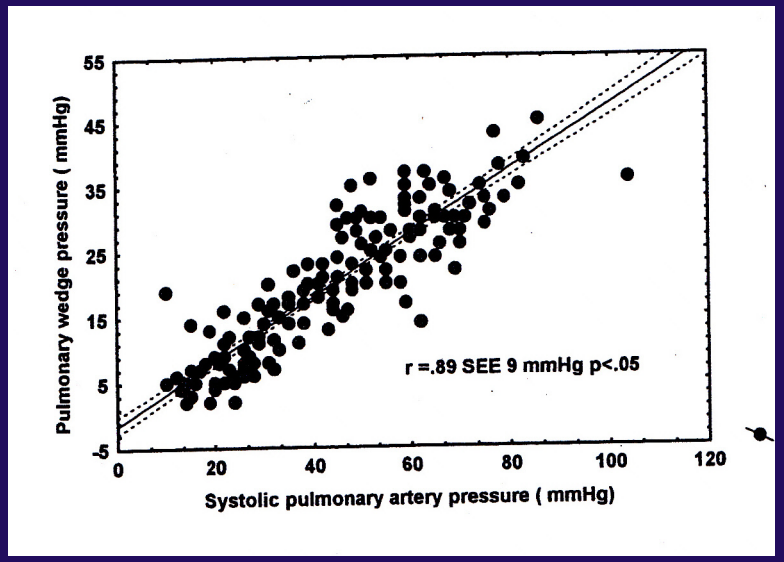

Figure 2: **Effect of concomitant β-blockade on cardiac output and pulmonary-capillary wedge pressure**
Interaction test p values based on ANCOVA with effects for treatment,




Shackar SF. JACC 1998; 31: 1336

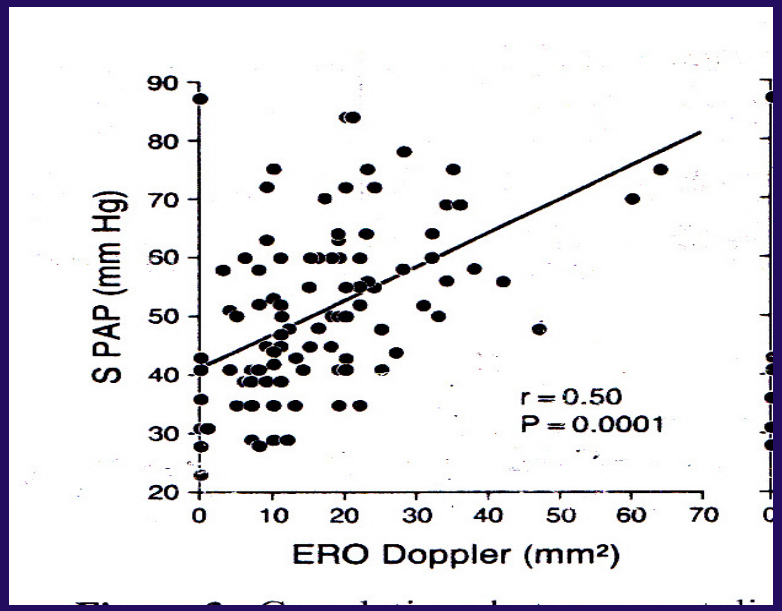
LIDO. Lancet 2002;360:196

# IM e ipertensione polmonare




**La pressione di incuneamento capillare è il più forte predittore di ipertensione polmonare ( 80 % della variabilità di PAP)**

**Capomolla S. J Heart Lung Transpl 2000;19:426**




**La severità dell'insufficienza mitralica (ERO) è correlata all'ipertensione polmonare.**

**Enriquez - Sarano M. JACC 1997;29:153**

# Prevalenza di IM in pazienti ricoverati per SC acuto

**Table 2** Biohumoral data at hospital admission and echocardiographic findings

| | Total ($n$ = 1855) | WHF ($n$ = 1058) | DN-HF ($n$ = 797) | $P$-value |
|---|---|---|---|---|
| LVEF (%)(mean ± SD) | 38 ± 14 | 37 ± 14 | 39 ± 14 | 0.007 |
| LVEF (%) | | | | 0.001 |
| <30% | 29.7 | 33.4 | 25.1 | |
| 30–50% | 51.8 | 48.9 | 55.4 | |
| >50% | 18.5 | 17.7 | 19.5 | |
| Severe mitral regurgitation (%) | 22.9 | 24.5 | 20.9 | 0.07 |

IN-CHF. EJHF 2012;14:1208

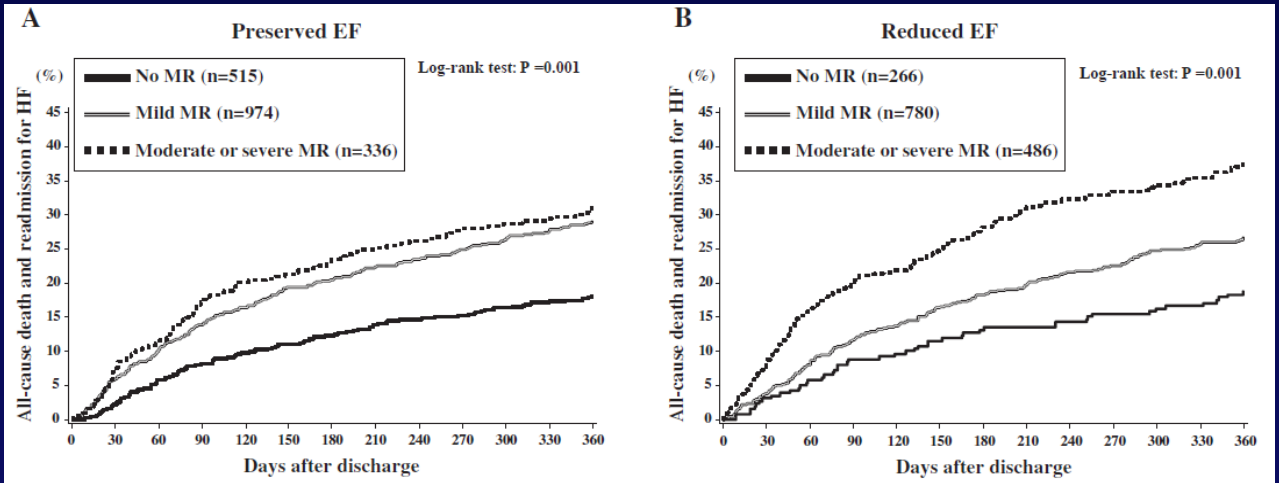
**Table 3** Echocardiographic findings by previous history of HF and by clinical class

| Variable | All | ADCHF | *De novo* AHF | Decomp HF | Pulm. oedema | Cardiog. shock | Hypert. HF | Right HF |
|---|---|---|---|---|---|---|---|---|
| Mitral regurgitation (%)* | | | | | | | | |
| None | 20.2 | 15.7 | 27.9 | 18.4 | 23.4 | 19.5 | 22.4 | 33.0 |
| Mild | 36.6 | 35.1 | 39.1 | 34.3 | 38.8 | 39.8 | 43.0 | 45.7 |
| Moderate | 31.2 | 34.6 | 25.3 | 33.3 | 30.8 | 28.3 | 24.9 | 13.8 |
| Severe | 12.1 | 14.6 | 7.7 | 14.0 | 7.0 | 12.4 | 9.7 | 7.4 |

Euro Heart Survey II. EHJ 2006;27:2725

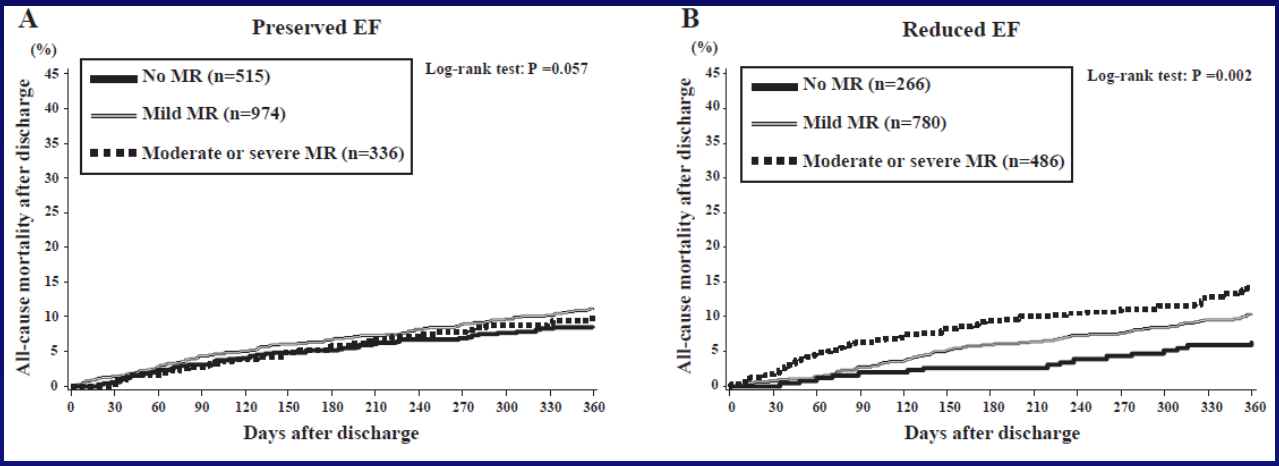
# Prognosi IM: studio ATTEND

## Morte e readmission




correlate con IM nei pz con HFpEF, correlate con IM medio-severa nei pz con HFrEF

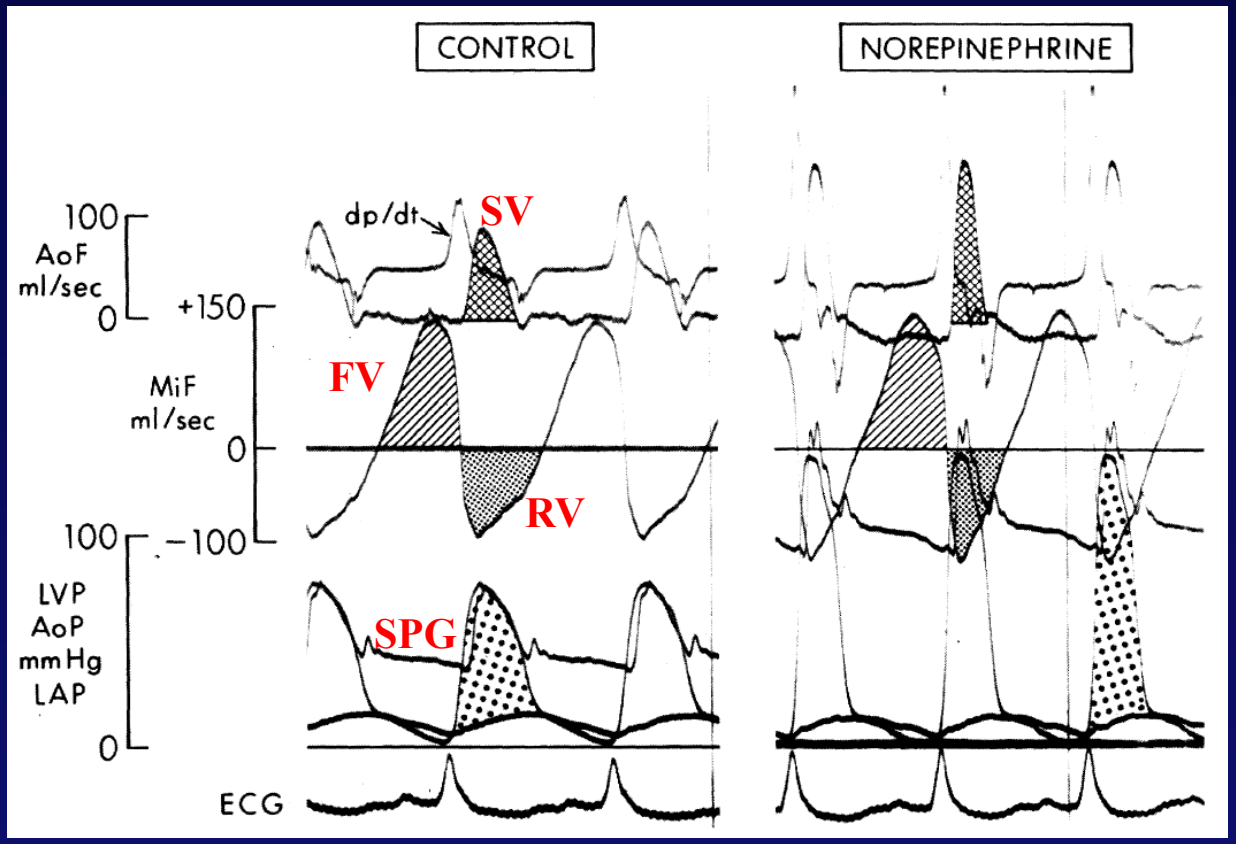
## Mortalità globale




correlata con IM nei pz con HFpEF, nei pz con HFrEF e IM moderato-severa è maggiore ma NS

EJHF 2016; 18:1051

# IM funzionale: inotropi




**SV: ↑ gittata sistolica anterograda**

**FV: = volume di riempimento VS**

**RV: = volume rigurgitante**

**SPG: ↑ gradiente pressorio transmitralico**

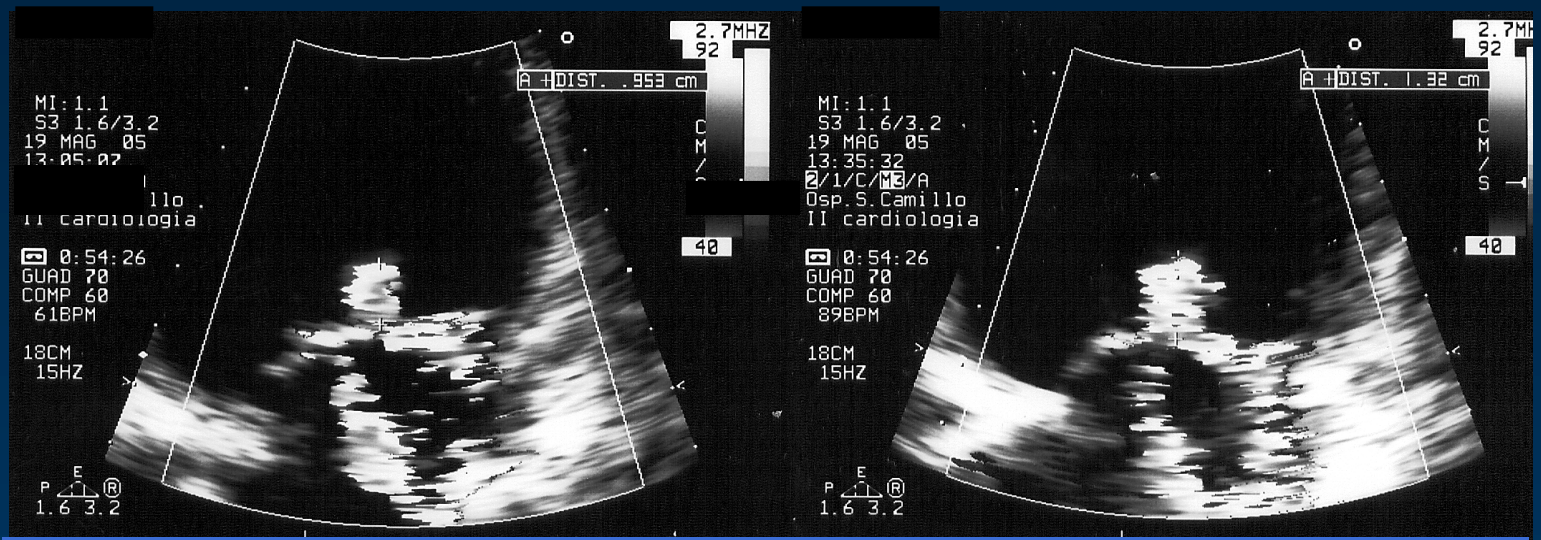
**l'inotropo può ridurre l'insufficienza mitralica se:**

**1) riducendo la pressione telediastoloica del ventricolo sinistro riduce i volumi e quindi l'EROA;**

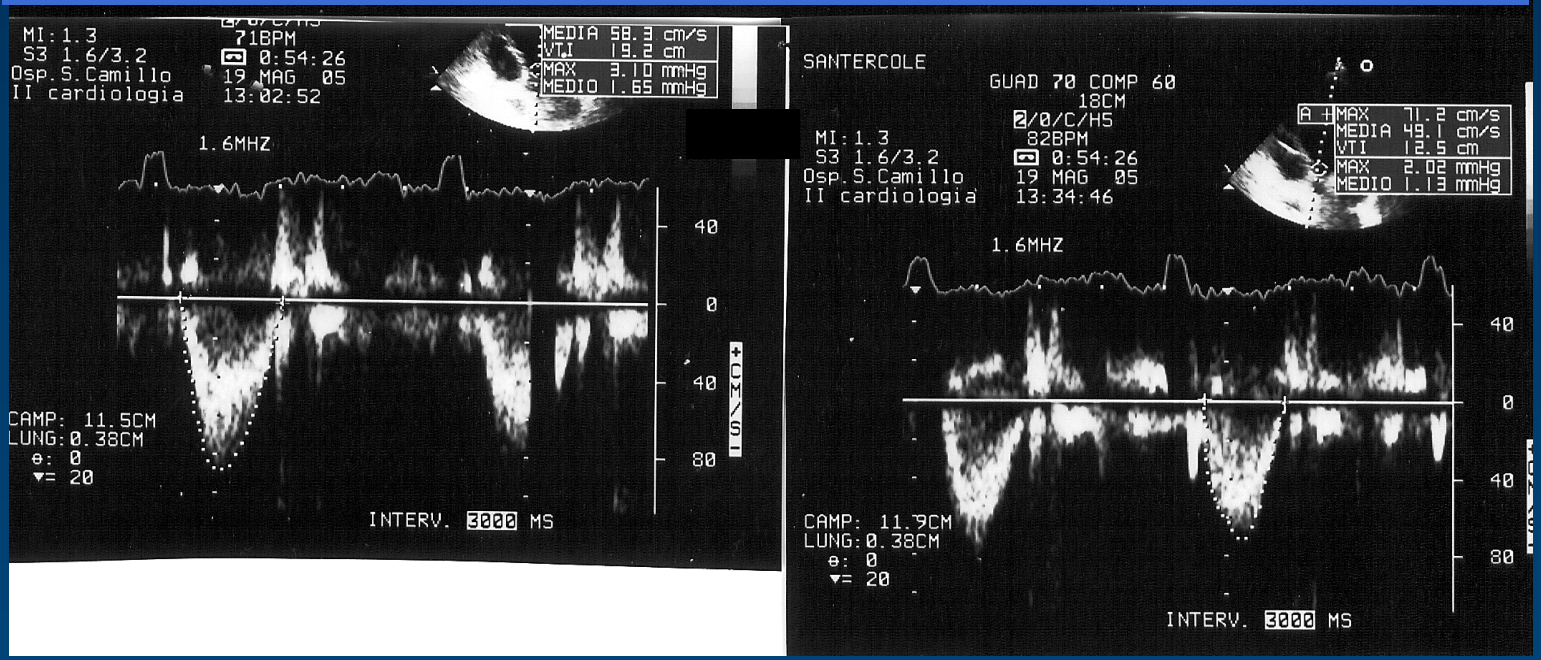
**2) aumentando il dP/dt aumenta il gradiente di pressione trans-mitralico che si oppone al tenting**

**Circ 1979;60:170**
**JACC 2003;41:765**
**EHJ 2016;17:471**

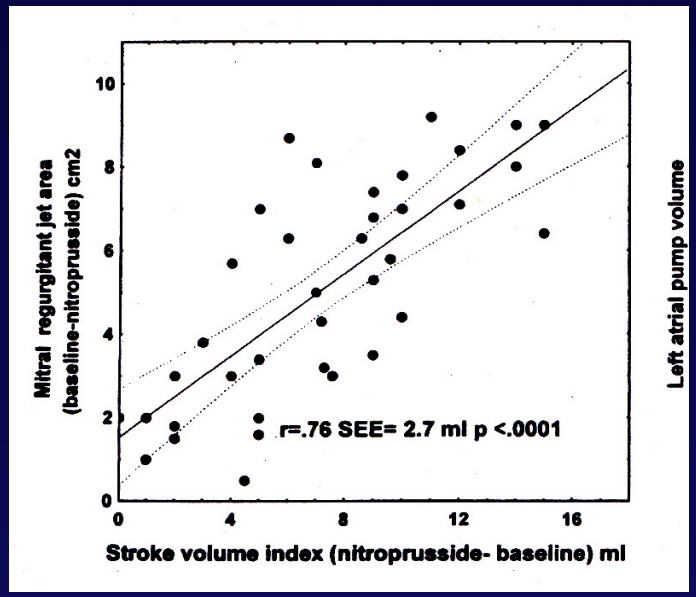
## PISA: base 0,9 cm dobutamina 1,32 cm

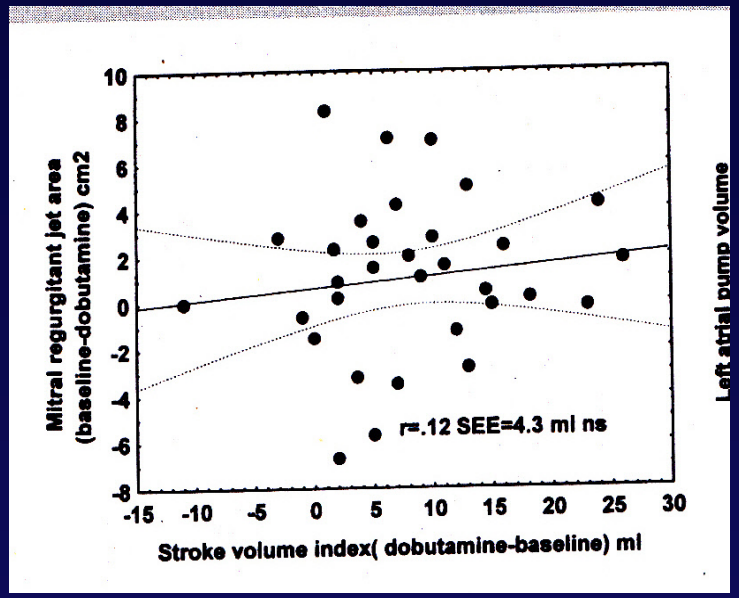


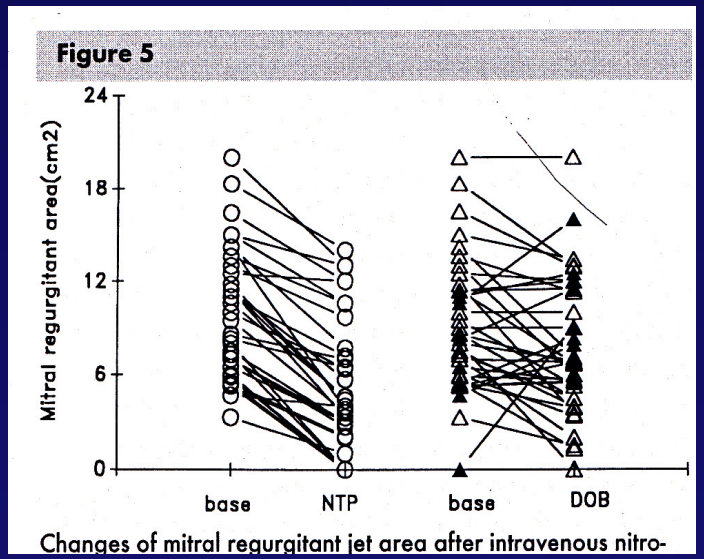

## VTI LVOT: base 19,2 cm dobutamina 12,5 cm

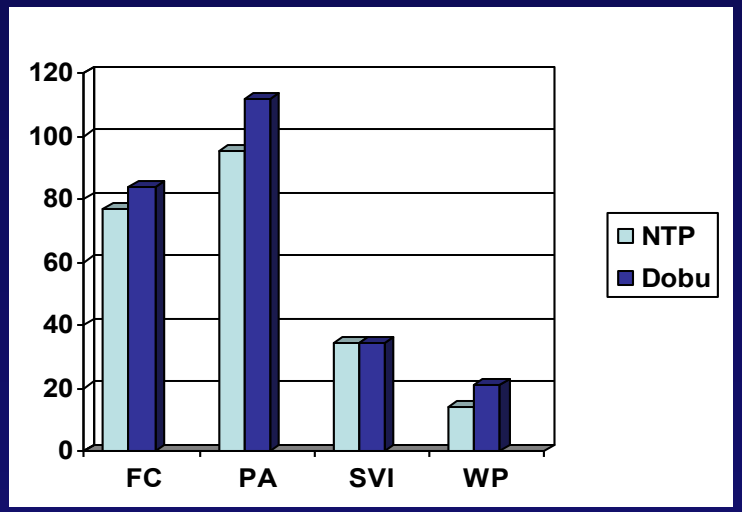


# Vasodilatatori vs inotropi: effetti emodinamici



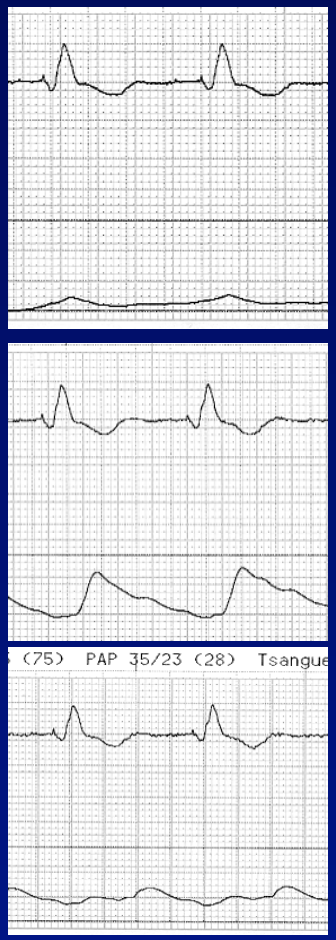




Capomolla S.
Am Heart J
1997:134:1089

# Nitroprussiato vs dobutamina: effetti emodinamici

MS, uomo, 35 anni; CMPD, CF III, wet - warm;
Eco: VS: 80/66, FE 35% , VDx TAPSE 22, FE 47%;
IM +++, IT +, PAPS 42




| | base | NTP 1,5 γ | dobutamina |
|---|---|---|---|
| FC | 67 | 66 | 65 |
| PA | 97/59/70 | 89/45/56 | 111/70/82 |
| P polm | 37/15/24 | 19/6/10 | 65/27/43 |
| Padx | 1 | 0 | 2 |
| WP | 14 | 5 | 24 |
| CI | 2,79 | 2,99 | 2,43 |

# Ipertensione polmonare con IM severa

**Base:**

| | | |
|---|---|---|
| BP | 102/61 (71) | mmHg |
| HR | 74/min | |
| CVP | 8 | mmHg |
| PAP | 74/36 (49) | mmHg |
| Wp | 33 | mmHg |
| CO | 3.59 | L/min (termodiluizione) |
| CI | 1.7 | L/min/$m^2$ |
| SV | 45 | ml/batt |
| SVR | 1403 | dyne-sec-$cm^{-5}$ |
| SVRI | 2961 | dyne-sec-$cm^{-5}/m^2$ |
| PVR | 356 | dyne-sec-$cm^{-5}$ |
| PVRI | 7528 | dyne-sec-$cm^{-5}/m^2$ |
| RVSW | 25.02 | mmHg-ml |
| RVSWI | 11.86 | mmHg-ml/$m^2$ |

**Dopo test farmacologico:**
**sodio nitroprussiato 2 mcg/Kg/min:**

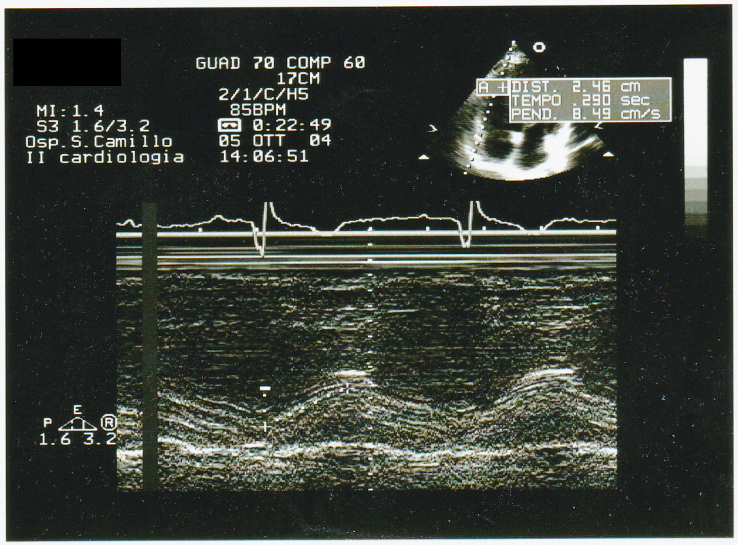
| | | |
|---|---|---|
| BP | 90/64 (69) | mmHg |
| HR | 68 bpm | |
| CVP | 2 | mmHg |
| PAP | 28/12 (18) | mmHg |
| Wp | 10 | mmHg |
| CO | 4.86 L/min | (termodiluizione) |
| CI | 2.30 | L/min/$m^2$ |
| SV | 58 | ml/batt |
| SVR | 1133 | dyne-sec-$cm^{-5}$ |
| SVRI | 2361 | dyne-sec-$cm^{-5}/m^2$ |
| PVR | 112 | dyne-sec-$cm^{-5}$ |
| PVRI | 236 | dyne-sec-$cm^{-5}/m^2$ |
| RVSW | 11,88 | mmHg-ml |
| RVSWI | 5,63 | mmHg-ml/$m^2$ |

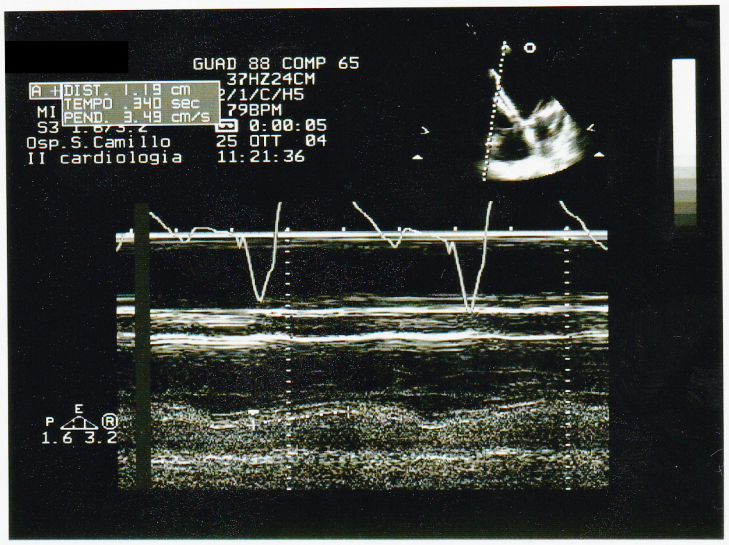
**PAP – 66%, WP -70 %, ΔP – 50%, CO + 35%**

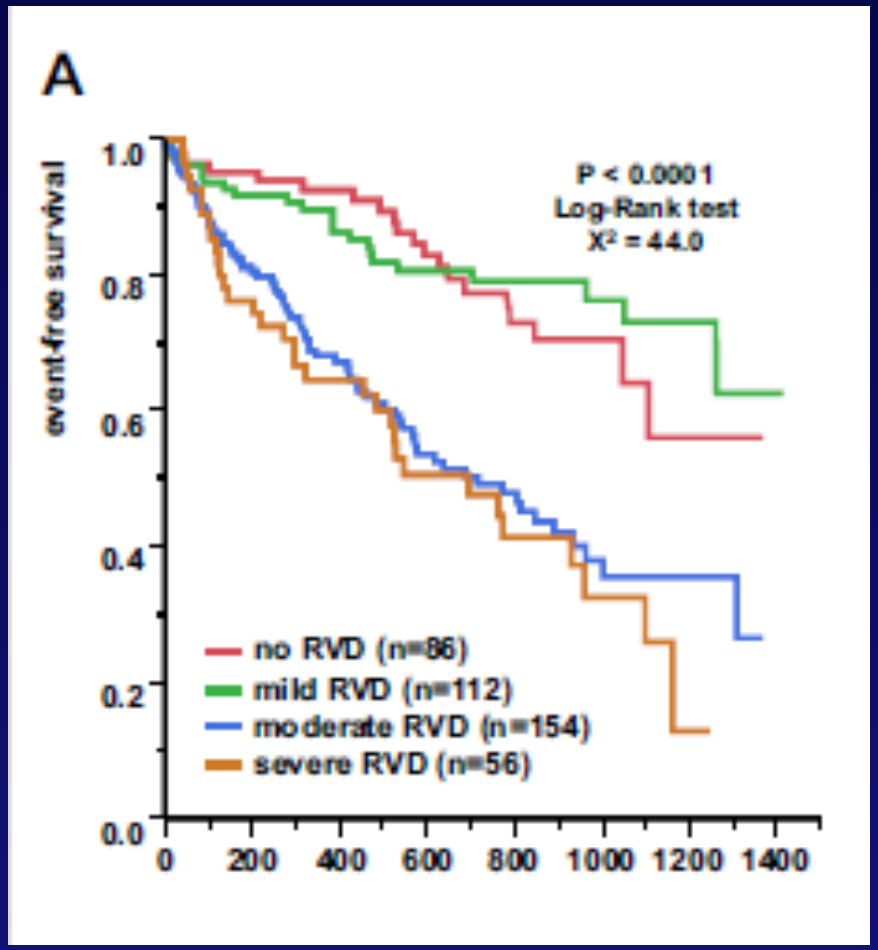
**B.G. , uomo, 60 aa, CMPD, FE 23%, IM severa**

**CF IV, profilo wet / cold**

# Disfunzione ventricolare destra e prognosi

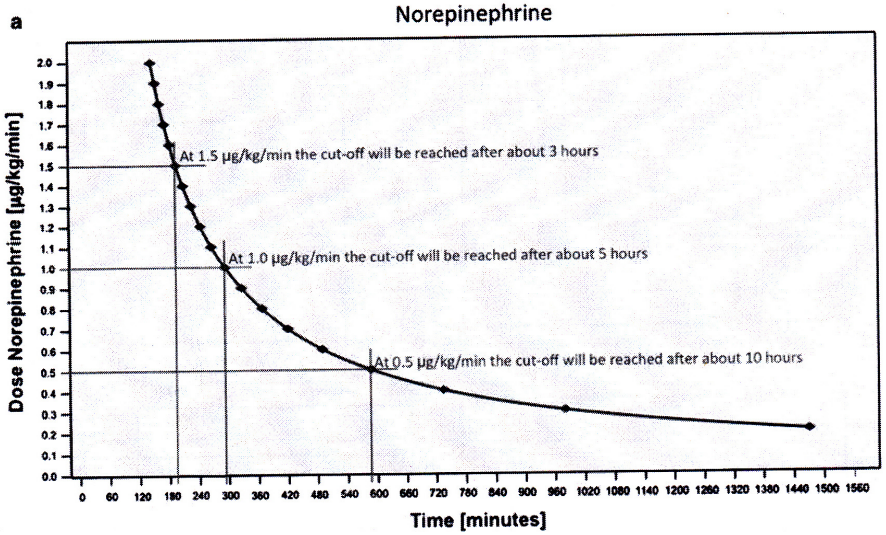


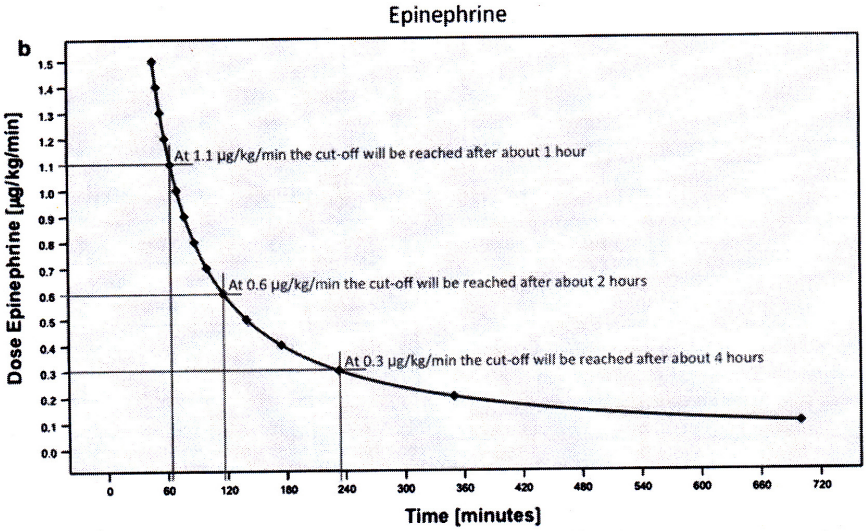




JACC 2016;62:1660 Melenovsky V et al

# Qual è la dose oltre la quale la sopravvivenza è improbabile?




Time to reach the cut-off of the AUC = 294 in dependence on the dose of norepinehrine




Time to reach the cut-off of the AUC = 70 in dependence on the dose of epinephrine

**1543 pazienti da quattro terapie intensive non cardiologiche di Berlino**

**Kastrup M. World J Surg. 2013;37:766**

**Clinical Use of Inotropic Therapy for Heart Failure: Looking Backward or Forward?**

**Part I: Inotropic Infusions During Hospitalization**

Lynne Warner Stevenson, MD

**Bridge**

**Shock / ipoperfusione**

**Risoluzione cause reversibili**

**Trapianto / VAD**

**Terapia palliativa**

**Obiettivi e tempi diversi a seconda dell'uso**

# Quando usare gli inotropi

**Current Uses of Inotropic Agents in Heart Failure: Possible Trials**

Therapy during hospitalization

Critical support until definitive therapy (cardiogenic shock)

*Placebo-controlled trial unlikely because of perception of immediate benefit from initiation, high risk from progressive shock, and hetergeneity of population*

Support until resolution of other conditions

Recovery from sustained tachyarrhythmia or infarction

Noncardiac illness, eg, pneumonia, gastrointestinal bleed

Recovery from noncardiac surgery

*Trial of aggressive therapy to increase oxygen delivery in medical intensive care unit showed no obvious benefit.[34] No trials of therapy aimed at normal cardiac output in this setting, in which it would be difficult to define homogeneous population.*

Resolution of congestion with apparent hypoperfusion (without shock)

*Placebo-controlled and active control trials feasible with allowance for crossover to active therapy, would require consistent application of clinical criteria to ensure compromised population*

Resolution of congestion with impaired renal responses

*Placebo-controlled trials feasible with allowance for crossover to active therapy*

*Comparison of 2 active therapies feasible, eg, inotropic agent compared with specific intervention for renal function or direct fluid removal*

Routine use for heart failure hospitalization without complicating features

*One trial successfully completed that demonstrated increased adverse events without benefit.[20] Other trials feasible in different patient cohorts.*

Intermittent outpatient therapy

*Placebo-controlled and active comparison trials feasible; previous experience warrants review.*

Chronic therapy "until. . ."

Bridging until cardiac transplantation

*Comparison trial of 2 active therapies feasible, with well-defined crossover options*

Destination: end of life

Placebo-controlled drug trial probably not compatible with compassionate care. Comparison trial of 2 approaches could be considered, with liberal allowance for changing patient preferences

**Circ 2003;108:367**

**Table 28 Patients in whom palliative care should be considered**

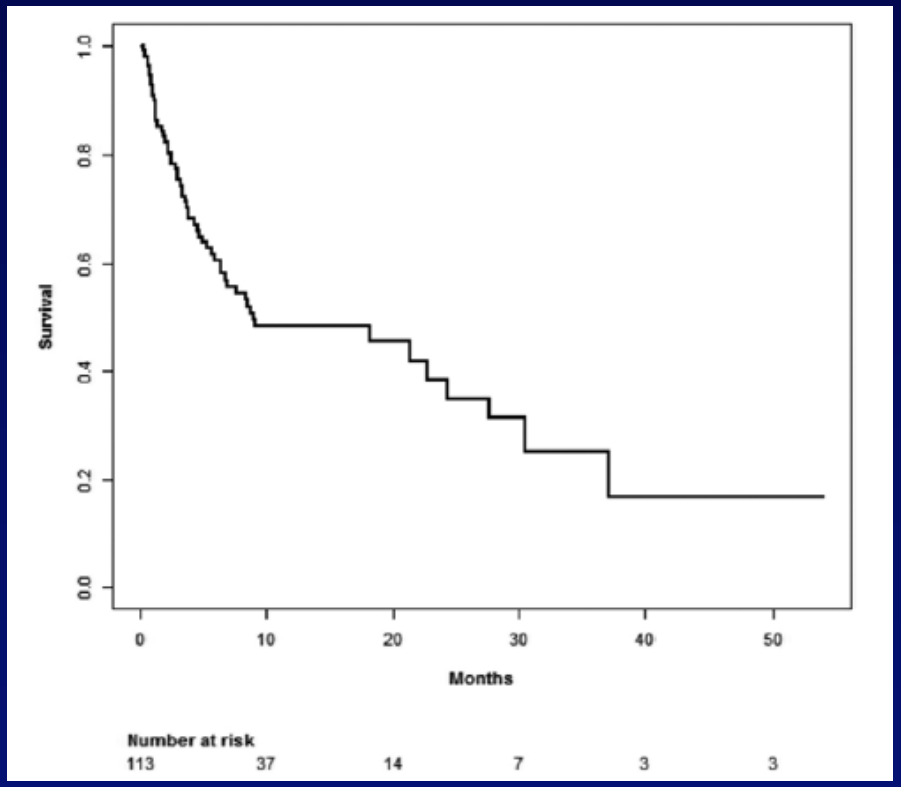
| |
|---|
| • Frequent admission to hospital or other serious episodes of decompensation despite optimized treatment |
| • Heart transplantation and mechanical circulatory support ruled out |
| • Chronic poor quality of life with NYHA class IV symptoms |
| • Cardiac cachexia/low serum albumin |
| • Dependence in most activities of daily living |
| • Clinically judged to be close to the end of life |

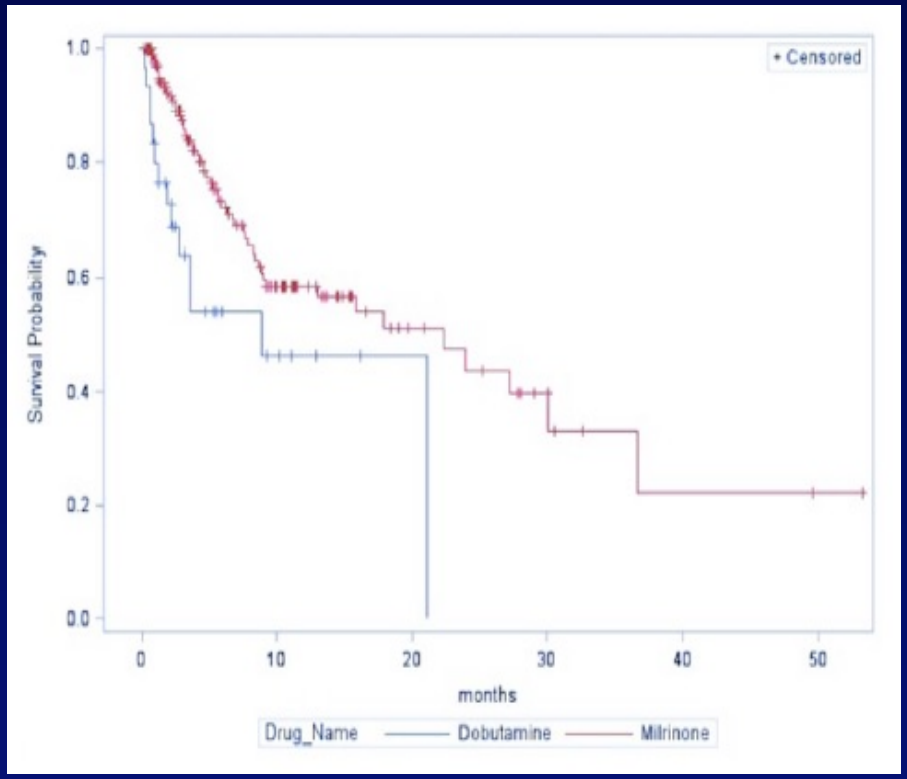
NYHA = New York Heart Association. **Eur Heart J 2012;33:1787**

# Quando usare gli inotropi

| | | | |
|---|---|---|---|
| **Vasodilators** | | | |
| i.v. vasodilators should be considered for symptomatic relief in AHF with SBP >90 mmHg (and without symptomatic hypotension).<br>Symptoms and blood pressure should be monitored frequently during administration of i.v. vasodilators. | IIa | B | 537, 550–555 |
| In patients with hypertensive AHF, i.v. vasodilators should be considered as initial therapy to improve symptoms and reduce congestion. | IIa | B | 537, 551–554 |
| **Inotropic agents – dobutamine, dopamine, levosimendan, phosphodiesterase III (PDE III) inhibitors** | | | |
| Short-term, i.v. infusion of inotropic agents may be considered in patients with hypotension (SBP <90 mmHg) and/or signs/symptoms of hypoperfusion despite adequate filling status, to increase cardiac output, increase blood pressure, improve peripheral perfusion and maintain end-organ function. | IIb | C | |
| An intravenous infusion of levosimendan or a PDE III inhibitor may be considered to reverse the effect of beta-blockade if beta-blockade is thought to be contributing to hypotension with subsequent hypoperfusion. | IIb | C | |
| Inotropic agents are not recommended unless the patient is symptomatically hypotensive or hypoperfused because of safety concern. | III | A | 556, 557 |
| **Vasopressors** | | | |
| A vasopressor (norepinephrine preferably) may be considered in patients who have cardiogenic shock, despite treatment with another inotrope, to increase blood pressure and vital organ perfusion. | IIb | B | 558 |
| It is recommended to monitor ECG and blood pressure when using inotropic agents and vasopressors, as they can cause arrhythmia, myocardial ischaemia, and in the case of levosimendan and PDE III inhibitors also hypotension. | I | C | 540, 559–563 |
| In such cases intra-arterial blood pressure measurement may be considered. | IIb | C | |

# Sopravvivenza in terapia continua con inotropi




**197 pz, in terapia ottimale con ACEI, BB, AICD/CRT**

**137 non in lista per Htx/VAD: sopravvivenza a 1 anno 48%, a 2 anni 38%**

**60 in lista per Htx/VAD eseguito nel 92%**

**Circ Heart Fail 2015;8:880-86**

# Inotropi intermittenti: le "storie" del passato

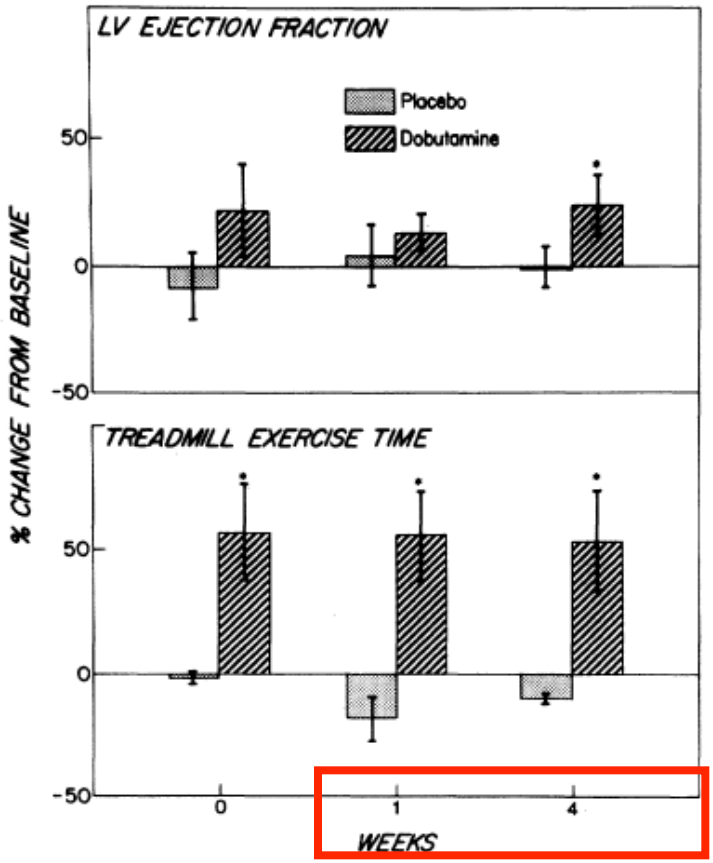



**FIGURE 3.** Changes in left ventricular ejection fraction and treadmill exercise time immediately (week 0), 1 week, and 4 weeks after infusion in the dobutamine and placebo groups. Asterisks indicate the values in the dobutamine group that differ significantly from those in the placebo group at $p < .05$ (two-tailed).

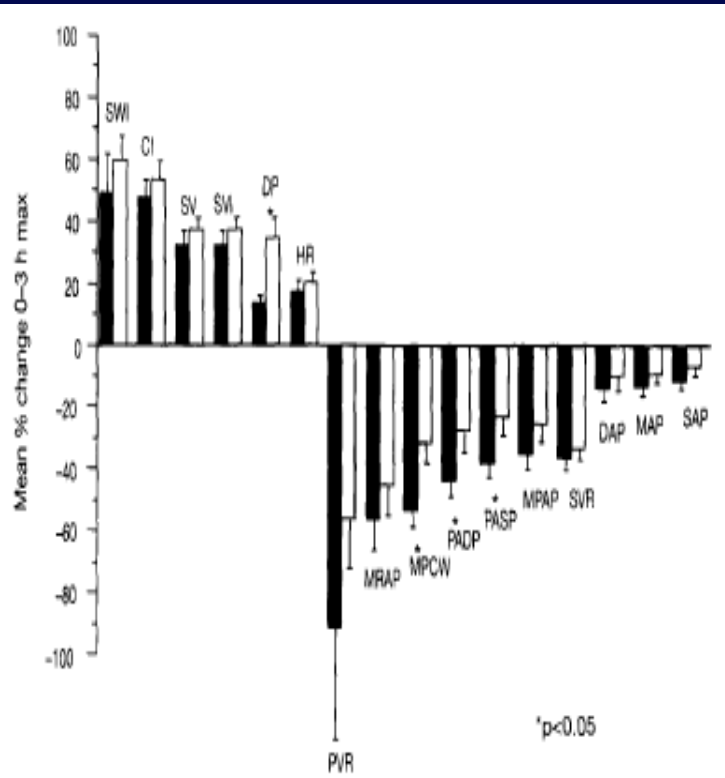


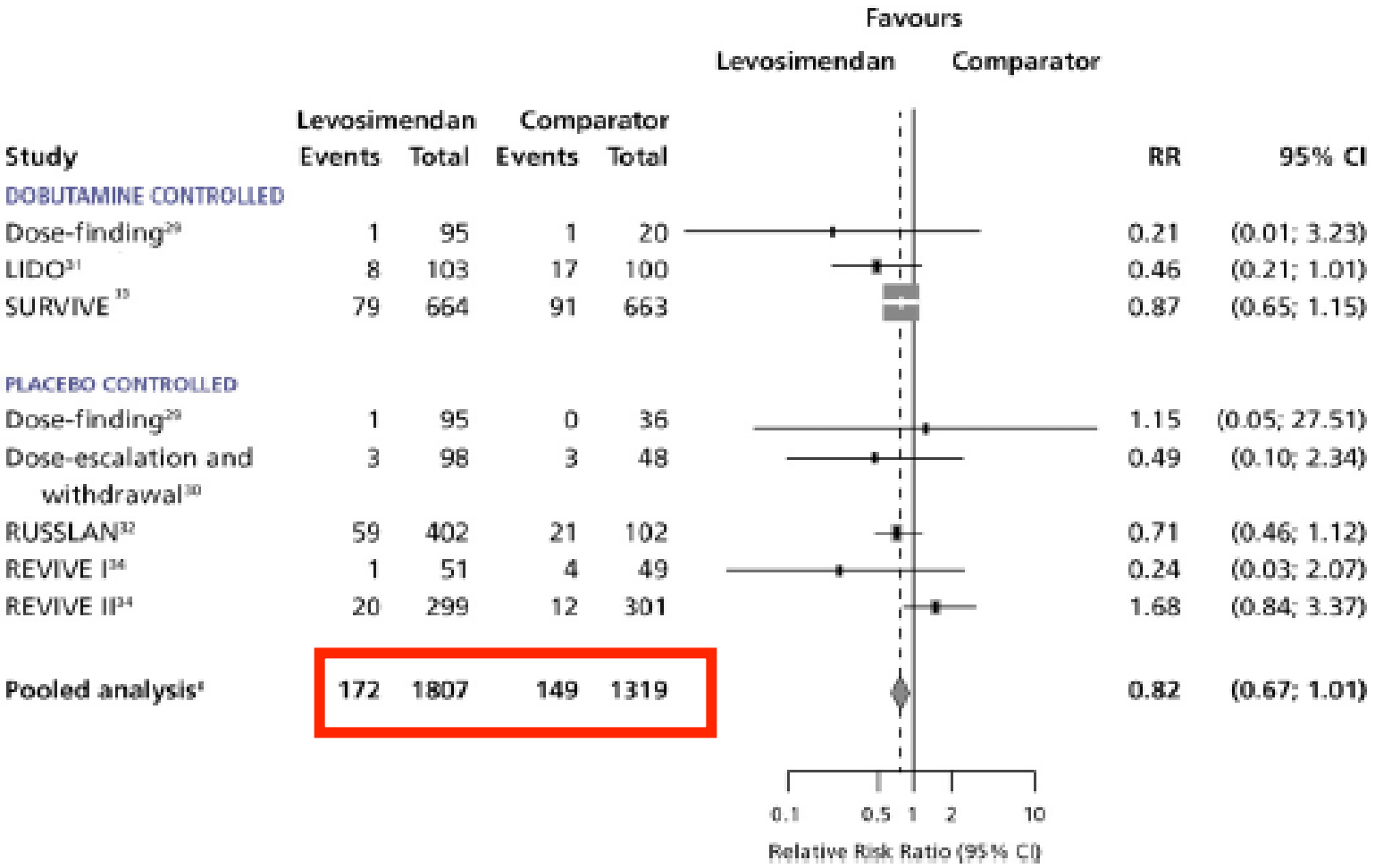

FIG. 2 Mean (±SEM) percent change for all hemodynamic variables at the maximal 0–3 h interval: stroke work index (SWI), cardiac index (CI), stroke volume (SV), stroke volume index (SVI), double product (DP), heart rate (HR), pulmonary vascular resistance (PVR), mean right atrial pressure (MRAP), mean pulmonary capillary wedge pressure (MPCWP), pulmonary arterial diastolic pressure (PADP), pulmonary arterial systolic pressure (PASP), mean pulmonary arterial pressure (MPAP), systemic vascular resistance (SVR), diastolic arterial pressure (DAP), mean arterial pressure (MAP), and systolic arterial pressure (SAP). Measures of left ventricular performance and heart rate were increased and are shown above the abscissa; measures of vasodilation were enhanced and are shown below the abscissa. MPCWP, PADP, and PASP reductions were greater for milrinone at the maximal 0–3 h interval ($p \leq 0.05$). —■— = Milrinone, —□— = dobutamine.

Circ 1984; 69:113. " l' effetto della dobutamina dura settimane"

Clin Cardiol 1996;19:21. "il milrinone è preferibile alla dobutamina nell' infarto"

# Revisione delle metaanalisi: levosimendan e mortalità






Pollesello et al. Int J Cardiol 2016;209:77

# Quali pazienti per le infusioni ripetute di levosimendan

**Table 3**
Criteria for the definition of advanced chronic heart failure indicated by the Study Group on Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology [67].

| Definition of advanced heart failure |
|---|
| Severe symptoms of heart failure (NYHA class III or IV) |
| Episodes of fluid retention and/or peripheral hypoperfusion |
| Objective evidence of severe cardiac dysfunction |
| Severe impairment of functional capacity |
| History of ≥ 1 heart failure hospitalisation in the past 6 months |
| Presence of all of the previous features despite "attempts to optimise" therapy |

**Table 4**
High-risk setting defining the patients who could benefit from repetitive use of levosimendan in chronic advanced HF.

| Indication for levosimendan use in advanced heart failure |
|---|
| • Severe systolic dysfunction (LVEF <35%) |
| • and/or NYHA IIIb-IV and/or INTERMACS levels 4, 5, 6 |
| • and/or Repeated hospitalisation or emergency department visits (≥ 2 in the past year) |
| • All of the above despite optimal treatment for heart failure |

Nieminen et al .Int J Cardiol 2014; 174:360

# Infusioni ripetute di levosimendan: expert panel consensus



| Study or Subgroup | Levosimendan Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Altenberger 2013 | 1 | 63 | 4 | 57 | 3.3% | 0.23 [0.03, 1.96] |
| Berger 2007 | 6 | 19 | 7 | 21 | 19.0% | 0.95 [0.39, 2.32] |
| Bonios 2012 | 4 | 21 | 8 | 21 | 14.2% | 0.50 [0.18, 1.41] |
| Kleber 2009 | 0 | 16 | 1 | 8 | 1.6% | 0.18 [0.01, 3.91] |
| Malfatto 2012 | 4 | 22 | 4 | 11 | 10.9% | 0.50 [0.15, 1.63] |
| Mavrogeni 2007 | 2 | 25 | 8 | 25 | 7.3% | 0.25 [0.06, 1.06] |
| Nanas 2005 | 7 | 18 | 17 | 18 | 43.8% | 0.41 [0.23, 0.74] |
| Total (95% CI) | | 184 | | 161 | 100.0% | 0.47 [0.32, 0.70] |
| Total events | 24 | | 49 | | | |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.16$, $df = 6$ ($P = 0.66$); $I^2 = 0\%$

Test for overall effect: $Z = 3.76$ ($P = 0.0002$)

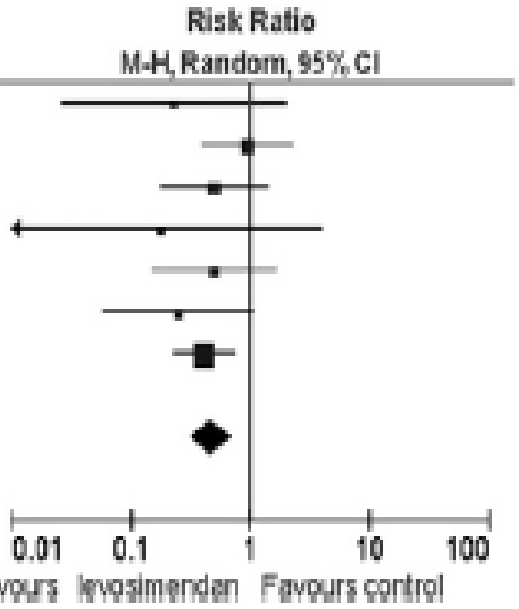



Fig. 1. Meta-analysis: reduction in mortality rates using repetitive levosimendan therapy.

**Totale di 345 pazienti, 184 con levosimendan e 161 controllo**

**24/184 (12%) vs 49/161 (30%)**

**Numero di eventi troppo basso per conclusioni definitive ma solo "hypothesis generating"**

**Nieminen et al. Int J Cardiol 2014; 174:360**

# Meta-analisi sulle infusioni ripetute di levosimendan: mortalità

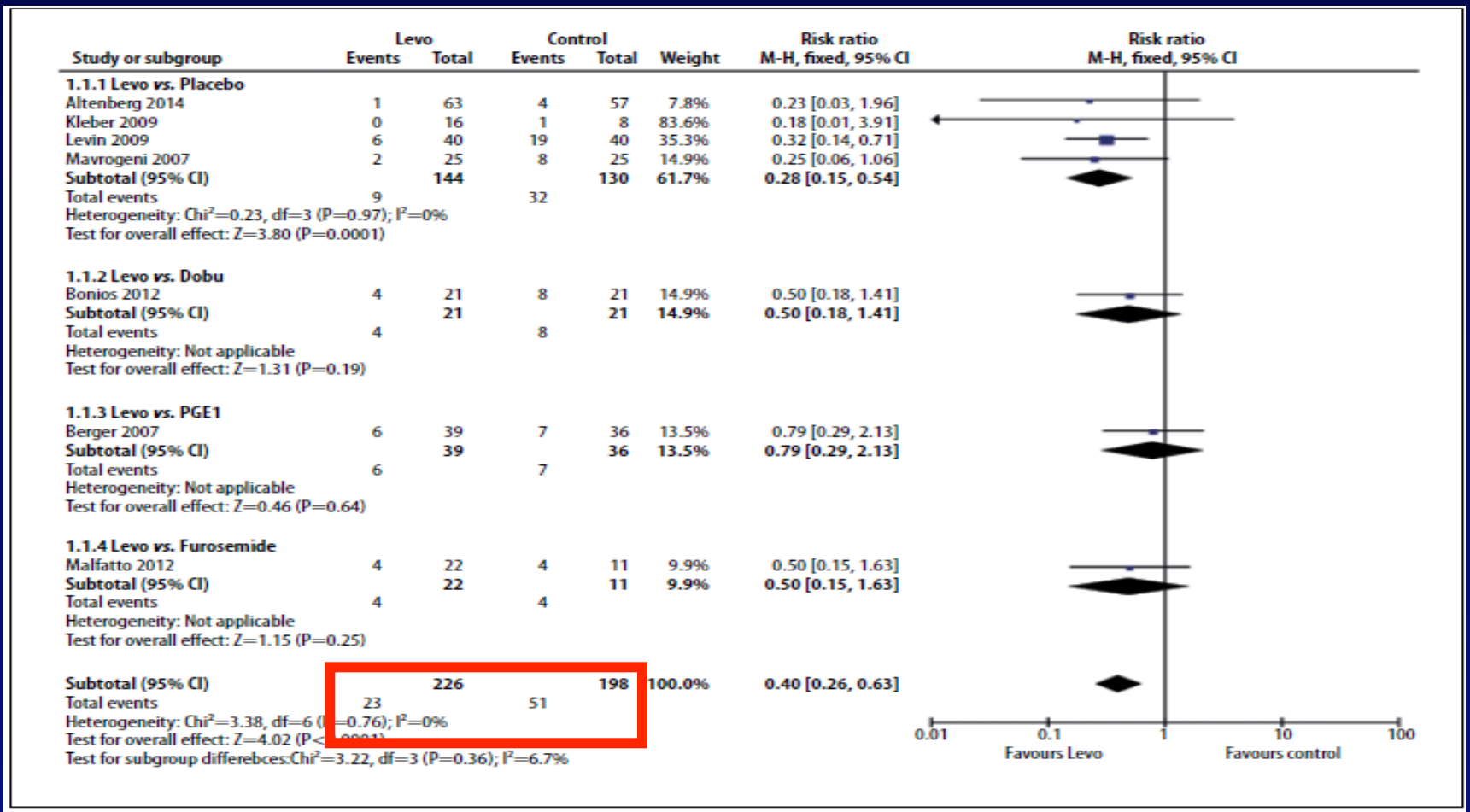



**Figure 2.** Meta-analysis of mortality rate at the end of follow-up.

**Mortalità ridotta nel gruppo levo 23/226(10,2) vs 53/198(26,8% (RR 0,40, p>0,0001):**
**- significativa vs placebo (RR 0,28, p=0,0001)**
**- - non significativa vs dobutamina**

**Med Sci Monit 2015;21:895**

# Meta-analisi sulle infusioni ripetute di levosimendan: FE

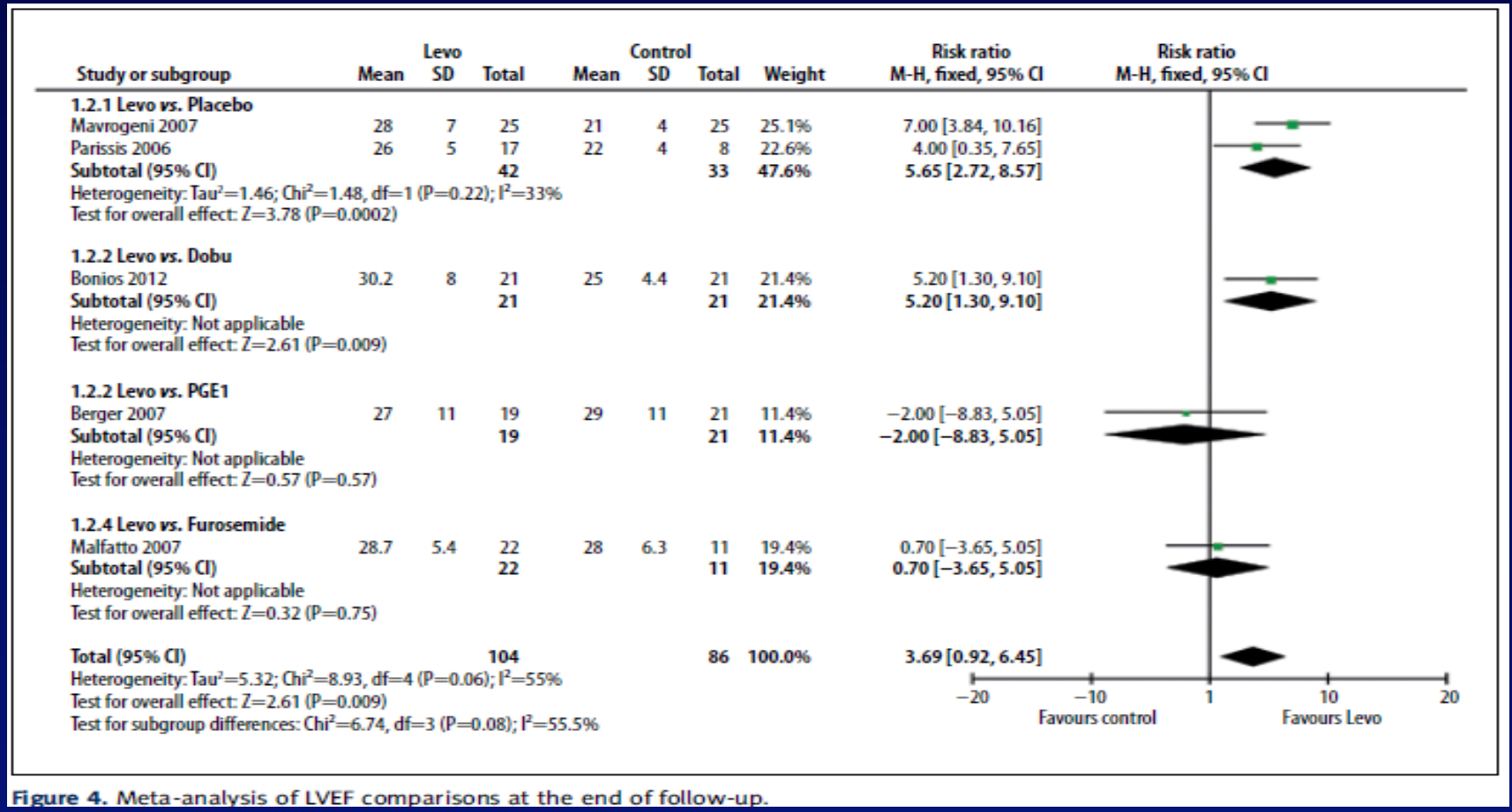



Figure 4. Meta-analysis of LVEF comparisons at the end of follow-up.

**Miglioramento della FE ( 3,69%, p=0.009) nel gruppo levo:**
**significativo vs placebo (5,65%, p=0,0002);**
**non valutabile vs dobutamina per piccolo numero pazienti**

Med Sci Monit 2015;21:895

# Infusioni intermittenti: conclusioni

## A chi:

Pazienti esclusi dal trapianto per migliorare qualità di vita e ridurre le ospedalizzazioni

Pazienti in lista trapianto per mantenere la funzione d'organo

## Protocolli variabili:

Dosi: 0,1 – 0,2 mcg/Kg/min, senza bolo

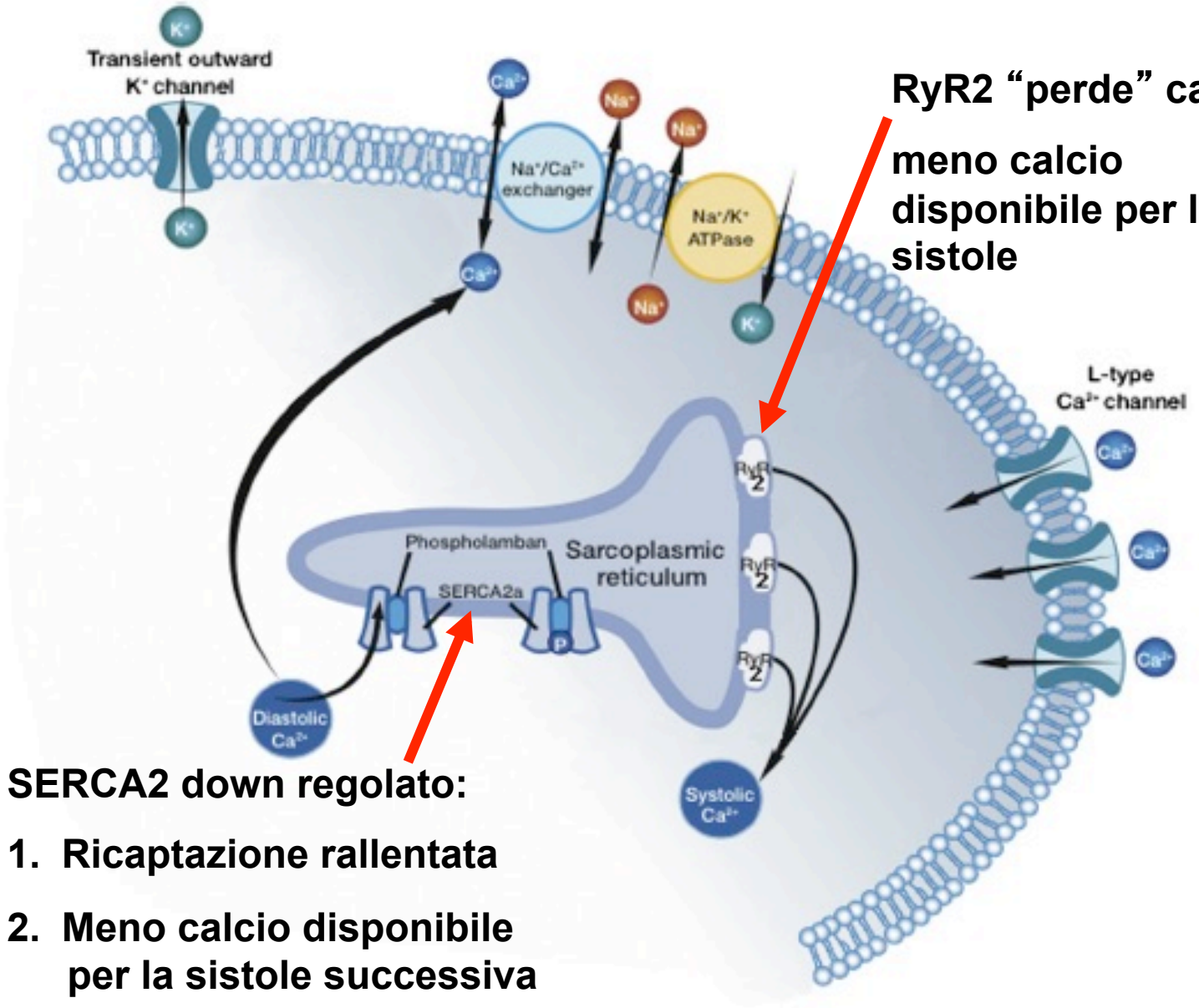
Frequenza: settimanale, bisettimanale, mensile

## Risultati:

Gli studi non hanno dimensioni idonee per conclusioni definitive

Le meta-analisi sono incoraggianti

Necessari studi omogenei, su popolazioni selezionate, progettati per dimostrare efficacia




**RyR2 "perde" calcio:**

**meno calcio disponibile per la sistole**

**SERCA2 down regolato:**

1. **Ricaptazione rallentata**
2. **Meno calcio disponibile per la sistole successiva**

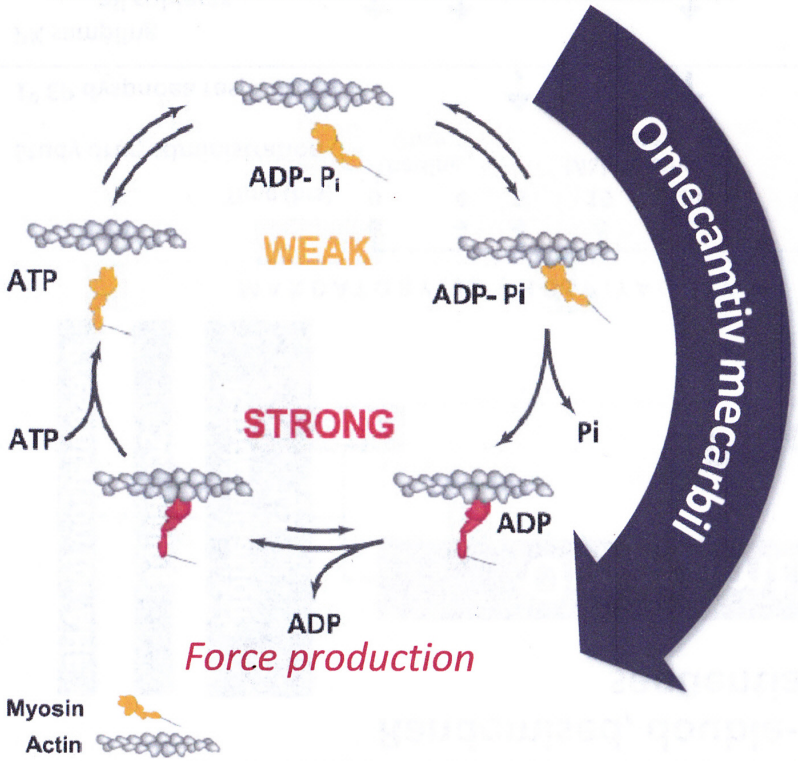
JACC HF 2014; 2:84-92

# Nuovi inotropi: omecamtiv

ATOMIC-AHF

## Omecamtiv Mecarbil (OM) is a Novel Selective Cardiac Myosin Activator

### Mechanochemical Cycle of Myosin



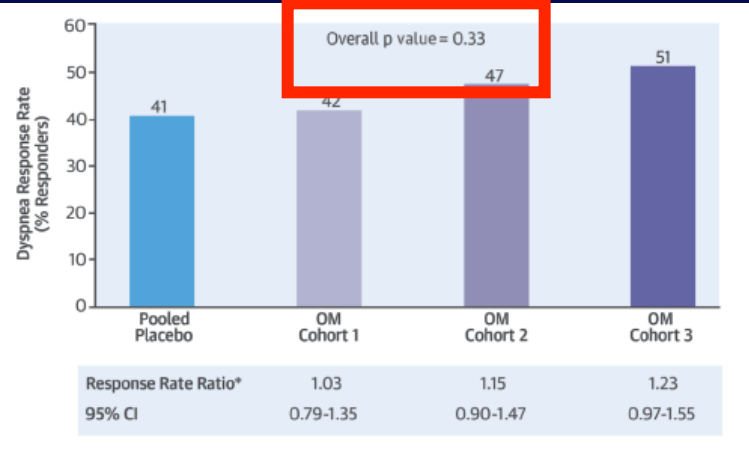

**Omecamtiv mecarbil increases the entry rate of myosin into the tightly-bound, force-producing state with actin**

**"More hands pulling on the rope"**

- Increases duration of systole
- Increases stroke volume
- No increase in myocyte calcium
- No change in $dP/dt_{max}$
- No increase in $MVO_2$

Malik FI, *et al.* *Science* 2011; 331:1439-43.

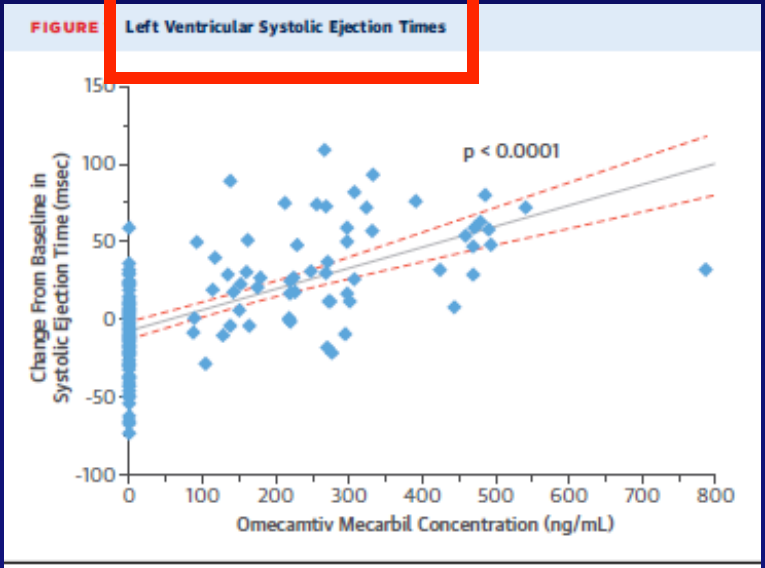
# Nuovi inotropi: omecamtiv ATOMIC-AHF

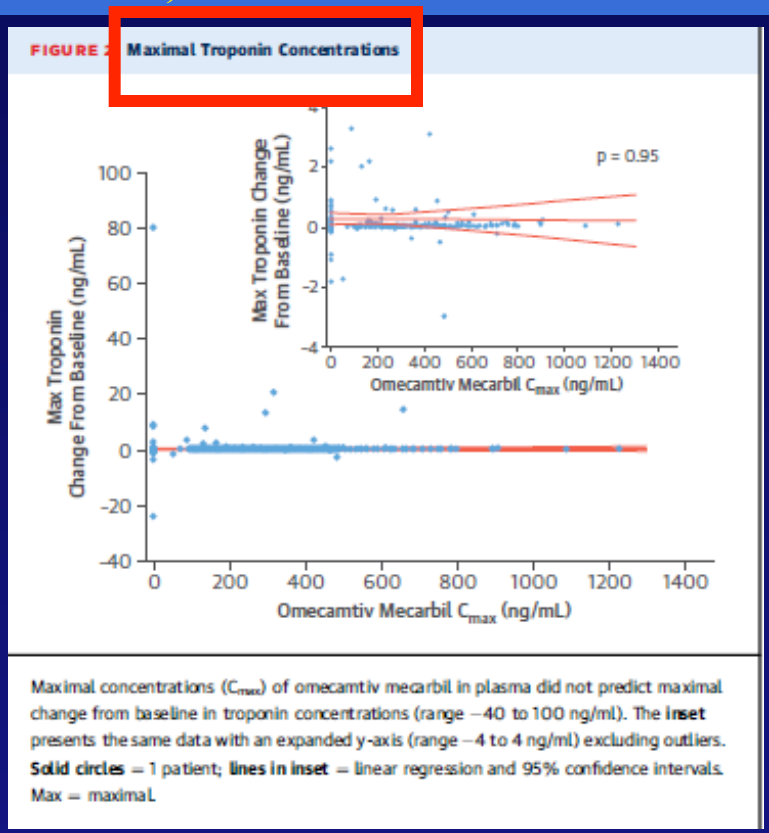



606 pazienti, FE < 40%, AHF

Randomizzazione 3 dosaggi omecamtiv

End point primario:miglioramento dispnea; end point secondari: altri sintomi, eventi clinici



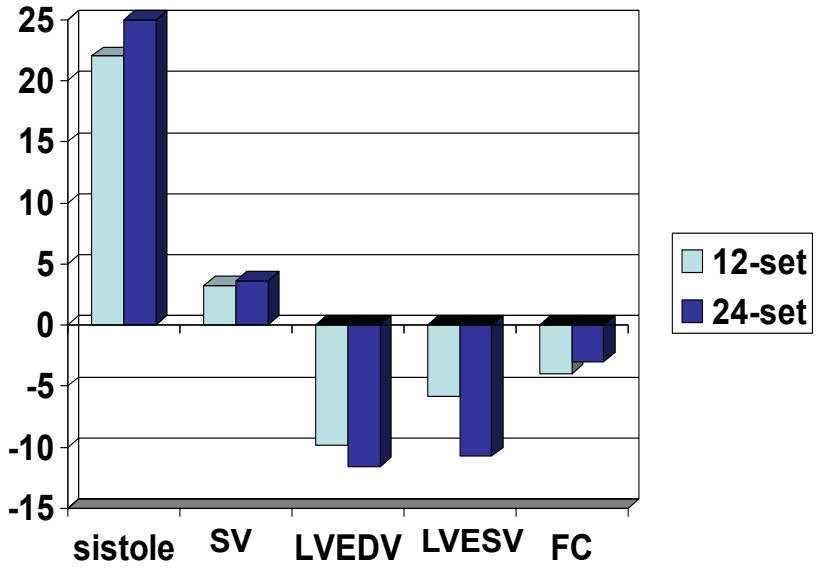




JACC 2016; 67:1444

# Nuovi inotropi: omecamtiv COSMIC-HF

**Table.** KCCQ Total Symptom Score (TSS) by Treatment Group (*$P$ < .10; **$P$ < .05)

| | Placebo | OM 25 mg po BID | OM PK-Titration |
|---|---|---|---|
| **TSS-Overall (n)** | 149 | 150 | 146 |
| Baseline—Mean (SD) | 69.7 (21.2) | 70.9 (22.0) | 67.3 (21.3) |
| Change from baseline at Week 20 - Mean (SD) | 5.0 (1.6) | 6.6 (1.6) | 9.9 (1.6) |
| Difference vs. Placebo—Mean (95%CI) | — | 1.7 (−2.8, 6.1) | 4.9 (0.5, 9.4)** |
| **TSS-Group 1: Asymptomatic to Mildly Sx (n)** | 81 | 86 | 75 |
| Baseline—Mean (SD) | 77.3 (16.4) | 80.2 (18.3) | 78.4 (17.4) |
| Change from baseline at Week 20 - Mean (SD) | 1.6 (1.8) | 2.7 (2.0) | 4.3 (1.6) |
| Difference vs. Placebo—Mean (95%CI) | — | 1.2 (−4.1, 6.4) | 2.7 (−2.2, 7.6) |
| **TSS-Group 2: Moderately to Very Severely Sx (n)** | 67 | 64 | 71 |
| Baseline—Mean (SD) | 60.2 (22.6) | 58.3 (20.2) | 55.5 (18.7) |
| Change from baseline at Week 20 - Mean (SD) | 9.5 (2.7) | 11.3 (2.6) | 16.0 (2.7) |
| Difference vs. Placebo—Mean (95%CI) | — | 1.8 (−5.7, 9.3) | 6.5 (−1.0, 14.0)* |



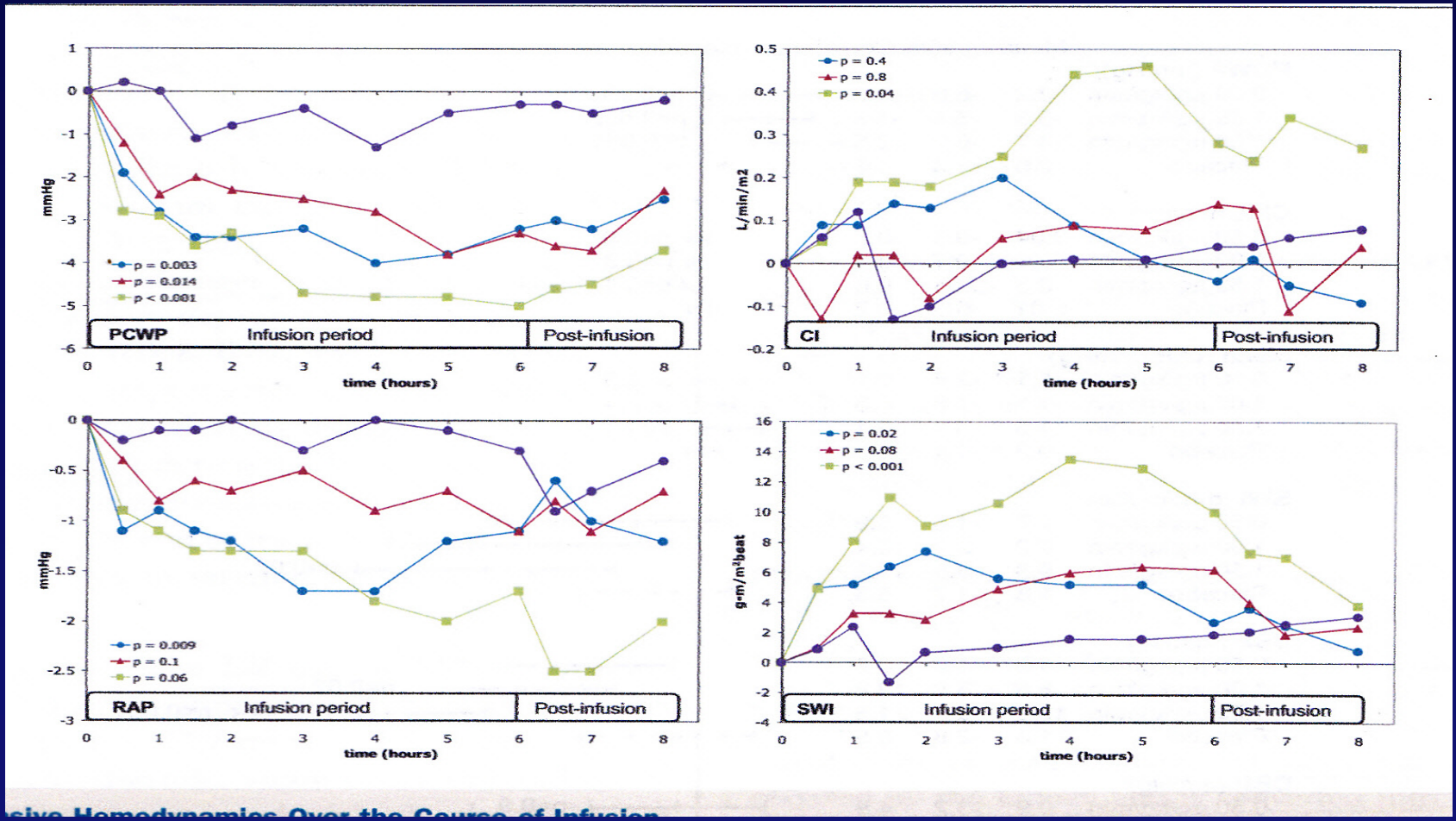

Pazienti ambulatoriali, FE ≤ 40%,, NT-proBNP ≥200

Randomizzati 1:1 placebo vs omecamtiv 25 mg x 2, fino a 50 mg x 2

Valutazione clinica (scala Likert e KCCQ) ed eco a 12 e 24 settimane

Teerlink JR. 20° Meeting HFSA, Orlando 17-20/9/2016

# Nuovi inotropi: istaroxima




**Istaroxima: inibisce ATPasi Na-K > aumenta la liberazione di calcio in sistole;**
**stimola SERCA2 > aumenta la ricaptazione di calcio in diastole**

**Emivita 1 ore, non eliminato dai reni, tre metaboliti parzialmente attivi**

**Effetti collaterali: nausea , vomito, dolore nel punto infusione** **JACC 2008;51:2276**

# STRUTTURA DEGLI ADENOVIRUS

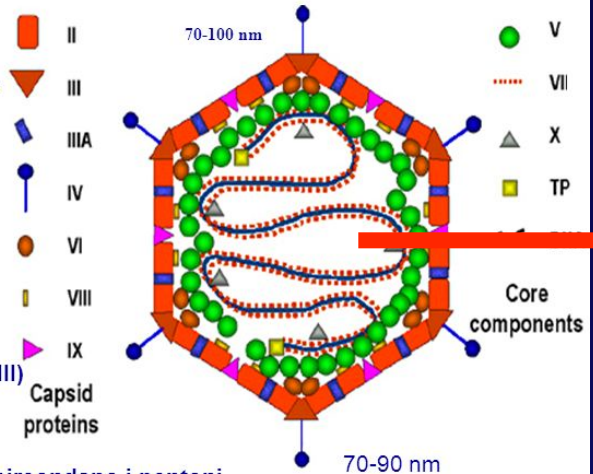
**Core :** ds DNA
- covalentemente legato alla proteina TP
- complessato alla proteina VII

proteina X (proteasi)
proteina V → core

**Capside** (252 capsomeri)

240 esoni : trimeri di proteina II

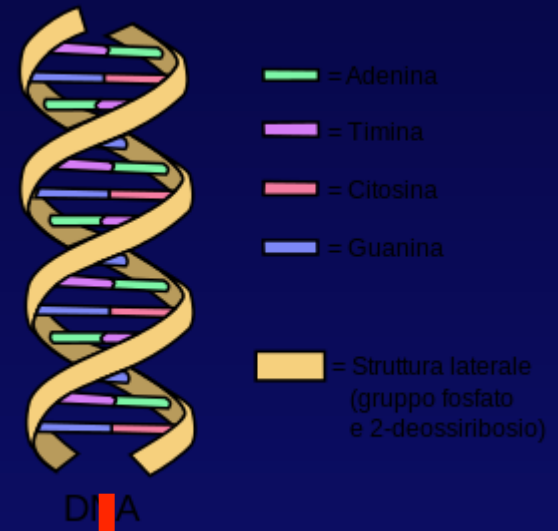
12 pentoni : Base (pentameri di proteina III)
Fibra (trimeri di proteina IV)

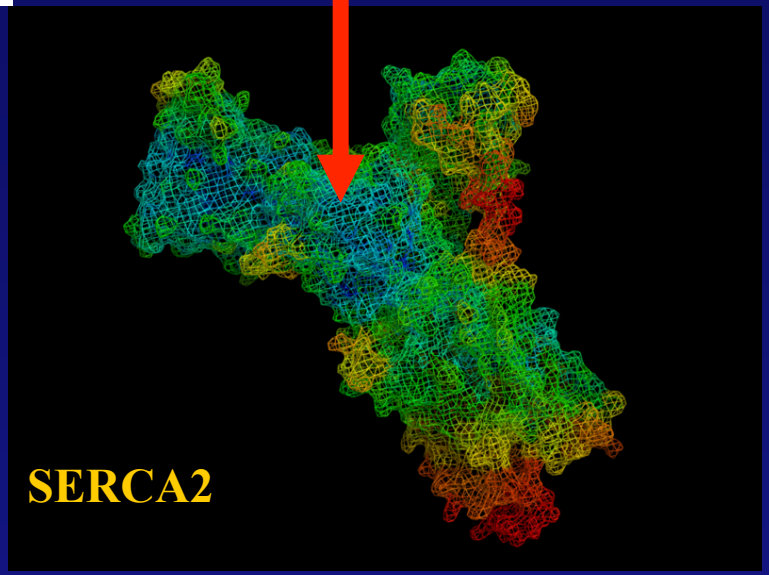



proteina IIIA → esoni che circondano i pentoni
proteina IX → esoni delle facce

proteina VI ancora l'anello di esoni che circondano ipentoni con il core
proteina VIII ancora gli esoni delle facce al core

## Terapia genica mirata al SERCA



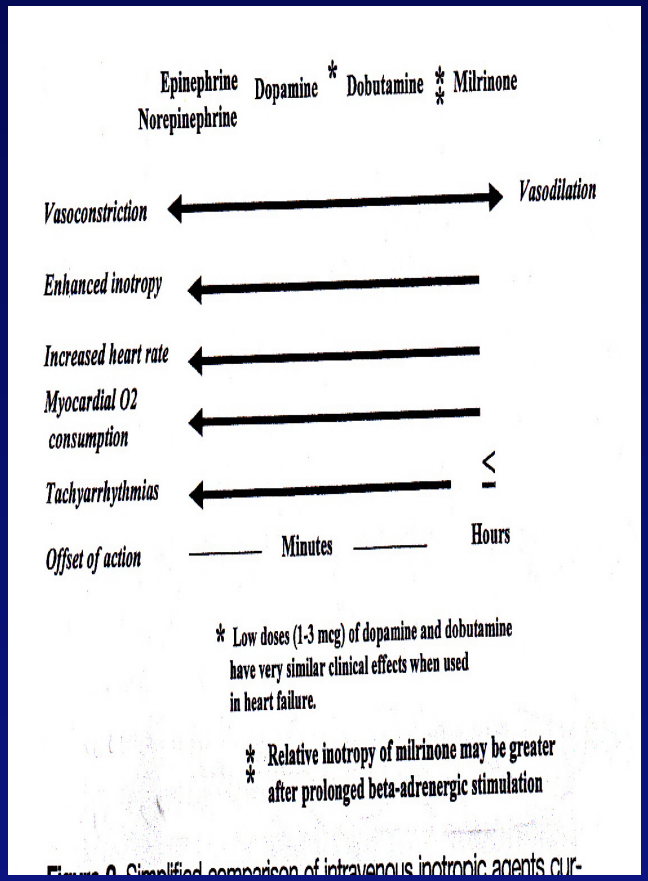




## Studi CUPID:

**2011: 39 pazienti, miglioramento sintomi, capacità funzionale, biomarcatori, funzione Vsin, eventi clinici (Circ 2011; 124:304)**

**2015: CUPID 2 (ESC, Londra): 243 pazienti,**
**end point primario: WHF a 12 mesi: NS**
**end point secondari: morte, VAD/trapianto, NYHA, 6MWT, QOL : NS**

# Inotropi: conclusioni




**Inotropi:**

**Dovrebbero essere usati come bridge per il tempo e dose minima efficace per valutare :**

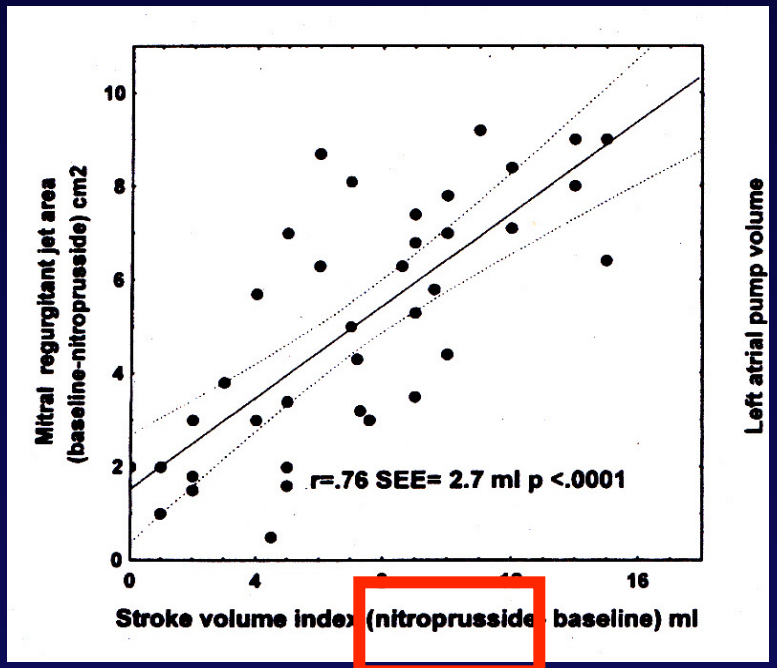
1. **Risoluzione dello shock**
2. **Trapianto / VAD**
3. **Risoluzione di cause precipitanti**
4. **Terapia palliativa**

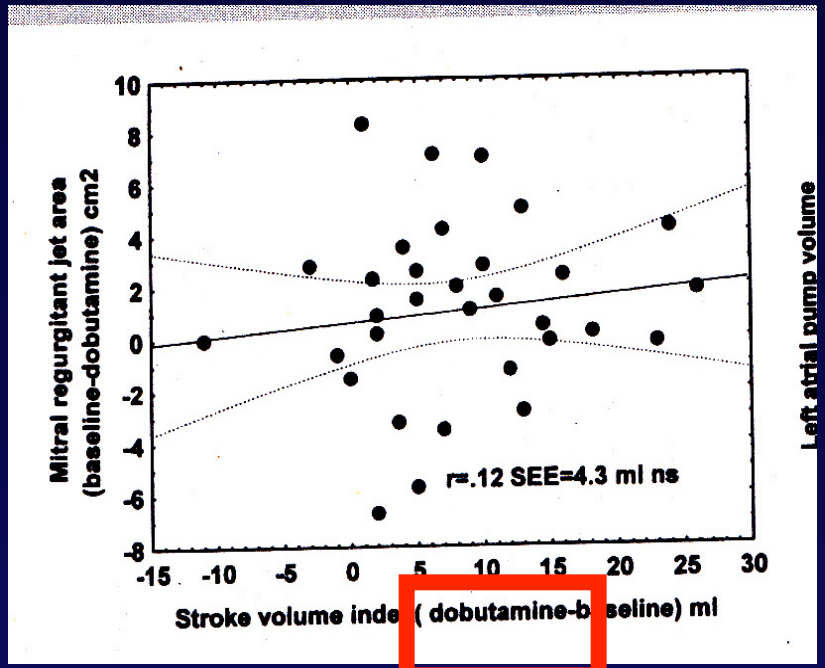
**Prima scelta nel paziente ipoteso e ipoperfuso, wet and cold**

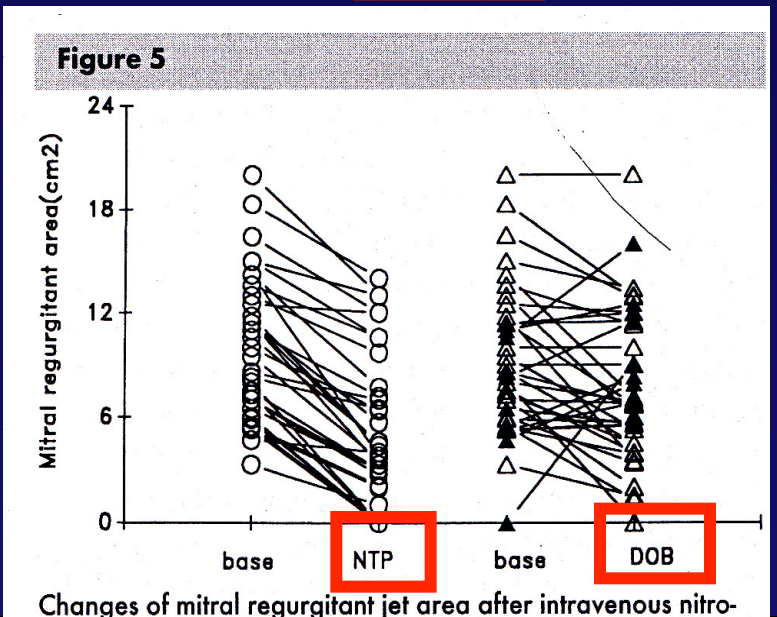
**Prima scelta nel paziente con severa disfunzione destra, senza ipertensione polmonare**

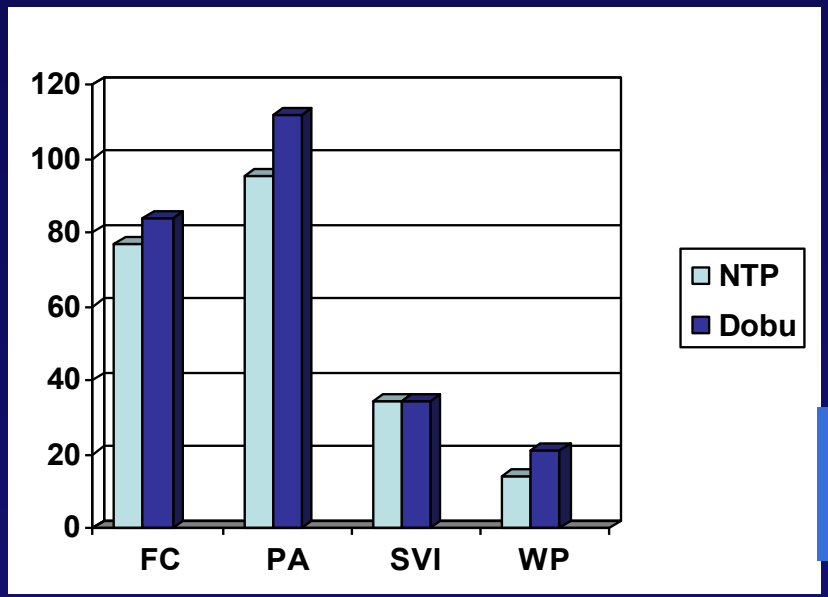
**Nel paziente beta bloccato tenere presente variabilità di risposta in relazione al beta bloccante e all' inotropo**

# Vasodilatatori vs inotropi: effetti emodinamici

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