31 GIORNATE CARDIOLOGICHE TORINESI
TURIN
October
24th-26th
2019

## MANAGEMENT FOR CARDIOGENIC SHOCK: CLINICAL SESSION

# *Appropriate use of drugs is sufficient in most cases*

**Pierluigi Sbarra**
**Giovanni Bosco Hospital - Turin**


# Medical therapy: lack of evidence

Cochrane Library

Cochrane Database of Systematic Reviews

**Inotropic agents and vasodilator strategies for acute myocardial infarction complicated by cardiogenic shock or low cardiac output syndrome (Review)**

Unverzagt S, Wachsmuth L, Hirsch K, Thiele H, Buerke M, Haerting J, Werdan K, Prondzinsky R

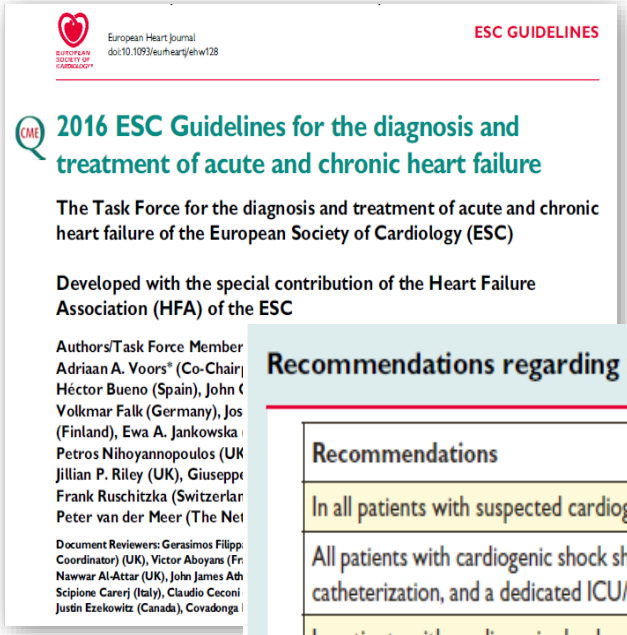
## AUTHORS' CONCLUSIONS

### Implications for practice

At present there are no robust and convincing data to support a specific inotropic or vasodilator drug therapy as the best solution to reduce mortality in haemodynamically unstable patients with CS complicating AMI.

Cochrane Database of Systematic Reviews 2014, Issue 1.

# Medical therapy of Cardiogenic Shock (CS): lack of evidence



European Heart Journal doi:10.1093/eurheartj/ehw128

ESC GUIDELINES

## 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

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

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Authors/Task Force Member
Adriaan A. Voors* (Co-Chair
Héctor Bueno (Spain), John
Volkmar Falk (Germany), Jos
(Finland), Ewa A. Jankowska
Petros Nihoyannopoulos (UK
Jillian P. Riley (UK), Giuseppe
Frank Ruschitzka (Switzerlar
Peter van der Meer (The Ne

Document Reviewers: Gerasimos Filipp
Coordinator) (UK), Victor Aboyans (Fr
Nawwar Al-Attar (UK), John James Ad
Scipione Carerj (Italy), Claudio Ceconi
Justin Ezekowitz (Canada), Covadonga

**Table 1.2 Level of evidence**

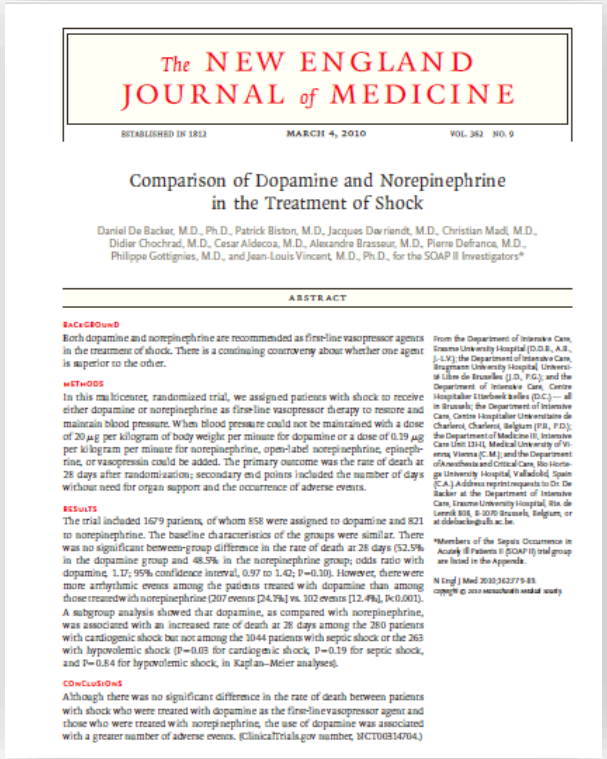
| | |
|---|---|
| Level of evidence A | Data derived from multiple randomized clinical trials or meta-analyses. |
| Level of evidence B | Data derived from a single randomized clinical trial or large non-randomized studies. |
| Level of evidence C | Consensus of opinion of the experts and/or small studies,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

**Recommendations regarding management of patients with cardiogenic shock**

| Recommendations | Class [a] | Level [b] | Ref [c] |
|---|---|---|---|
| In all patients with suspected cardiogenic shock, immediate ECG and echocardiography are recommended. | I | C | |
| All patients with cardiogenic shock should be rapidly transferred to a tertiary care center which has a 24/7 service of cardiac catheterization, and a dedicated ICU/CCU with availability of short-term mechanical circulatory support. | I | C | |
| In patients with cardiogenic shock complicating ACS an immediate coronary angiography is recommended (within 2 hours from hospital admission) with an intent to perform coronary revascularization. | I | C | |
| Continous ECG and blood pressure monitoring are recommended. | I | C | |
| Invasive monitoring with an arterial line is recommended. | I | C | |
| Fluid challenge (saline or Ringer's lactate, >200 ml/15–30 min) is recommended as the first-line treatment if there is no sign of overt fluid overload. | I | C | |
| Intravenous inotropic agents (dobutamine) may be considered to increase cardiac output. | IIb | C | |
| Vasopressors (norepinephrine preferable over dopamine) may be considered if there is a need to maintain SBP in the presence of persistent hypoperfusion. | IIb | B | 558 |
| IABP is not routinely recommended in cardiogenic shock. | III | B | 585, 586 |
| Short-term mechanical circulatory support may be considered in refractory cardiogenic shock depending on patient age, comorbidities and neurological function. | IIb | C | |

92: 200

# Medical therapy: first comparison…



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 4, 2010 VOL. 362 NO. 9

## Comparison of Dopamine and Norepinephrine in the Treatment of Shock

Daniel De Backer, M.D., Ph.D., Patrick Biston, M.D., Jacques Devriendt, M.D., Christian Madl, M.D., Didier Chochrad, M.D., Cesar Aldecoa, M.D., Alexandre Brasseur, M.D., Pierre Defrance, M.D., Philippe Gottignies, M.D., and Jean-Louis Vincent, M.D., Ph.D., for the SOAP II Investigators*

ABSTRACT

BACKGROUND

Both dopamine and norepinephrine are recommended as first-line vasopressor agents in the treatment of shock. There is a continuing controversy about whether one agent is superior to the other.

METHODS

In this multicenter, randomized trial, we assigned patients with shock to receive either dopamine or norepinephrine as first-line vasopressor therapy to restore and maintain blood pressure. When blood pressure could not be maintained with a dose of 20 μg per kilogram of body weight per minute for dopamine or a dose of 0.19 μg per kilogram per minute for norepinephrine, open-label norepinephrine, epinephrine, or vasopressin could be added. The primary outcome was the rate of death at 28 days after randomization; secondary end points included the number of days without need for organ support and the occurrence of adverse events.

RESULTS

The trial included 1679 patients, of whom 858 were assigned to dopamine and 821 to norepinephrine. The baseline characteristics of the groups were similar. There was no significant between-group difference in the rate of death at 28 days (52.5% in the dopamine group and 48.5% in the norepinephrine group; odds ratio with dopamine, 1.17; 95% confidence interval, 0.97 to 1.42; P=0.10). However, there were more arrhythmic events among the patients treated with dopamine than among those treated with norepinephrine (207 events [24.7%] vs. 102 events [12.4%], P<0.001). A subgroup analysis showed that dopamine, as compared with norepinephrine, was associated with an increased rate of death at 28 days among the 280 patients with cardiogenic shock but not among the 1044 patients with septic shock or the 263 with hypovolemic shock (P=0.03 for cardiogenic shock, P=0.19 for septic shock, and P=0.84 for hypovolemic shock, in Kaplan–Meier analyses).

CONCLUSIONS

Although there was no significant difference in the rate of death between patients with shock who were treated with dopamine as the first-line vasopressor agent and those who were treated with norepinephrine, the use of dopamine was associated with a greater number of adverse events. (ClinicalTrials.gov number, NCT00814704.)

From the Department of Intensive Care, Erasme University Hospital (D.D.B., A.B., J.-L.V.); the Department of Intensive Care, Brugmann University Hospital, Université Libre de Bruxelles (J.D., P.G.); and the Department of Intensive Care, Centre Hospitalier Universitaire de Charleroi, Charleroi, Belgium (P.B., P.D.); the Department of Medicine III, Intensive Care Unit (3I+), Medical University of Vienna, Vienna (C.M.); and the Department of Anesthesia and Critical Care, Río Hortega University Hospital, Valladolid, Spain (C.A.). Address reprint requests to Dr. De Backer at the Department of Intensive Care, Erasme University Hospital, Rte. de Lennik 808, B-1070 Brussels, Belgium, or at ddebacker@ulb.ac.be.

*Members of the Sepsis Occurrence in Acutely Ill Patients II (SOAP II) trial group are listed in the Appendix.

N Engl J Med 2010;362:779-89.



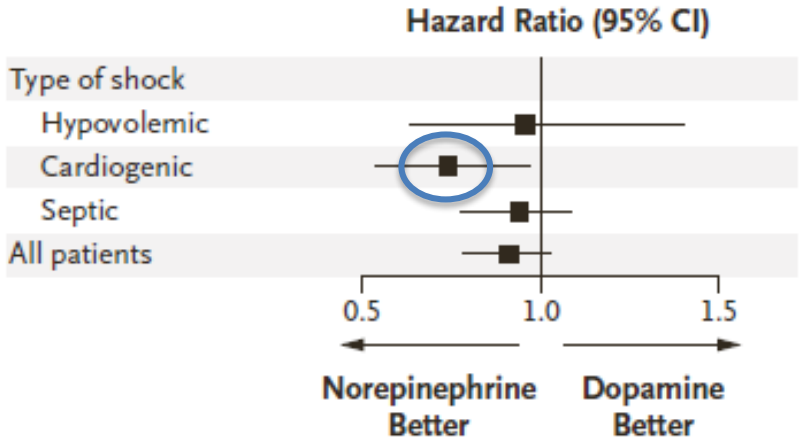
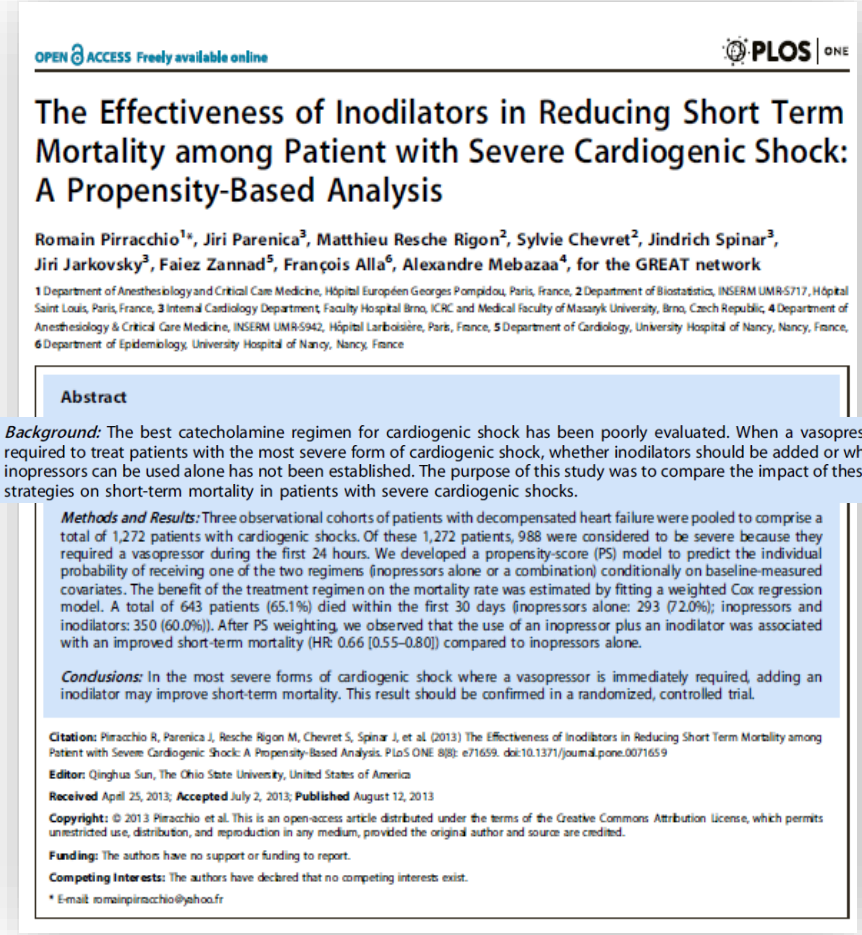



**Figure 3. Forest Plot for Predefined Subgroup Analysis According to Type of Shock.**

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.

N Engl J Med 2010; 362: 779-89

# Management of CS(ADHF): *Great Network*



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PLOS ONE

## The Effectiveness of Inodilators in Reducing Short Term Mortality among Patient with Severe Cardiogenic Shock: A Propensity-Based Analysis

Romain Pirracchio[1]*, Jiri Parenica[3], Matthieu Resche Rigon[2], Sylvie Chevret[2], Jindrich Spinar[3], Jiri Jarkovsky[3], Faiez Zannad[5], François Alla[6], Alexandre Mebazaa[4], for the GREAT network

1 Department of Anesthesiology and Critical Care Medicine, Hôpital Européen Georges Pompidou, Paris, France, 2 Department of Biostatistics, INSERM UMR-S717, Hôpital Saint Louis, Paris, France, 3 Internal Cardiology Department, Faculty Hospital Brno, ICRC and Medical Faculty of Masaryk University, Brno, Czech Republic, 4 Department of Anesthesiology & Critical Care Medicine, INSERM UMR-S942, Hôpital Lariboisière, Paris, France, 5 Department of Cardiology, University Hospital of Nancy, Nancy, France, 6 Department of Epidemiology, University Hospital of Nancy, Nancy, France

**Abstract**

*Background:* The best catecholamine regimen for cardiogenic shock has been poorly evaluated. When a vasopressor is required to treat patients with the most severe form of cardiogenic shock, whether inodilators should be added or whether inopressors can be used alone has not been established. The purpose of this study was to compare the impact of these two strategies on short-term mortality in patients with severe cardiogenic shocks.

*Methods and Results:* Three observational cohorts of patients with decompensated heart failure were pooled to comprise a total of 1,272 patients with cardiogenic shocks. Of these 1,272 patients, 988 were considered to be severe because they required a vasopressor during the first 24 hours. We developed a propensity-score (PS) model to predict the individual probability of receiving one of the two regimens (inopressors alone or a combination) conditionally on baseline-measured covariates. The benefit of the treatment regimen on the mortality rate was estimated by fitting a weighted Cox regression model. A total of 643 patients (65.1%) died within the first 30 days (inopressors alone: 293 (72.0%); inopressors and inodilators: 350 (60.0%)). After PS weighting, we observed that the use of an inopressor plus an inodilator was associated with an improved short-term mortality (HR: 0.66 [0.55–0.80]) compared to inopressors alone.

*Conclusions:* In the most severe forms of cardiogenic shock where a vasopressor is immediately required, adding an inodilator may improve short-term mortality. This result should be confirmed in a randomized, controlled trial.

**Citation:** Pirracchio R, Parenica J, Resche Rigon M, Chevret S, Spinar J, et al. (2013) The Effectiveness of Inodilators in Reducing Short Term Mortality among Patient with Severe Cardiogenic Shock: A Propensity-Based Analysis. PLoS ONE 8(8): e71659. doi:10.1371/journal.pone.0071659

**Editor:** Qinghua Sun, The Ohio State University, United States of America

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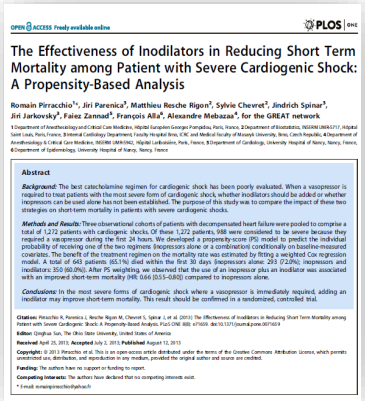
**Competing Interests:** The authors have declared that no competing interests exist.

* E-mail: romainpirracchio@yahoo.fr

- **Observational cohorts of 1272 patients with CS, derived from 3 registries (ALARM-HF, EFICA cohort , AHEAD)**
- **62% ACS (30% ADHF)**

PloS One 2013; 8: e71659

# Management of CS(ADHF): *Great Network*



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PLOS ONE

**The Effectiveness of Inodilators in Reducing Short Term Mortality among Patient with Severe Cardiogenic Shock: A Propensity-Based Analysis**

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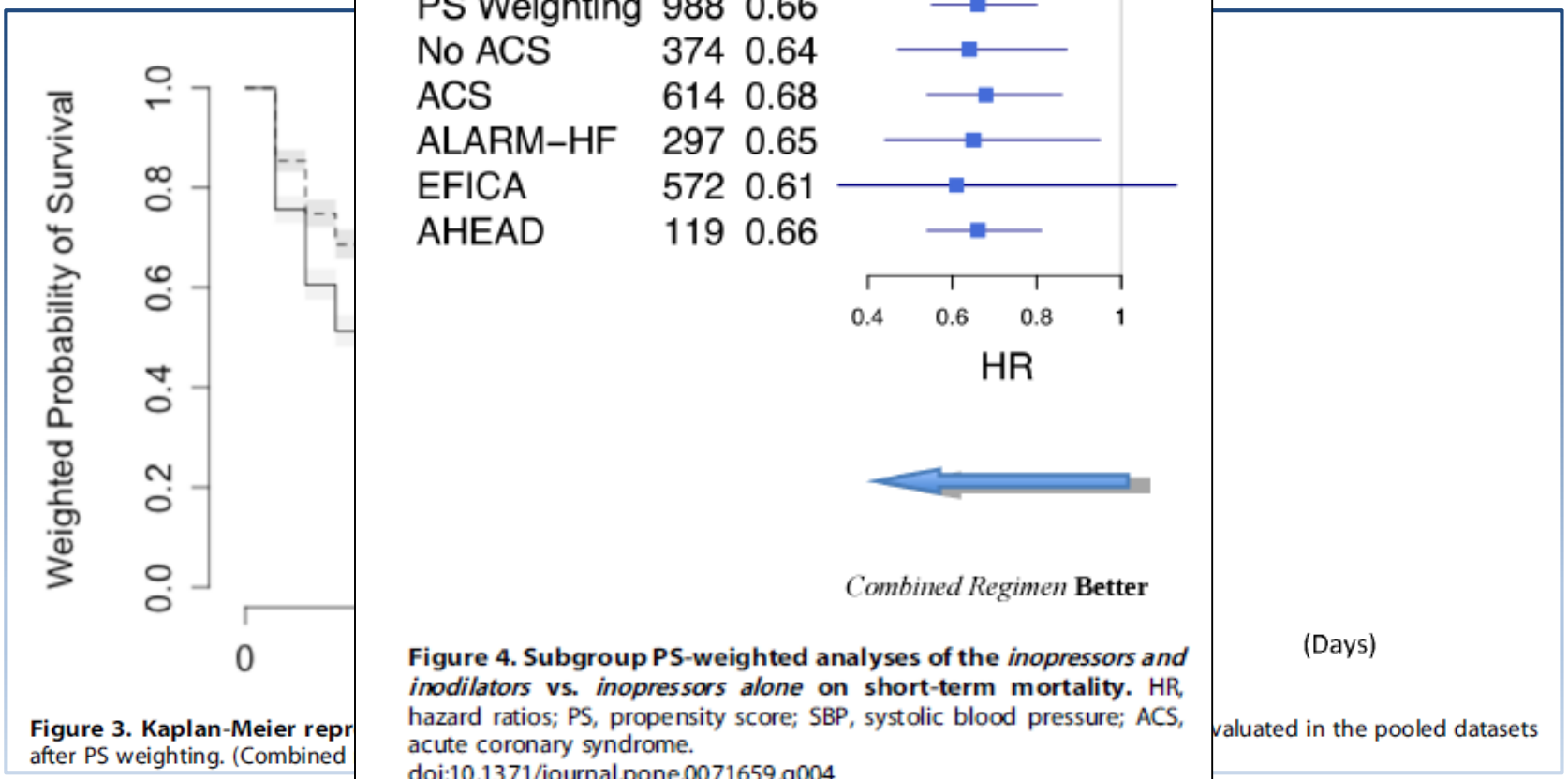



**Figure 3. Kaplan-Meier repr**
after PS weighting. (Combined

valuated in the pooled datasets

## Inopressors vs. Combined Regimen

| | n | HR |
|---|---|---|
| PS Weighting | 988 | 0.66 |
| No ACS | 374 | 0.64 |
| ACS | 614 | 0.68 |
| ALARM–HF | 297 | 0.65 |
| EFICA | 572 | 0.61 |
| AHEAD | 119 | 0.66 |

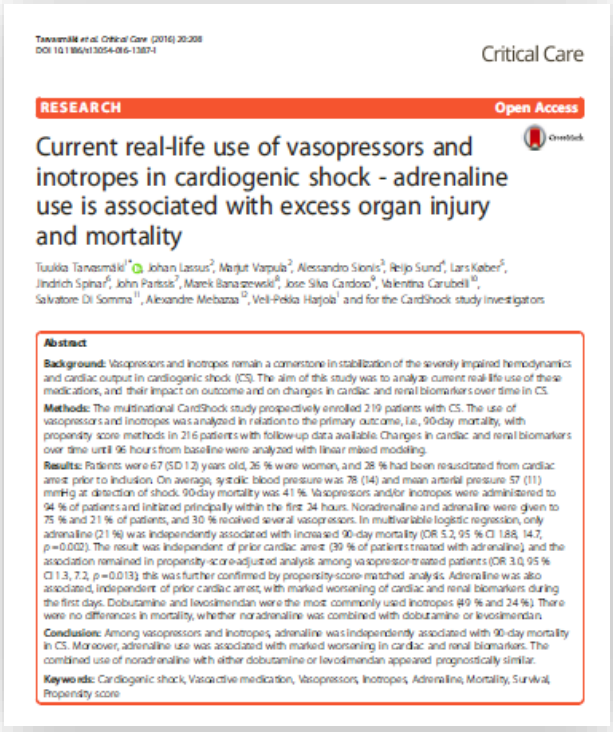



*Combined Regimen* **Better**

**Figure 4. Subgroup PS-weighted analyses of the *inopressors and inodilators* vs. *inopressors alone* on short-term mortality.** HR, hazard ratios; PS, propensity score; SBP, systolic blood pressure; ACS, acute coronary syndrome.
doi:10.1371/journal.pone.0071659.g004

PloS One 2013; 8: e71659

# Management of CS in AMI: *CardShock study*



Tarvasmäki et al. Critical Care (2016) 20:208
DOI 10.1186/s13054-016-1387-1

Critical Care

RESEARCH Open Access

Current real-life use of vasopressors and inotropes in cardiogenic shock - adrenaline use is associated with excess organ injury and mortality

Tuukka Tarvasmäki[1*], Johan Lassus[2], Marjut Varpula[2], Alessandro Sionis[3], Reijo Sund[4], Lars Køber[5], Jindrich Spinar[6], John Parissis[7], Marek Banaszewski[8], Jose Silva Cardoso[9], Valentina Carubelli[10], Salvatore Di Somma[11], Alexandre Mebazaa[12], Veli-Pekka Harjola[1] and for the CardShock study investigators


**Abstract**

**Background:** Vasopressors and inotropes remain a cornerstone in stabilization of the severely impaired hemodynamics and cardiac output in cardiogenic shock (CS). The aim of this study was to analyze current real-life use of these medications, and their impact on outcome and on changes in cardiac and renal biomarkers over time in CS.

**Methods:** The multinational CardShock study prospectively enrolled 219 patients with CS. The use of vasopressors and inotropes was analyzed in relation to the primary outcome, i.e., 90-day mortality, with propensity score methods in 216 patients with follow-up data available. Changes in cardiac and renal biomarkers over time until 96 hours from baseline were analyzed with linear mixed modelling.

**Results:** Patients were 67 (SD 12) years old, 26 % were women, and 28 % had been resuscitated from cardiac arrest prior to inclusion. On average, systolic blood pressure was 78 (14) and mean arterial pressure 57 (11) mmHg at detection of shock. 90-day mortality was 41 %. Vasopressors and/or inotropes were administered to 94 % of patients and initiated principally within the first 24 hours. Noradrenaline and adrenaline were given to 75 % and 21 % of patients, and 30 % received several vasopressors. In multivariable logistic regression, only adrenaline (21 %) was independently associated with increased 90-day mortality (OR 5.2, 95 % CI 1.88, 14.7, $p = 0.002$). The result was independent of prior cardiac arrest (39 % of patients treated with adrenaline), and the association remained in propensity-score-adjusted analysis among vasopressor-treated patients (OR 3.0, 95 % CI 1.3, 7.2, $p = 0.013$); this was further confirmed by propensity-score-matched analysis. Adrenaline was also associated, independent of prior cardiac arrest, with marked worsening of cardiac and renal biomarkers during the first days. Dobutamine and levosimendan were the most commonly used inotropes (49 % and 24 %). There were no differences in mortality, whether noradrenaline was combined with dobutamine or levosimendan.

**Conclusion:** Among vasopressors and inotropes, adrenaline was independently associated with 90-day mortality in CS. Moreover, adrenaline use was associated with marked worsening in cardiac and renal biomarkers. The combined use of noradrenaline with either dobutamine or levosimendan appeared prognostically similar.



**Keywords:** Cardiogenic shock, Vasoactive medication, Vasopressors, Inotropes, Adrenaline, Mortality, Survival, Propensity score


- Prospective study of **219 patients** (8 European coutries):
- **Vasopressors (98%):** Noradrenaline **75%** Dopamine 26% - Adrenaline 21%
- **Inotropes (94%):** Dobutamine 49% . Levosimendan 24%
- **Combination Vasopressor- Inotrope (55%)** (Noradrenaline-Dobutamine)
- 90 day Mortality: ***41%***

Critical Care (2016) 20: 208

# Management of CS in AMI: *CardShock study*

Tanaskmäki et al. Critical Care (2016) 20:208
DOI 10.1186/s13054-016-1387-1

Critical Care

RESEARCH Open Access

Current real-life use of vasopressors and inotropes in cardiogenic shock - adrenaline use is associated with excess organ injury and mortality

Tuukka Tarvasmäki[1*], Johan Lassus[2], Marjut Varpula[2], Alessandro Sionis[3], Reijo Sund[4], Lars Kober[5], Jindrich Spinar[6], John Parissis[7], Marek Banaszewski[8], Jose Silva Cardoso[9], Valentina Carubelli[10], Salvatore Di Somma[11], Alexandre Mebazaa[12], Veli-Pekka Harjola[1] and for the CardShock study investigators

**Table 2** The

| | ıfusion |
|---|---|
| | duration, h |
| Vasopressors | |
| Noradrenalin | 72) |
| Adrenaline | l) |
| Dopamine | l) |
| Vasopressin/t | 9) |
| Inotropes | |
| Dobutamine | 72) |
| Levosimenda | 51) |
| PDE3i | 72) |
| Combinations | |
| Vasopressor | |
| Dobutamine | |
| Levosimenda vasopressor(s | |

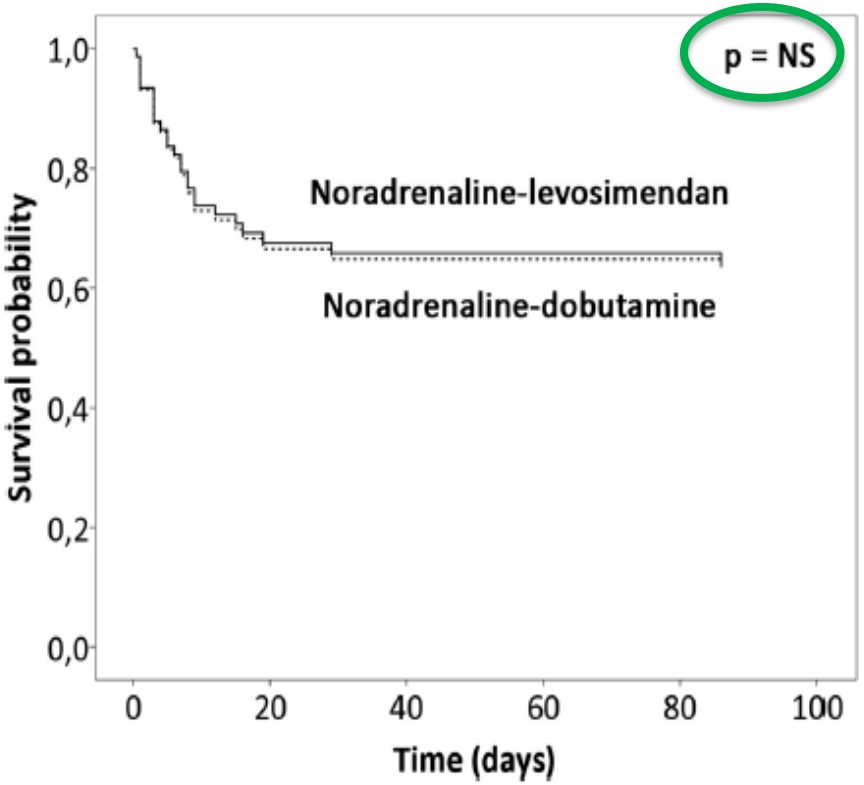



**Fig. 3** Survival-probability curves for propensity-score-adjusted Cox regression analysis for use of dobutamine (*dashed line*) and levosimendan (*solid line*) with noradrenaline. Adjusted for logit of the propensity score, which was estimated with the following variables: age, gender, medical history (myocardial infarction, coronary artery bypass graft surgery, hypertension, renal insufficiency), CS of acute coronary syndrome etiology, resuscitation prior to inclusion and initial presentation (confusion, blood lactate, creatinine, systolic blood pressure, sinus rhythm, and left ventricular ejection fraction). Of note, patients who received both dobutamine and levosimendan, or adrenaline were excluded. *NS* not significant

Critical Care (2016) 20: 208

**Key messag**

- Adrenalin
  associate
- Adrenali
  aggravati
  kidney d
- Combine
  with nora

There are some limitations to be acknowledged. First, there was no formal standardization of management in the CardShock study. However, the primary goal was to describe the current use of vasopressors and inotropes in CS and data on vasoactive treatments were prospectively collected. Second, the total dose of vasoactive medications, and duration of the maximum dose might have given further depth to the interpretation of data. However, these details were not registered. Third, the numbers of patients in the treatment groups including adrenaline or levosimendan were limited, and caution in the interpretation of the results is advocated. As the study lacks randomization, confounding by indication is a possible bias when assessing possible effect of adrenaline on mortality. Propensity score methods were used to minimize this bias; however, these methods allowed us only to account for the measured variables and the estimates of treatment effect may be susceptible to bias due to unknown and unmeasured confounding variables. Nevertheless, the association between adrenaline use and poor outcome seemed consistent. Finally, we classified dopamine as a vasopressor, although actual doses used and combining with other vasopressors might suggest a pursuit of "renal-preserving" or inotropic effect.


Critical Care (2016) 20: 208

# Sodium Nitroprusside(SNP) in ADHF

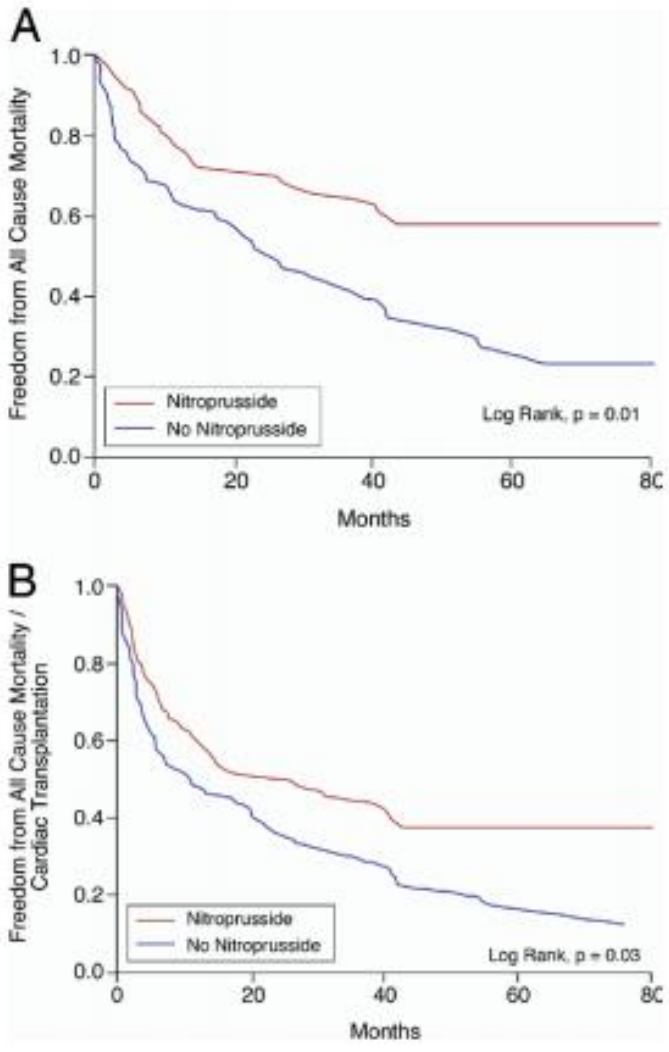
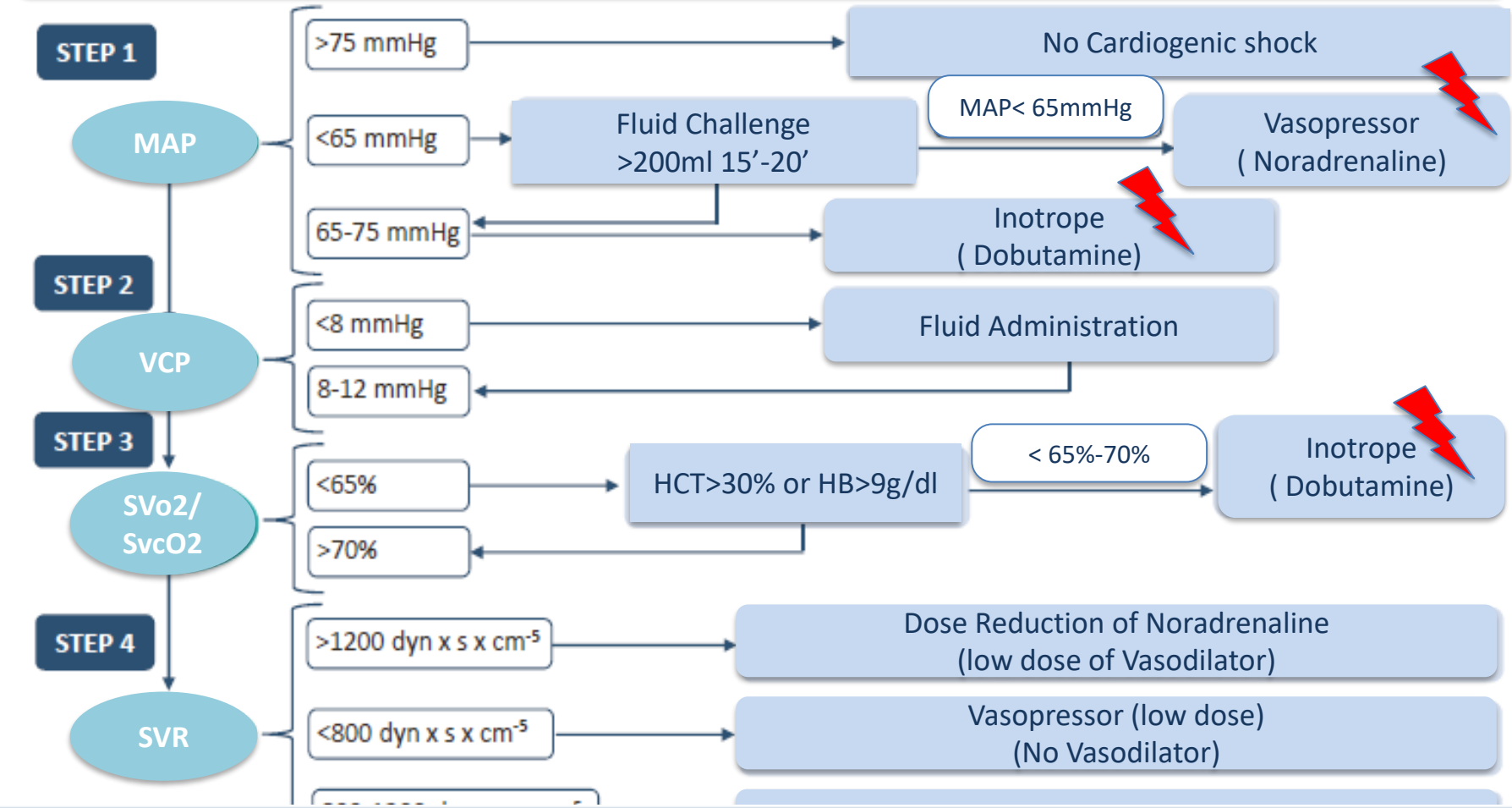



**Figure 1** Clinical Outcomes According to Use of Sodium Nitroprusside

**Protocol for intensive medical therapy.** The pharmacologic approach and hemodynamic goals of intravenous therapy for ADHF have been previously described (16). Briefly, optimal hemodynamic response is defined as a decrease in PCWP to ≤18 mm Hg, decrease in mean pulmonary arterial pressure (mPAP) by at least 20%, decrease in right atrial pressure to ≤8 mm Hg, and improvement in cardiac index to ≥2.2 l/min/m$^2$, all while maintaining MAP >65 mm Hg. The systemic blood pressure was generally measured noninvasively by an automatic cuff sphygmomanometer every 15 min. To achieve the hemo-

JACC 2008 Vol. 52, No. 3:101

# Hemodynamic Target Therapy of CARDIOGENIC SHOCK




**Non raggiungimento target**

Lattati <2 mmol/l, $SvO^2/SvcO^2$ >65-70% (con Hb >9 g/dl e $SaO^2$ >93%), PAM >65 mmHg, FC <110 b/min
diuresi oraria 1 ml/kg/h, PVC 8-12 mmHg, pH 7.3-7.5, CI >2 l/min/$m_2$

G Ital Cardiol 2017;18(10):708-718

# Management of CS complicating AMI without MSC

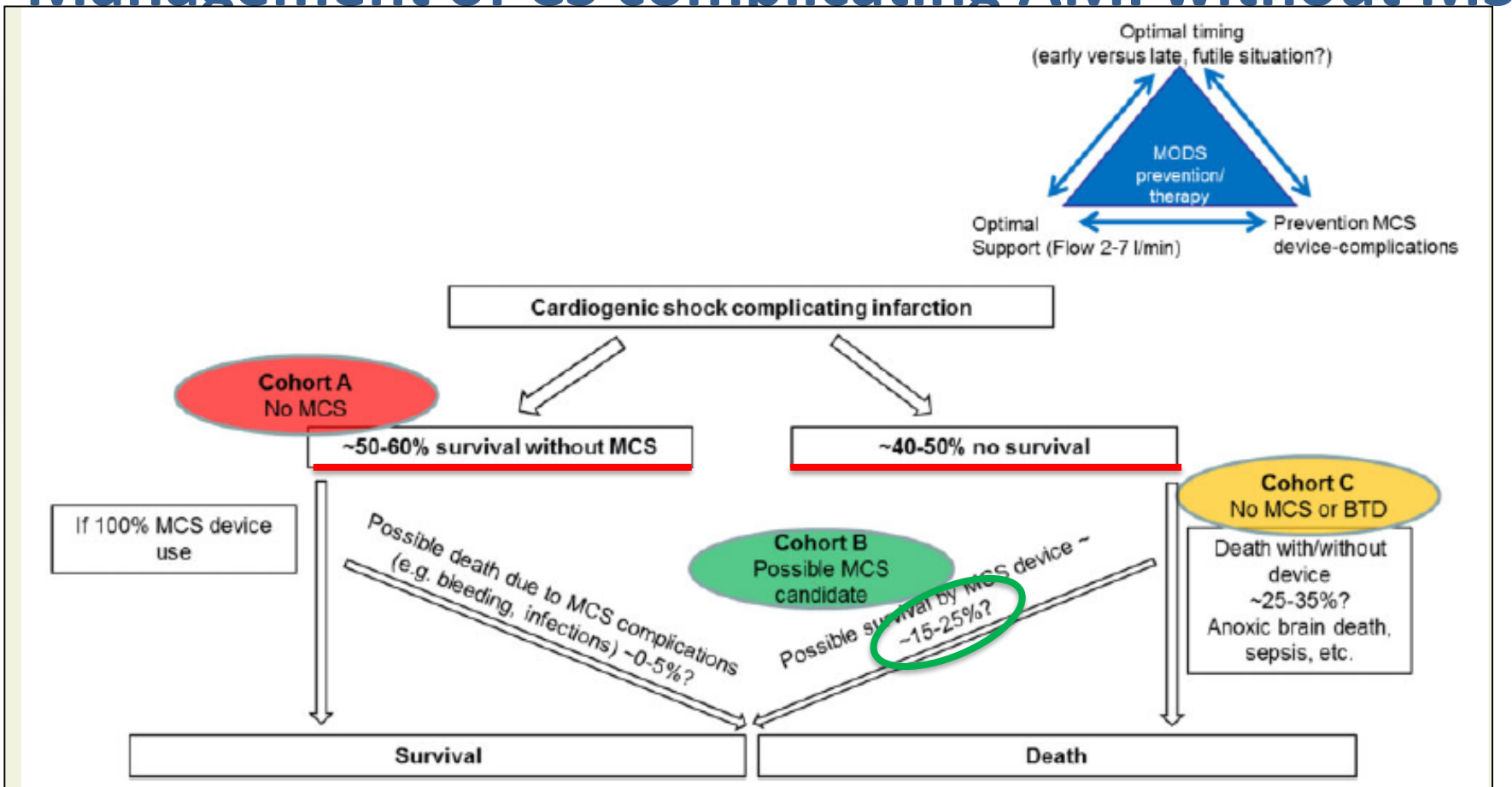



**Figure 4** Considerations on use of mechanical circulatory support for multiorgan system dysfunction prevention and therapy. Approximately 50–60% of patients currently survive without any device (Cohort A, no MCS). Inserting a device in this group will have no impact on survival or may even lead to some complications by the device itself possibly resulting in death (white arrow to the right). Approximately 40–50% currently do not survive. In this group, there may be futile situations where a mechanical circulatory support will not change clinical outcome (Cohort C, no MCS or MCS as bridge-to-decision). Based on Cohort A and C, approximately 15–25% of cardiogenic shock patients might be appropriate candidates for mechanical circulatory support (Cohort B). The right upper corner reflects current open questions in mechanical circulatory support selection and possible complications. BTD, bridge-to-decision; MCS, mechanical circulatory support; MODS, multiorgan dysfunction syndrome.

European Heart Journal (2019) 40, 2671–2683

# Conclusions

Vasopressors and inotropes are usually the first-line therapy **at the lowest dose and short times interval to avoid end-organ hazard**

**Quick multistep approach**

**Rigid time-dependent protocol**

**Shock Team** (Cardiac Shock Care Centers)

# *Thanks!*