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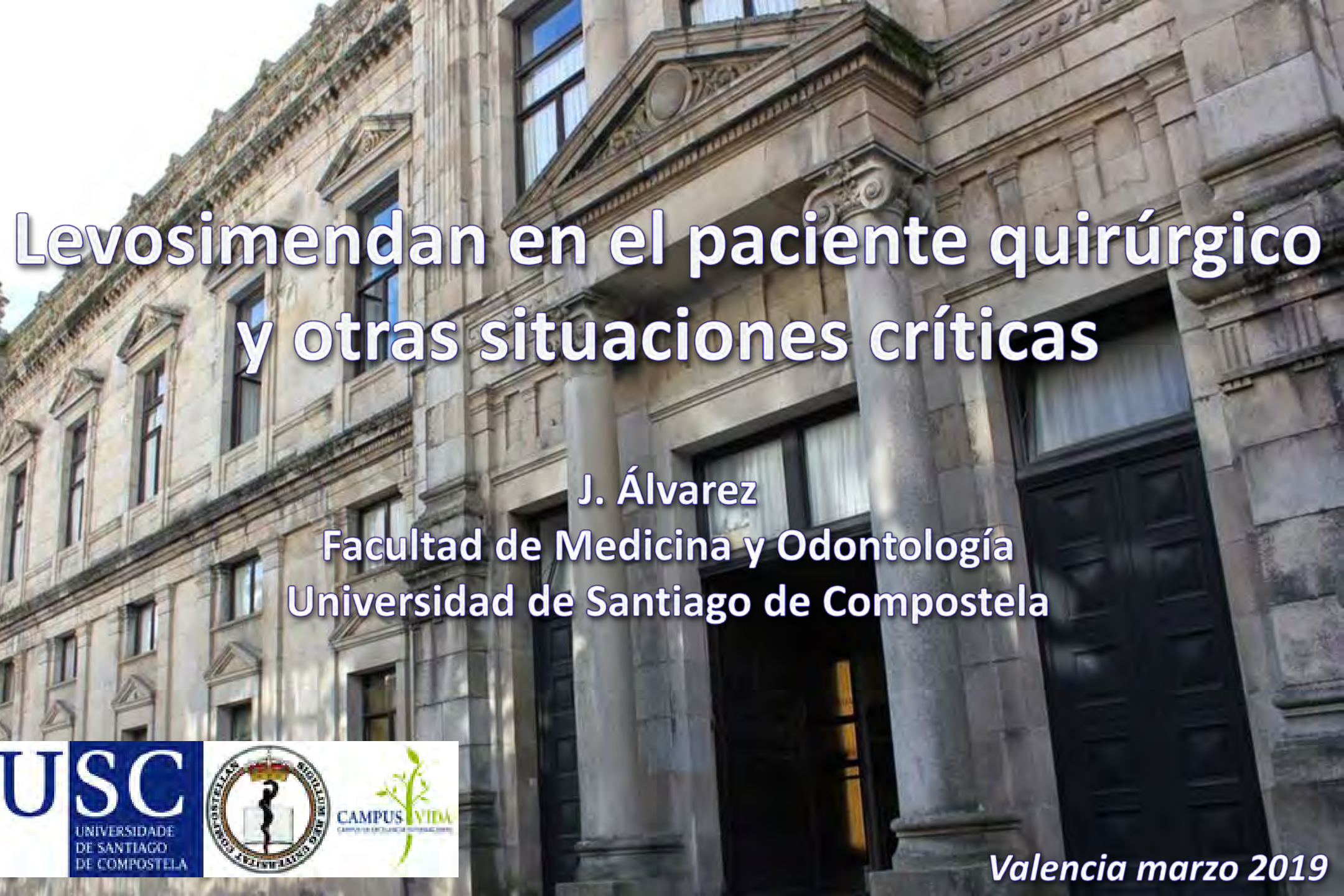
Levosimendan en el paciente quirúrgico y otras situaciones críticas

Julian Álvarez

Facultad de Medicina y Odontología

Universidad de Santiago de Compostela

SARTD-CHGUV Sesión de Formación Continuada
Valencia 25 de Marzo de 2019



Levosimendan en el paciente quirúrgico y otras situaciones críticas

J. Álvarez
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Valencia marzo 2019

Coflicto de intereses

ORION PHARMA	1,2	Baxter	2
GRÜNENTHAL	1	Edwards	1
cardiva 2	1	ferrer	1
CSL Behring	1	Medtronic	1
MENARINI group	2	almirall	2

1. Becas de investigación clínica o experimental
2. Pago por asesoramiento o por conferencias

International Journal of CARDIOLOGY

ELSEVIER

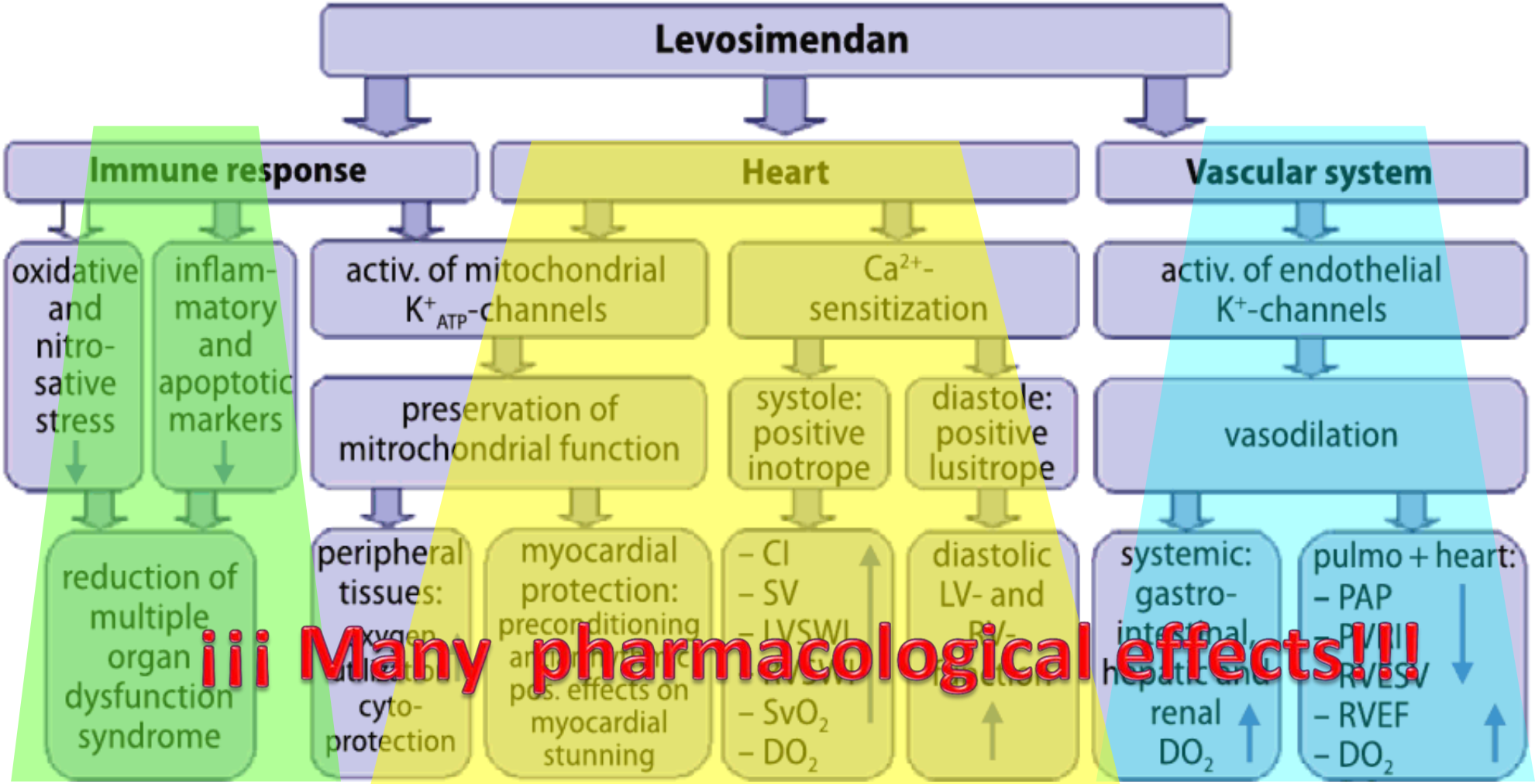
Levosimendan beyond inotropy and acute heart failure: Evidence of pleiotropic effects on the heart and other organs: An expert panel position paper

Dimitrios Farmakis [a], Julian Alvarez [b], Tuvia Ben Gal [c], Dulce Brito [d], Francesco Fedele [e], Candida Fonseca [f], Anthony C. Gordon [g], Israel Gotsman [h], Elena Grossini [i], Fabio Guarracino [j], Veli-Pekka Harjola [k], Yaron Hellman [l], Leo Heunks [m], Visnja Ivancan [n], Apostolos Karavidas [o], Matti Kivikko [p], Vladimir Lomivorotov [q], Dan Longrois [r], Josep Masip [s], Marco Metra [t], Andrea Morelli [u], Maria Nikolaou [v], Zoltán Papp [w], Alexander Parkhomenko [x], Gerhard Poelzl [y], Piero Pollesello [p], Hanne Berg Ravn [z], Steffen Rex [aa], Hynek Riha [ab], Sven-Erik Ricksten [ac], Robert H.G. Schwinger [ad], Bojan Vrtovec [ae], M. Birhan Yilmaz [af], Marzenna Zielinska [ag], John Parissis [a]

[a] Heart Failure Unit, Department of Cardiology, National and Kapodistrian University of Athens, Athens University Hospital Attikon, Athens, Greece

[b] Department of Anesthesia and Surgical ICU, University of Santiago de Compostela, Santiago de Compostela, Spain

Volume 222, 1 November 2016, Pages 303-312



Rehberg S et al. Rolle von Levosimendan in der intensivmedizinischen Behandlung des myokardialen Pumpversagens. Anaesthesist. 2007; 56: 30-43.

ORIGINAL ARTICLE

Rev Esp Cardiol. 2006;59(4):338-45

Hemodynamic Effects of Levosimendan Compared With Dobutamine in Patients With Low Cardiac Output After Cardiac Surgery

Julián Álvarez,[a] Mercedes Bouzada,[a] Ángel L. Fernández,[b] Valentín Caruezo,[a] Manuel Taboada,[a] Jaime Rodríguez,[a] Vicente Ginesta,[a] José Rubio,[b] José B. García-Bengoechea,[b,c] and José R. González-Juanatey[c]

REVISTA ESPAÑOLA DE CARDIOLOGIA

EDITORIAL

Levosimendan in Acute Heart Failure: Past, Present, and Future

Rev Esp Cardiol. 2006;59(4):309-12

Juan F. Delgado

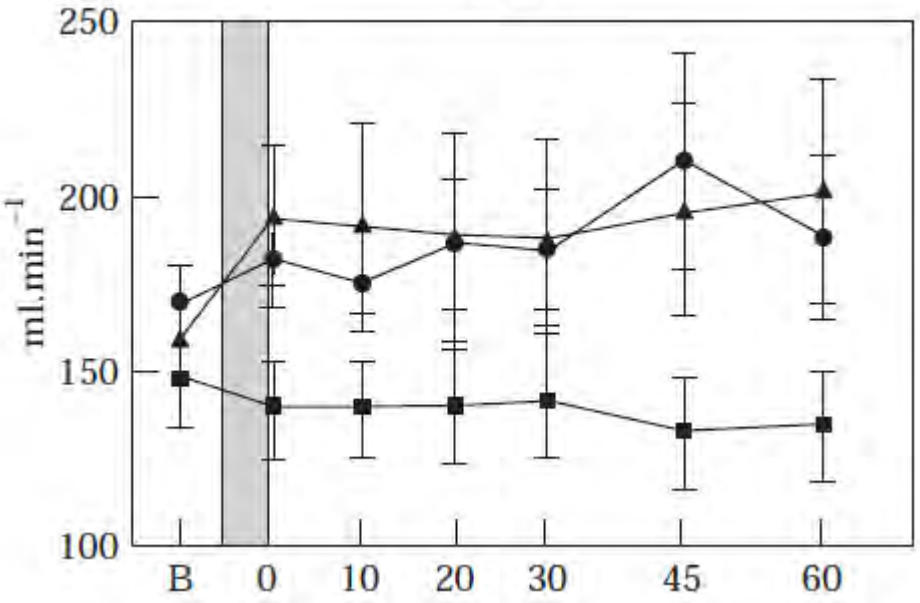
Along these lines, Álvarez et al[13] report a modest but novel and elegant contribution to the clinical development of levosimendan in a specific indication—low cardiac output syndrome after extracorporeal circulation.

European Heart Journal (1998) **19**, 660–668

Effects of a new calcium sensitizer, levosimendan, on haemodynamics, coronary blood flow and myocardial substrate utilization early after coronary artery bypass grafting

J. Lilleberg*, M. S. Nieminen*, J. Akkila†, L. Heikkilä‡, A. Kuitunen§, L. Lehtonen†, K. Verkkala‡, S. Mattila‡ and M. Salmenperä§

Aims The aim of the study was to evaluate the effects



lar resistance decreased significantly after both doses. Coronary sinus blood flow increased by 28 and 42 ml/(P=0·054 for the combined effect) after the lower and higher dose, respectively. Myocardial oxygen consumption or substrate extractions did not change statistically significantly.

Conclusion Despite improved cardiac performance, levosimendan did not increase myocardial oxygen consumption or change myocardial substrate utilization. Thus levosimendan has the potential to treat low cardiac output states after cardiopulmonary bypass surgery.
(Eur Heart J 1998; 19: 660–668)

Key Words: Coronary haemodynamics, cardiac surgery, calcium sensitizers, cardiac metabolism, levosimendan.

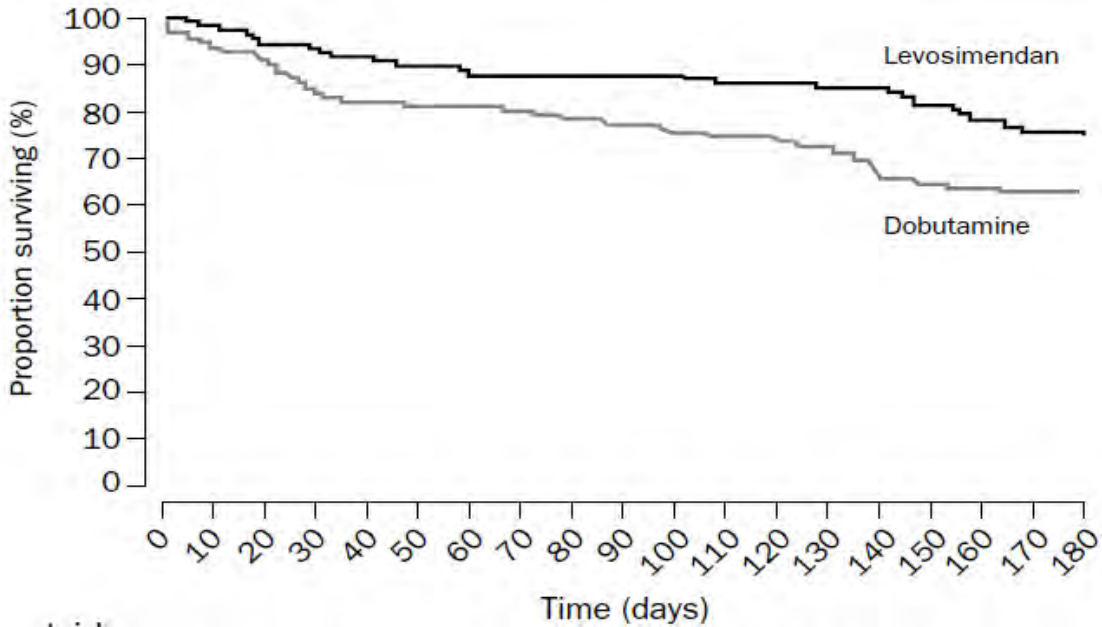
THE LANCET

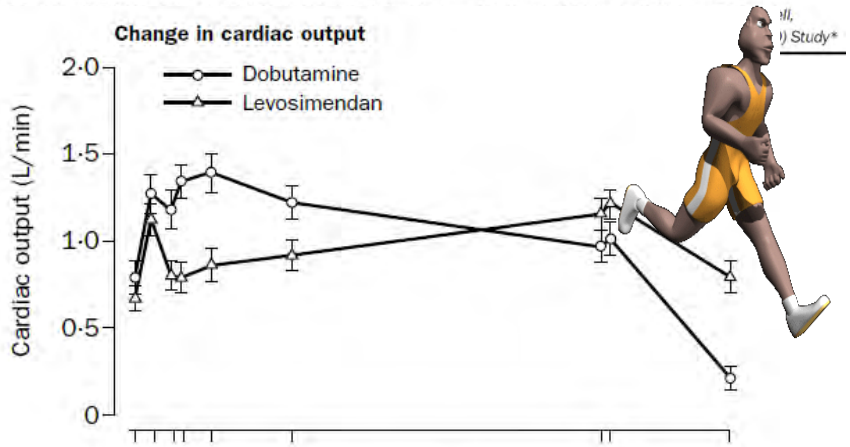
Lancet 2002; **360:** 196–202

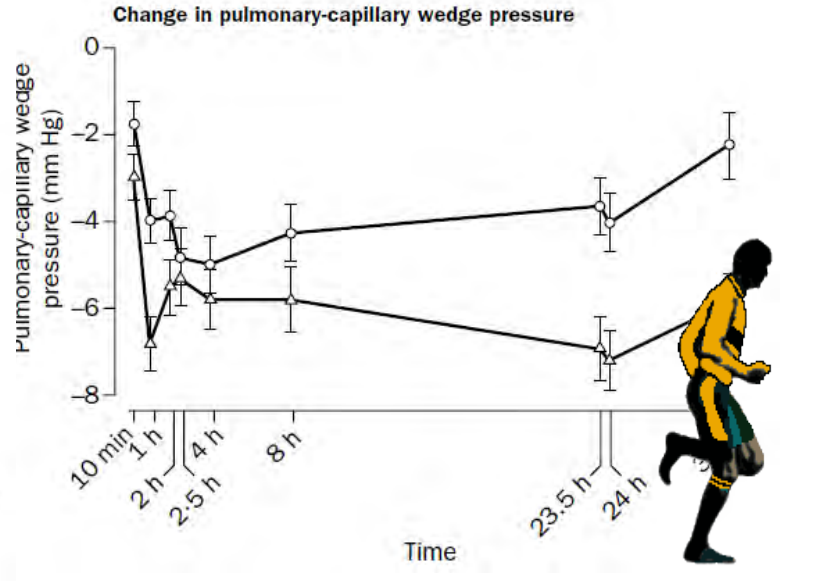
ARTICLES

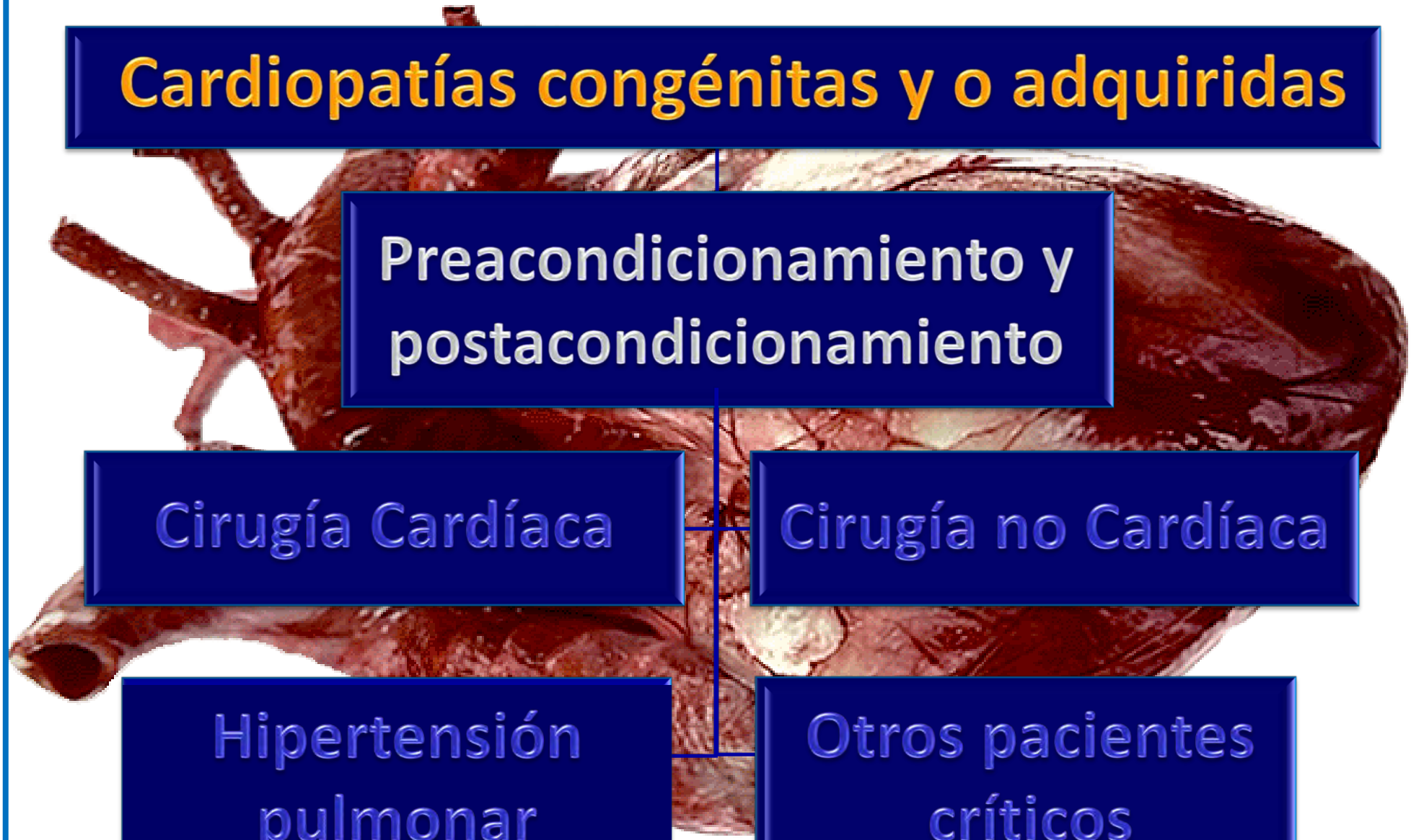
Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial

	Dobutamine (n=100)	Levosimendan (n=103)
Demography		
Mean (SD) age, years	60 (11)	58 (11)
M/F	85/15	91/12
Cause of heart failure		
Ischaemic	50 (50%)	46 (45%)
Other	50 (50%)	57 (55%)
Clinical presentation		
Deterioration of chronic heart failure*	92 (92%)	86 (84%)
Acute heart failure	0	7 (7%)
Postoperative exacerbation	2 (2%)	4 (4%)
Awaiting heart transplant*	15 (15%)	19 (18%)








Cardiopatías congénitas y o adquiridas
Preacondicionamiento y postacondicionamiento
Cirugía Cardíaca
Cirugía no Cardíaca
Hipertensión pulmonar
Otros pacientes críticos

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association. Learn and Live.

Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium

CHARLES E. MURRY, B.S., ROBERT B. JENNINGS, M.D., AND KEITH A. REIMER, M.D., PH.D.

The preconditioning, is a biological response, wherein cell protective mechanisms are activated (antisquemia, antiarrhythmic, on stunned, antiapoptosis...) after an initial controlled injury .

followed, and animals (n = 9) then received a sustained 3 hr occlusion. Control animals (n = 7) received a single 3 hr occlusion. Animals were allowed 4 days of reperfusion thereafter. Histologic infarct size then was measured and was related to the major baseline predictors of infarct size, including the anatomic area at risk and collateral blood flow. In the 40 min study, preconditioning with ischemia

The preconditioning saves cells… and cell function

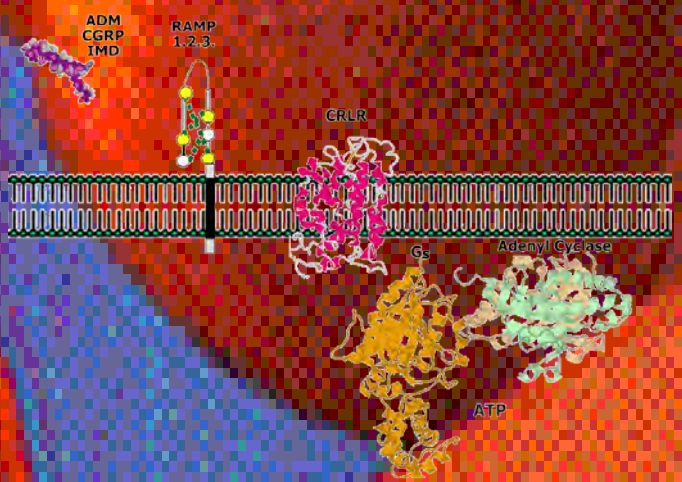
that often precede myocardial infarction in man may delay cell death after coronary occlusion, and thereby allow for greater salvage of myocardium through reperfusion therapy.

Circulation 74, No. 5, 1124–1136, 1986.

Preconditioning

Ischemic

Pharmacological



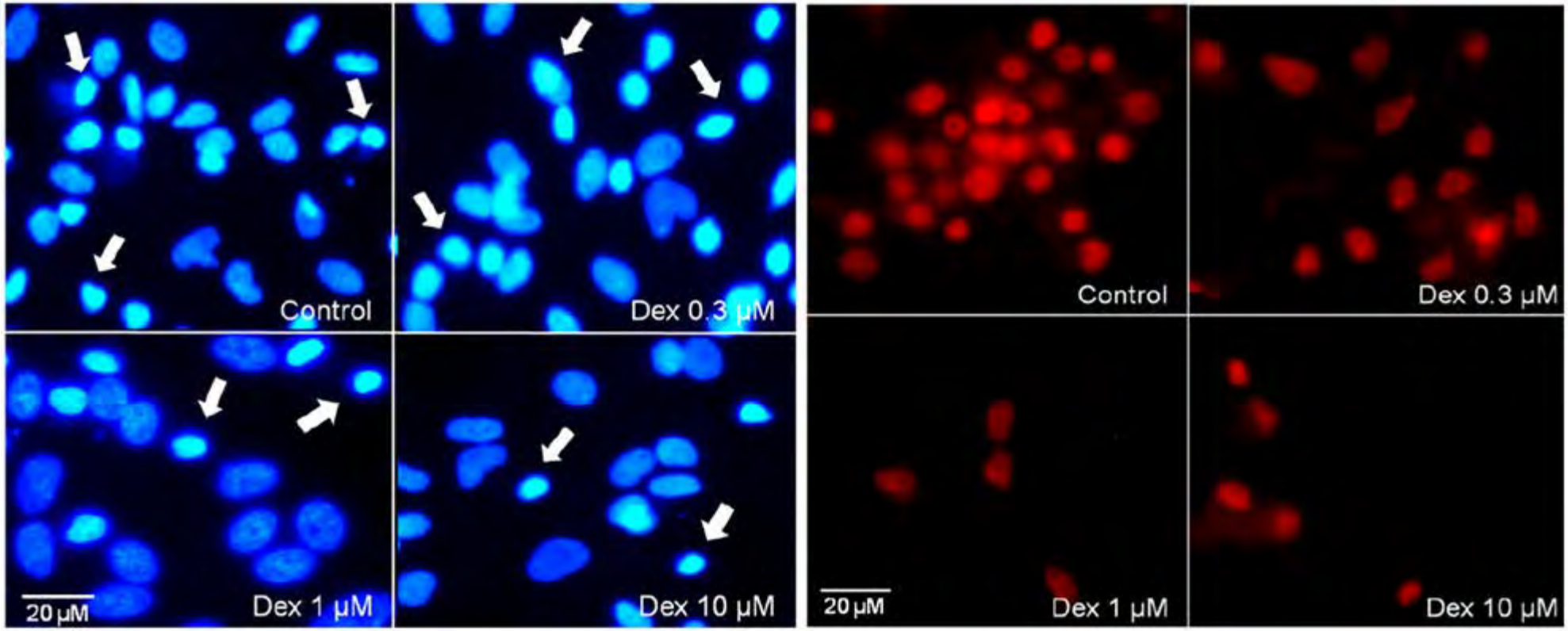
Levosimendan
Sevofluorane….

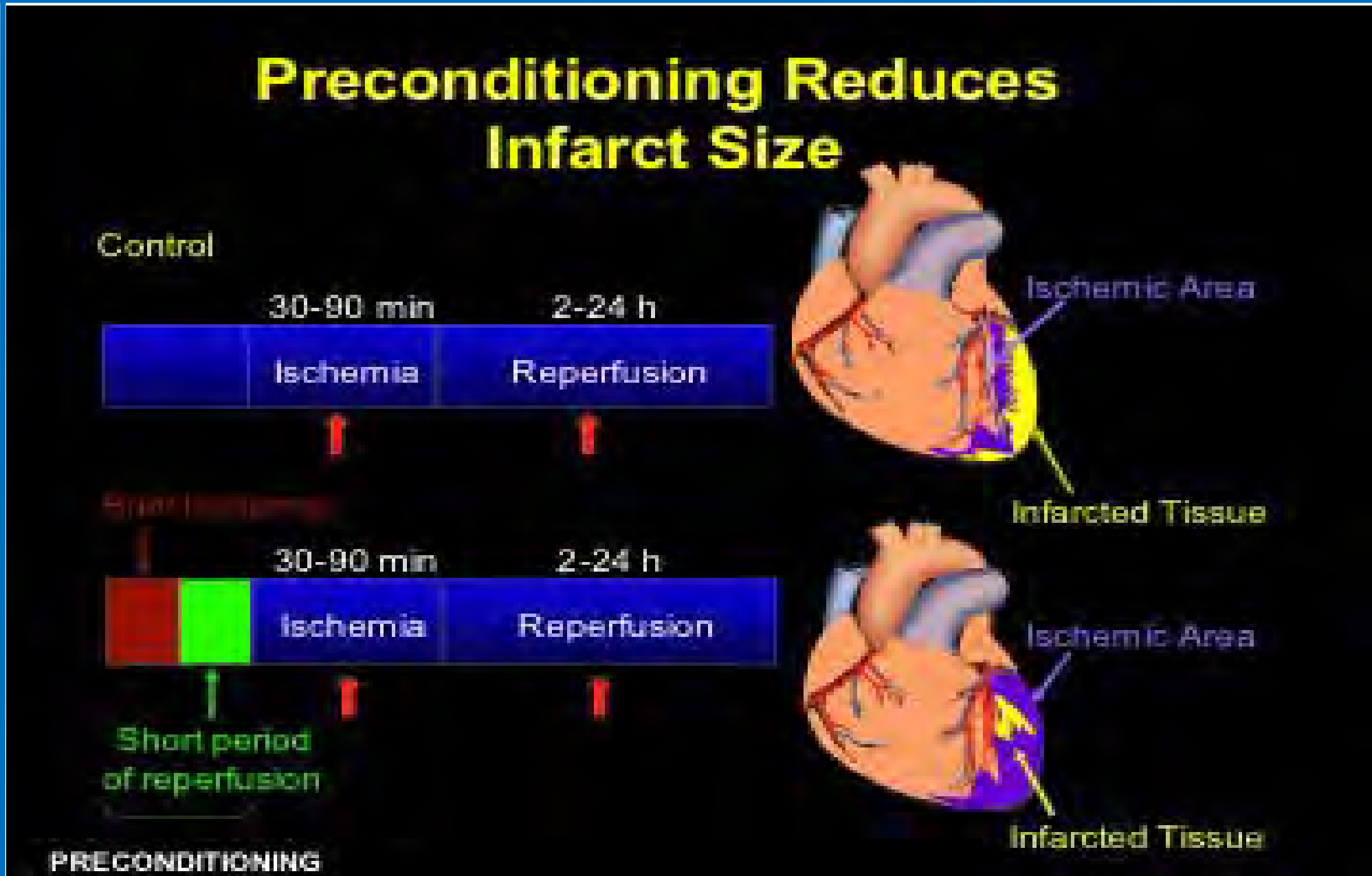
Contents lists available at ScienceDirect

Life Sciences 144 (2016) 162–169

journal homepage: www.elsevier.com/locate/lifescie

Neuroprotective effects of dexmedetomidine conditioning strategies: Evidences from an in vitro model of cerebral ischemia



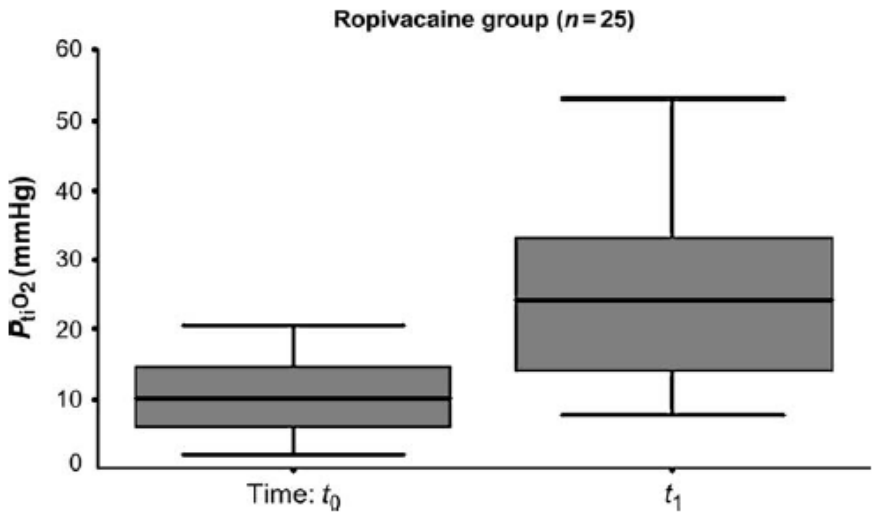

Preconditioning Reduces Infarct Size
Control
30-90 min
2-24 h
Ischemia
Reperfusion
Ischemic Area
Infarcted Tissue
30-90 min
2-24 h
Ischemia
Reperfusion
Short period of reperfusion
Ischemic Area
Infarcted Tissue
PRECONDITIONING

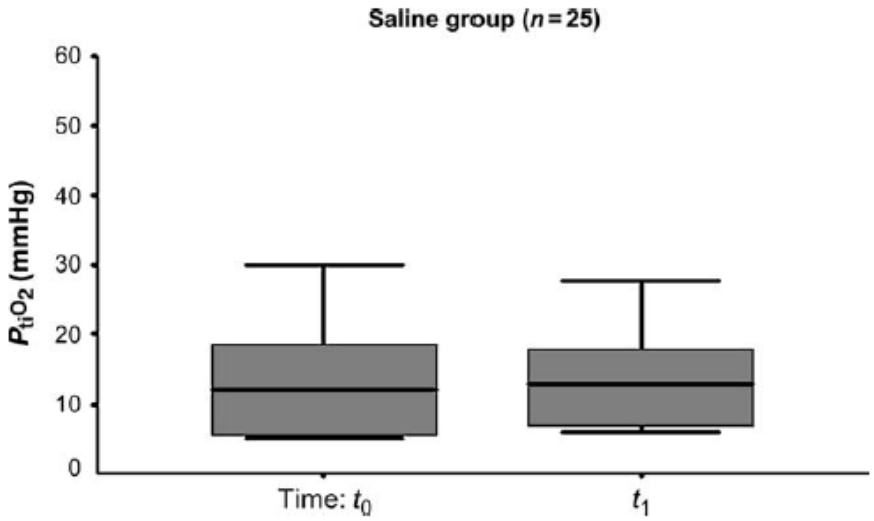
*Acta Anaesthesiol Scand 2006; **50**: 780–786*
Printed in Singapore. All rights reserved

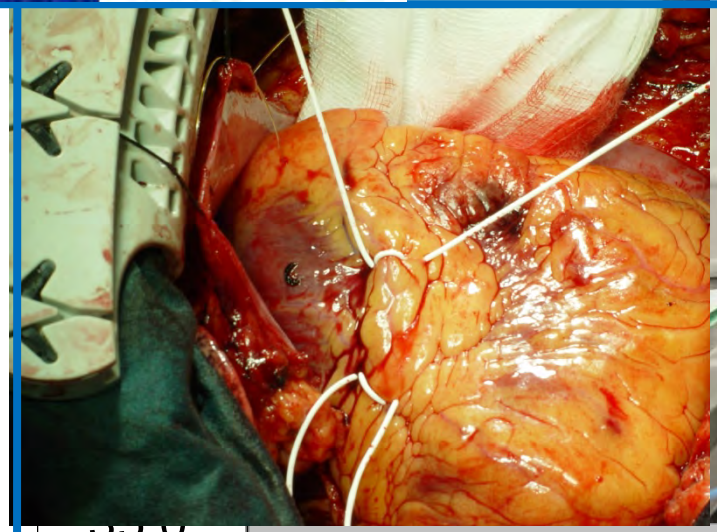
Acta Anaesthesiologica Scandinavica
AN INTERNATIONAL JOURNAL OF ANAESTHESIOLOGY AND INTENSIVE CARE, PAIN AND EMERGENCY MEDICINE

High thoracic epidural blockade increases myocardial oxygen availability in coronary surgery patients

J. LAGUNILLA[1], J. B. GARCÍA-BENGOCHEA[2], Á. L. FERNÁNDEZ[2], J. ALVAREZ[1], J. RUBIO[2], J. RODRÍGUEZ[1] and S. VEIRAS[1]
[1]*Department of Anesthesiology and Postoperative Intensive Care Unit and* [2]*Department of Cardiac Surgery, Hospital Clínico Universitario, University of Santiago de Compostela School of Medicine, Santiago de Compostela, Spain*





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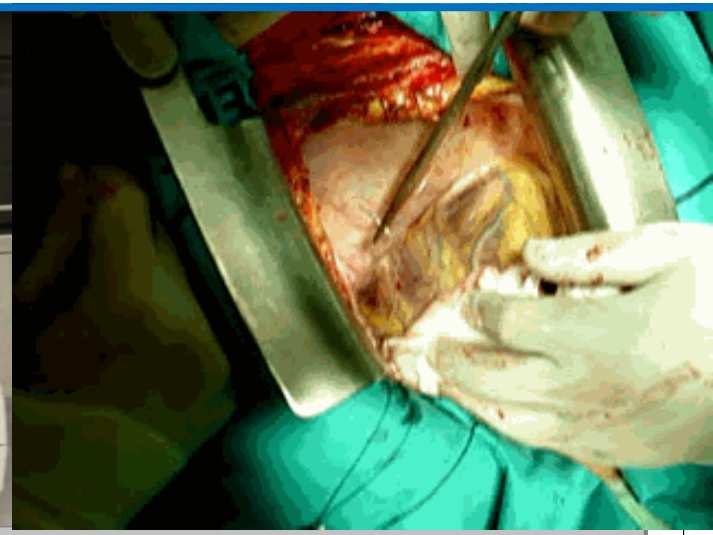
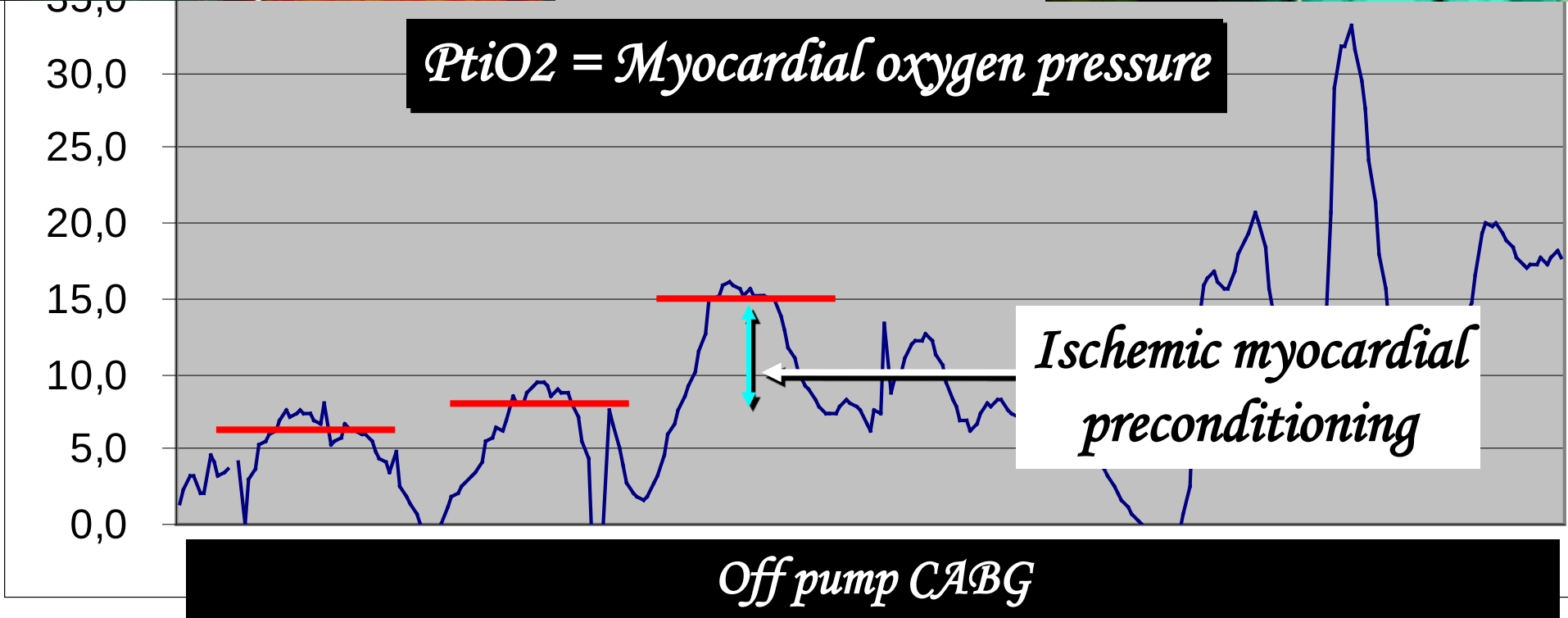
Probe card



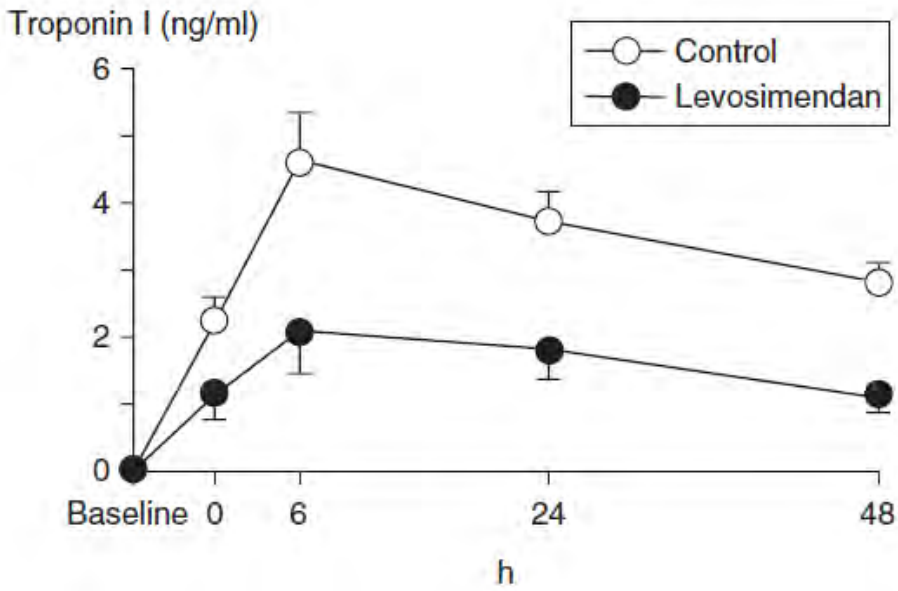

PtiO2 = Myocardial oxygen pressure
30,0
25,0
20,0
15,0
10,0
5,0
0,0
Ischemic myocardial preconditioning
Off pump CABG

British Journal of Anaesthesia 102 (2): 198–204 (2009)
doi:10.1093/bja/aen367

BJA

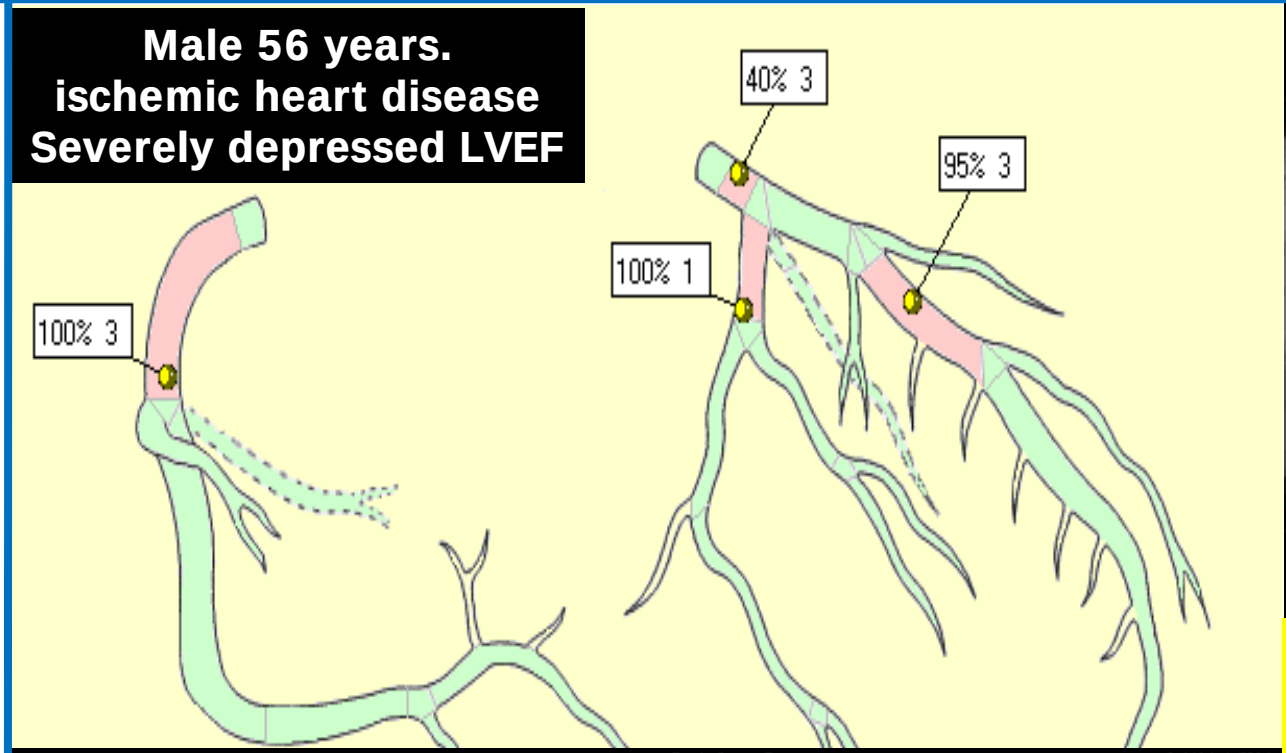
Levosimendan pre-treatment improves outcomes in patients undergoing coronary artery bypass graft surgery†

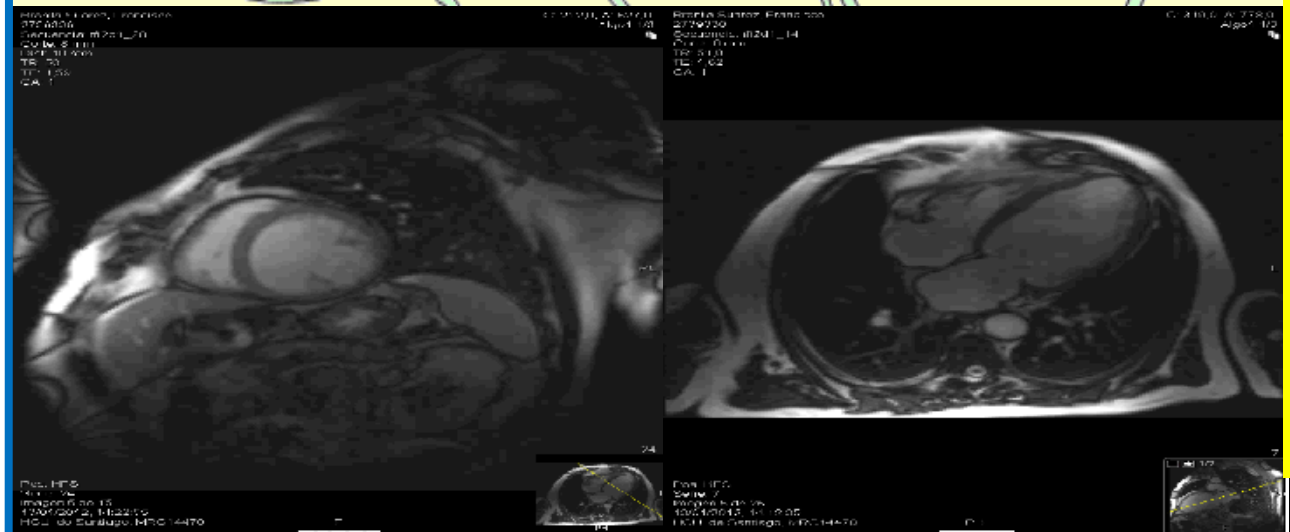
L. Tritapepe[1‡], V. De Santis[1*], D. Vitale[1], F. Guarracino[2‡], F. Pellegrini[3], P. Pietropaoli[1] and M. Singer[4‡]



Variable	Control	Treatment	*P*-value
n	50	52	
Thirty-day mortality	0	0	NS
MI, *n*	1	0	0.5
Atrial fibrillation, *n* (%)	10 (20.0)	12 (23.1)	0.7
Time on ventilator, h	13.6 (4.5)	11.3 (2.5)	0.02
Received inotropes, *n* (%)	17 (34.0)	9 (17.3)	0.053
Received inotropes >12 h, *n* (%)	9 (18.0)	2 (3.8)	0.02
Postoperative serum creatinine >130 μmol litre^{-1}, *n* (%)	4 (8)	2 (3.8)	0.4
ICU stay, h	32.7 (12.9)	24.8 (7.1)	0.002
Hospital stay, days	12.0 (2.5)	11.1 (2.3)	0.09
Re-admission to ICU, *n* (%)	1 (2.0)	0	0.5
Re-exploration for bleeding, *n* (%)	1 (2.0)	1 (1.9)	0.9

Male 56 years.
ischemic heart disease
Severely depressed LVEF

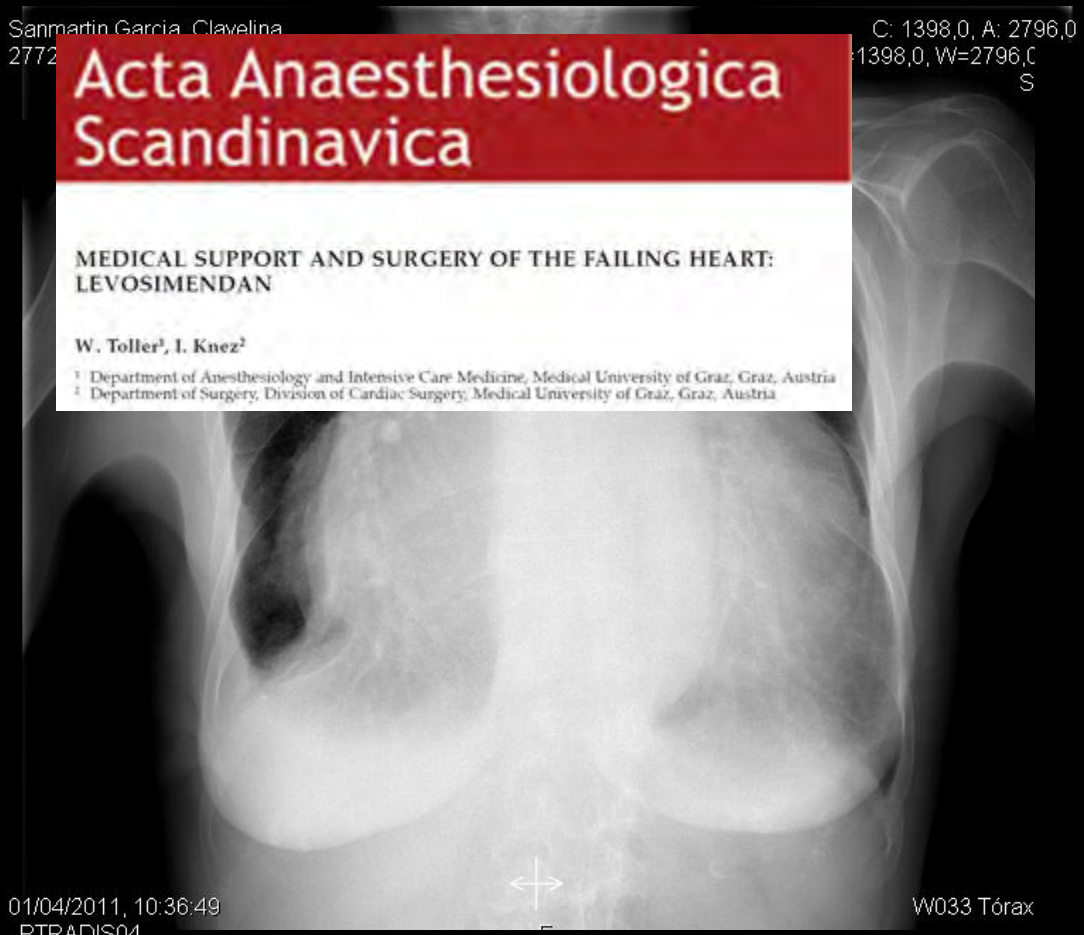




Transferred to Surgical ICU 12 hours before surgery. Administration of levosimendan 0.2 ug/kg / min.

During and after surgery levosimendan and DBT. No IABP

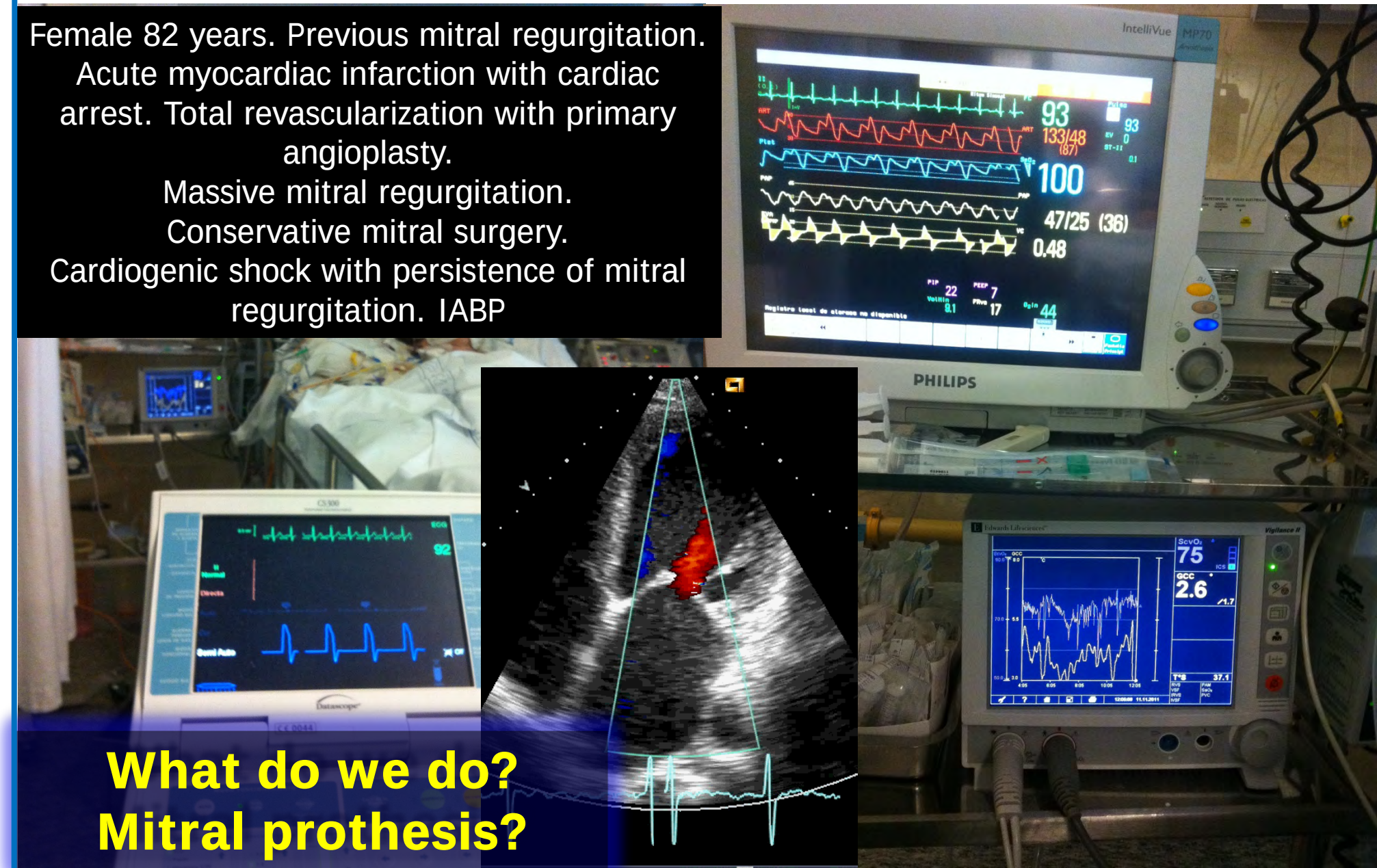
Women 79 years. Stenosis and mitral regurgitation, *aortic regurgitation*, tricuspid regurgitation. Normal coronary



Preconditioning

She was admitted to Surgical ICU 12 hours before surgery. Levosimendan 0,1µg/kg/min was started. During surgery and postoperative levosimendan was not discontinued and we use Dobutamine + Norepinefrine.

Female 82 years. Previous mitral regurgitation. Acute myocardiac infarction with cardiac arrest. Total revascularization with primary angioplasty.
Massive mitral regurgitation.
Conservative mitral surgery.
Cardiogenic shock with persistence of mitral regurgitation. IABP



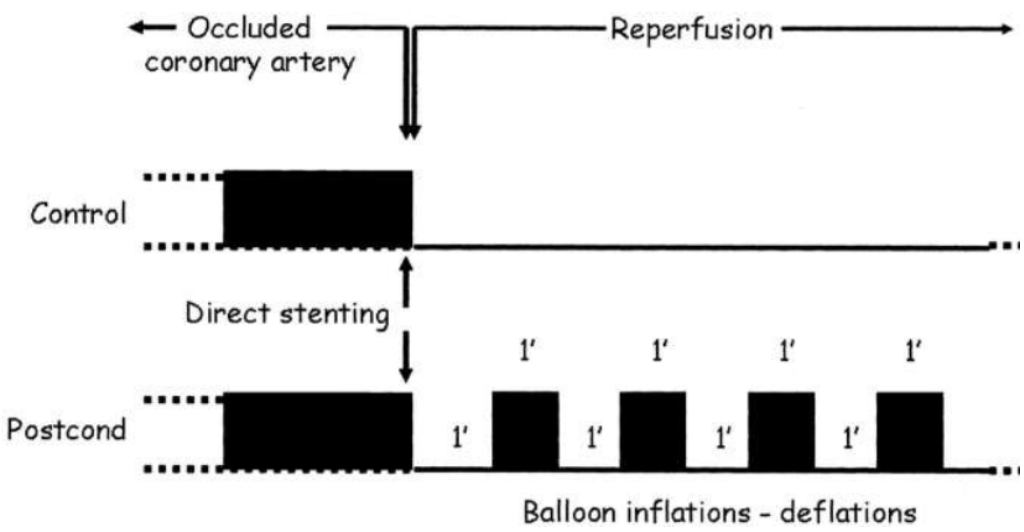
What do we do?
Mitral prothesis?

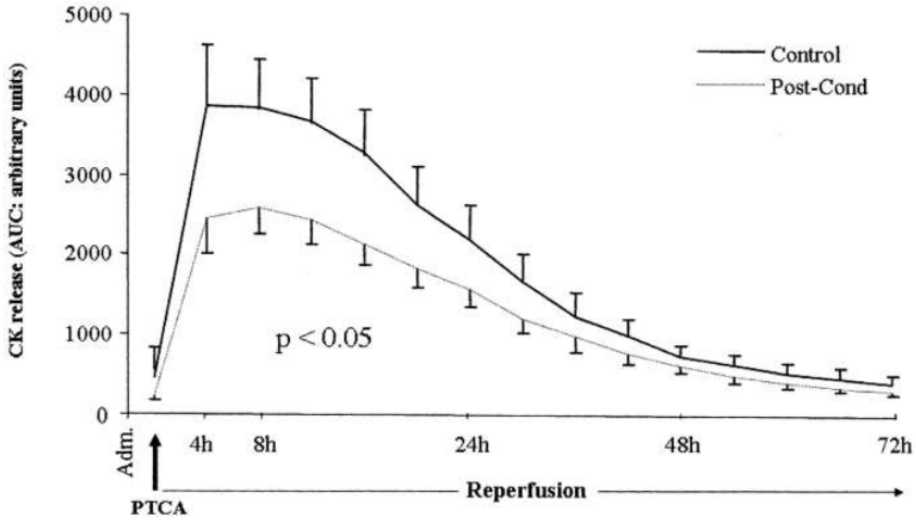

Levosimendan 0,1- 0,2 µg/kg/min (NO bolus)
¿Postconditioning....?
That is?
Monday
Friday
IABP removal 72 hours after levosimendan administration

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association®
Learn and Live℠
Circulation. 2005;112:2143-2148.

Postconditioning the Human Heart

Patrick Staat, MD; Gilles Rioufol, MD, PhD; Christophe Piot, MD, PhD; Yves Cottin, MD, PhD; Thien Tri Cung, MD; Isabelle L'Huillier, MD; Jean-François Aupetit, MD, PhD; Eric Bonnefoy, MD, PhD; Gérard Finet, MD, PhD; Xavier André-Fouët, MD; Michel Ovize, MD, PhD





Rodríguez-González et al. Journal of Translational Medicine 2013, 11:87
http://www.translational-medicine.com/content/11/1/87

JOURNAL OF TRANSLATIONAL MEDICINE

RESEARCH Open Access

Effects of sevoflurane postconditioning on cell death, inflammation and TLR expression in human endothelial cells exposed to LPS

Raquel Rodríguez-González[1,2,3], Aurora Baluja[1], Sonia Veiras Del Río[1], Alfonso Rodríguez[1], Jaime Rodríguez[1], Manuel Taboada[1], David Brea[4,5] and Julián Álvarez[1*]

Abstract

Background: Sevoflurane is an anesthetic agent which also participates in protective mechanisms in sepsis, likely due to anti-inflammatory properties. A key tissue in sepsis is the endothelium, which expresses TLR2 and TLR4 receptors, known regulators of inflammatory mechanisms and potential therapeutic targets for this pathology. In this context, we explored the effect of sevoflurane postconditioning in an *in vitro* sepsis model.

Methods: Primary cultures of human umbilical vein endothelial cells were used for two different experiments. In the first set, cultures were placed in an airtight incubation chamber and exposed to different concentrations of sevoflurane (0,1,3 or 7% vol,) for 1 hour. In the second set, lipopolysaccharide from *Escherichia coli* 0111:B4 (1 μg/mL) was added to culture medium for 3 hours and cells were subsequently exposed to sevoflurane (0,1,3 or 7% vol,) for 1 hour as explained before. In both cases, cell viability was measured by MTT and Trypan blue assays, TLR2 and TLR4 expression were analyzed by flow cytometry, and TNFα and IL-6 levels were quantified in cell culture media by an immunoassay immediately after exposure, at 6 and 24 hours.

Results: Exposure to 3% sevoflurane decreased TLR2 at 24 hours and TLR4 at 6 and 24 hours (both $p<0.05$), whereas exposure to 7% decreased TLR4 expression at 6 hours ($p<0.05$). Both 3 and 7% sevoflurane decreased TNF-α and IL-6 levels at 24 hours (both $p<0.05$). In LPS-stimulated cultures, exposure to 3% sevoflurane was cytoprotective at 6 and 24 hours ($p<0.05$) compared with control, and decreased TLR2 and TLR4 expression at 24 hours ($p<0.05$); whereas 7% decreased TLR4 expression at 24 hours ($p<0.05$). Both 3% and 7% sevoflurane decreased TNF-α and IL-6 levels at 24 hours (both $p<0.05$).

Conclusions: Postconditioning with the halogenated anesthetic agent sevoflurane after LPS stimulation shows a cytoprotective effect in an *in vitro* model, decreasing cell death and reducing TLR2 and TLR4 expression as well as levels of the inflammatory mediators TNF-α and IL-6 in human endothelial cells.

Keywords: Sevoflurane, Endothelium, Inflammation, TLR, Sepsis, Postconditioning

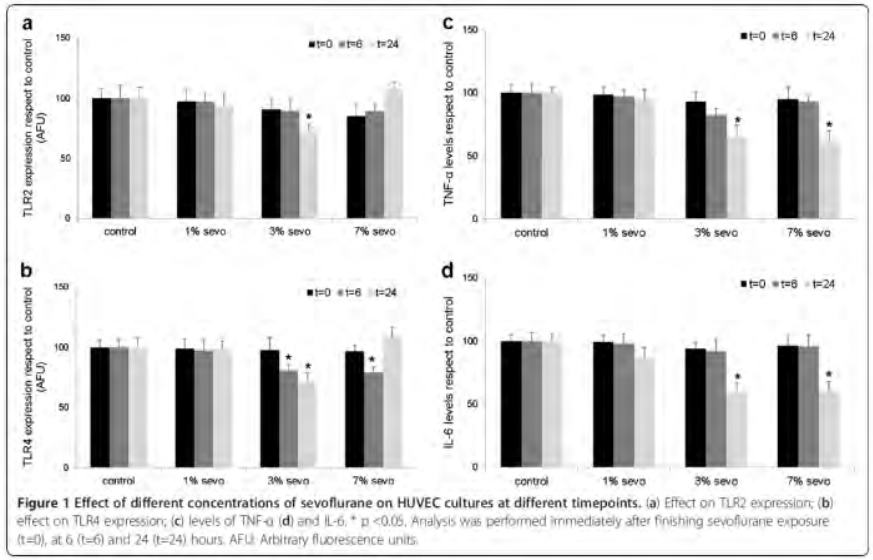


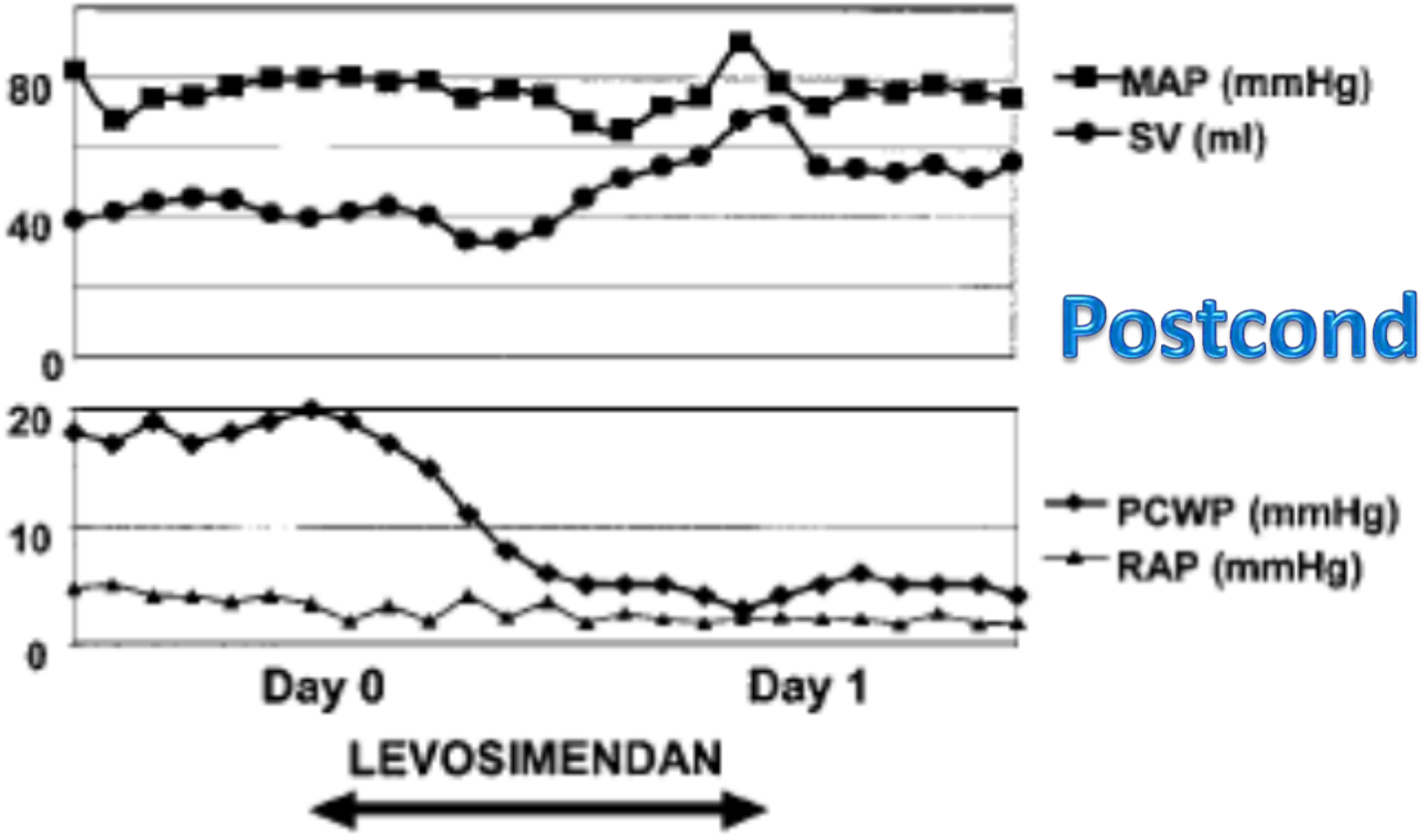
Figure 1 Effect of different concentrations of sevoflurane on HUVEC cultures at different timepoints. (**a**) Effect on TLR2 expression; (**b**) effect on TLR4 expression; (**c**) levels of TNF-α (**d**) and IL-6. * $p<0.05$. Analysis was performed immediately after finishing sevoflurane exposure (t=0), at 6 (t=6) and 24 (t=24) hours. AFU: Arbitrary fluorescence units.

Conclusions: Postconditioning with the halogenated anesthetic agent sevoflurane after LPS stimulation shows a cytoprotective effect in an *in vitro* model, decreasing cell death and reducing TLR2 and TLR4 expression as well as levels of the inflammatory mediators TNF-α and IL-6 in human endothelial cells.

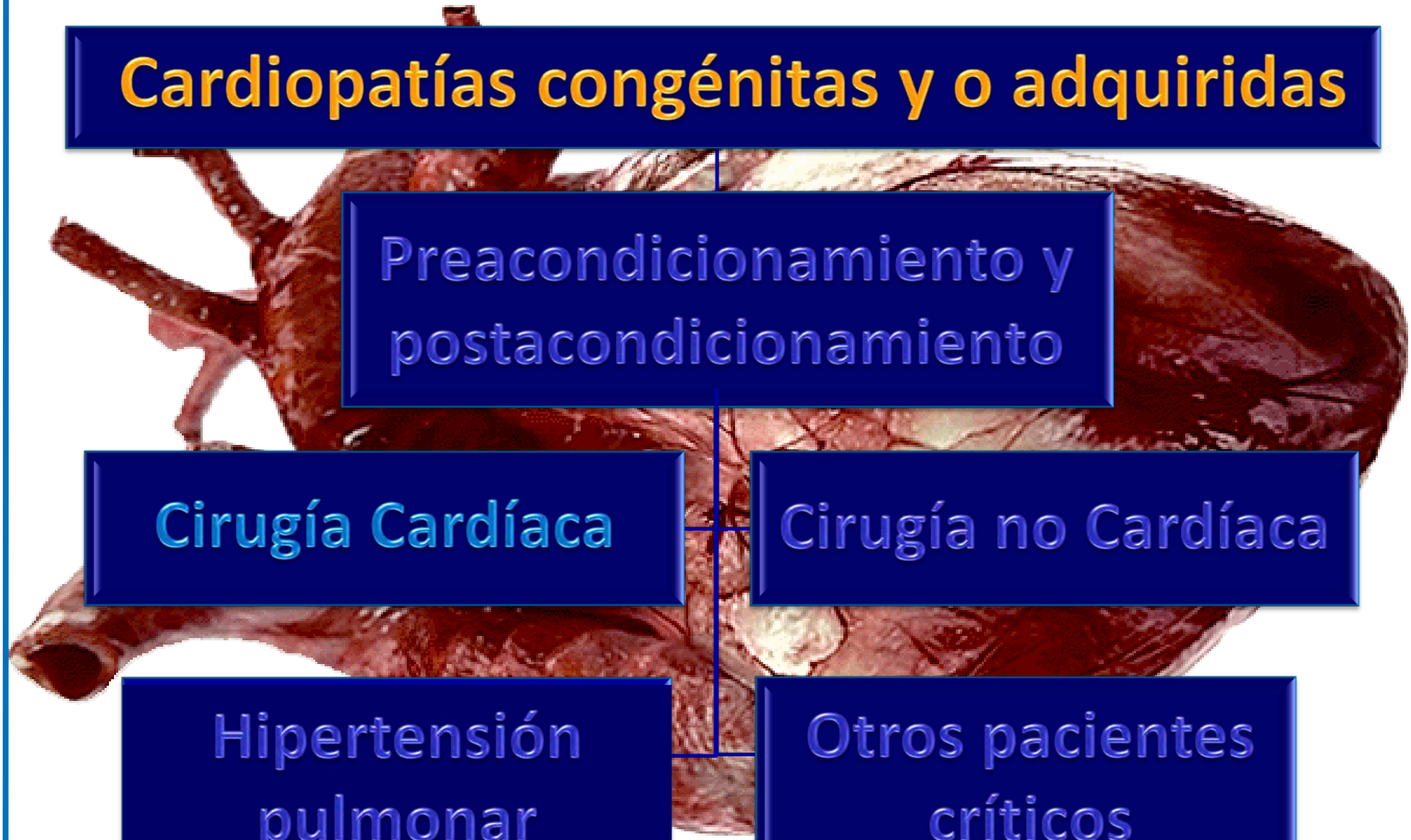
Successful Use of Levosimendan in a Patient with Peripartum Cardiomyopathy

Sidney Benlolo, MD, Cécile Lefoll, MD, Vahan Katchatouryan, MD, Didier Payen, MD, PhD, and Alexandre Mebazaa, MD, PhD

Anesth Analg 2004;98:822–4



Postconditioning?


Cardiopatías congénitas y o adquiridas
Preacondicionamiento y postacondicionamiento
Cirugía Cardíaca
Cirugía no Cardíaca
Hipertensión pulmonar
Otros pacientes críticos

Levosimendan and cardiac surgery… friend or foe

USC
UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

CAMPUS VIDA

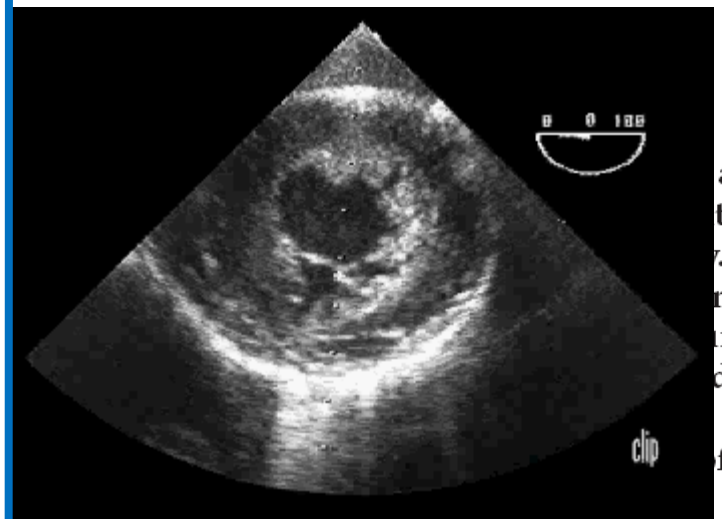
Case Report

Heart
Lung and Circulation

Pre-operative Use of Levosimendan in Two Patients with Severe Aortic Stenosis and Left Ventricular Dysfunction

David L. Prior, MBBS, BMedSc, PhD, FRACP, DDU [a,*], Brendan D. Flaim, MBBS [a], Andrew I. MacIsaac, MBBS, MD, FRACP [a] and Michael Y. Yii, MS, FRACS [b]

[a] *Cardiac Investigation Unit, St Vincent's Hospital, Melbourne, P.O. Box 2900, Fitzroy, Vic. 3065, Australia*
[b] *Department of Cardiothoracic Surgery, St Vincent's Hospital, Melbourne, P.O. Box 2900, Fitzroy, Vic. 3065, Australia*



Available online 10 May 2005

aortic stenosis, coronary artery disease, severe left ventricular dysfunction and
tising agent, levosimendan was administered prior to aortic valve replacement
. In both cases, drug infusion was well tolerated at the doses used, heart failure
nd peri-operative management was relatively uncomplicated in cases that would
rther investigation of the use of levosimendan both for treating heart failure in
d as pre-operative therapy is warranted.

(Heart Lung and Circulation 2006;15:56–58)

British Journal of Anaesthesia **106** (3): 298–304 (2011)
Advance Access publication 21 January 2011 · doi:10.1093/bja/aeq402

CARDIOVASCULAR

Preoperative levosimendan infusion in combined aortic valve and coronary bypass surgery

H. Leppikangas[1*], K. Järvelä[2], T. Sisto[2], P. Maaranen[2], M. Virtanen[2], P. Lehto[2], S. Karlsson[3], T. Kööbi[4] and L. Lindgren[1]

Results. The cardiac index (CI) and stroke volume index (SI) were higher in the levosimendan group (LG) for the 4 day postoperative period ($P<0.05$); on the fourth postoperative day, the CI was 3.0 litre m^{-2} min^{-1} in the LG compared with 2.4 litre m^{-2} min^{-1} in the control group (CG) and the SI was 30 *vs* 25 ml m^{-2}, respectively. The LVEF measured at baseline and on the fourth postoperative morning decreased in the CG, but was maintained in the LG.

Conclusions. Levosimendan improved haemodynamics compared with a placebo in patients undergoing high-risk cardiac surgery. The concentrations of levosimendan's metabolites were higher compared with earlier studies using perioperative dosing.

Safe and effective

EDITORIALS

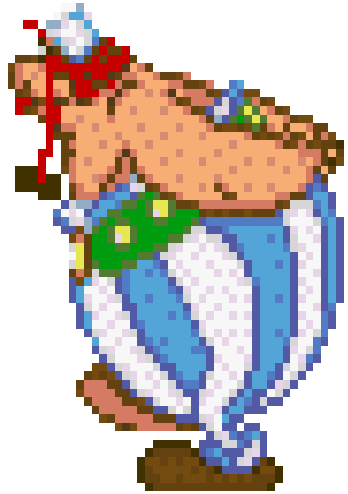
Levosimendan and Low Cardiac Output Syndrome. Does Mortality Really Decrease?

Julián Álvarez

Servicio de Anestesiología y Reanimación, Hospital Clínico Universitario, Santiago de Compostela, A Coruña, Spain

REVISTA ESPAÑOLA DE CARDIOLOGIA

Rev Esp Cardiol. 2008;61(5):454-7



Reducing Mortality in Cardiac Surgery With Levosimendan: A Meta-analysis of Randomized Controlled Trials

Giovanni Landoni, MD,* Anna Mizzi, MD,* Giuseppe Biondi-Zoccai, MD,† Gi
Elena Bignami, MD,* Laura Corno, MD,* Massimo Zambon, MD,* Chiara
Alberto Zangrillo, MD*

Journal of Cardiothoracic and Vascular Anesthesia

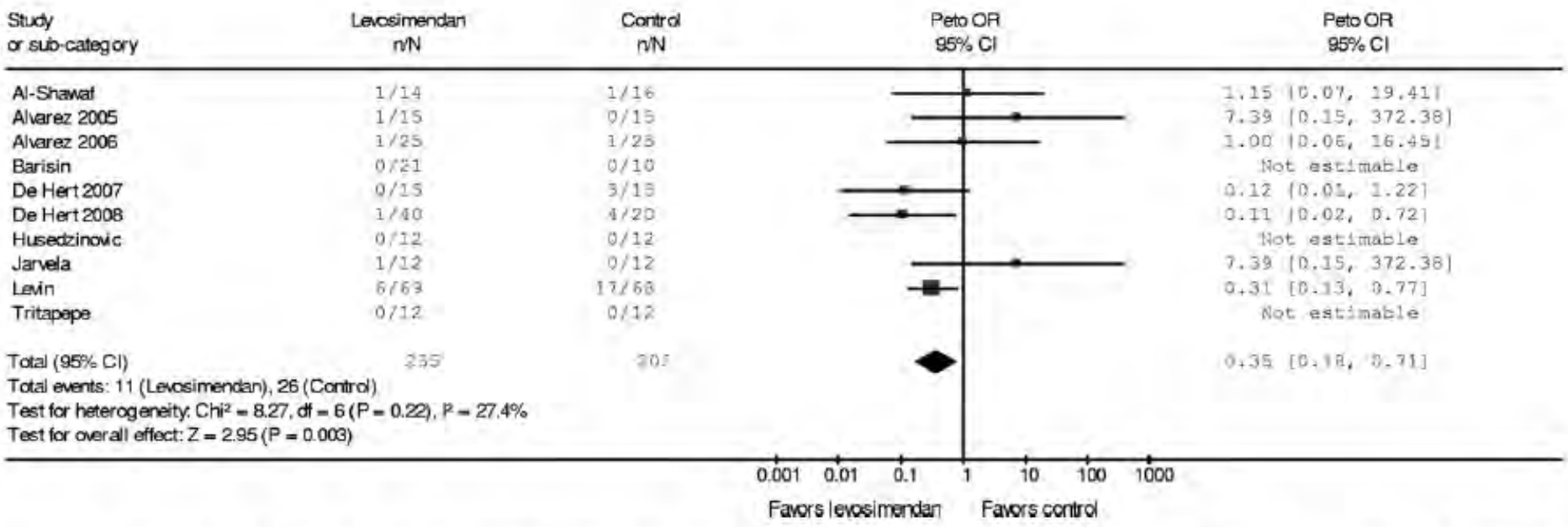


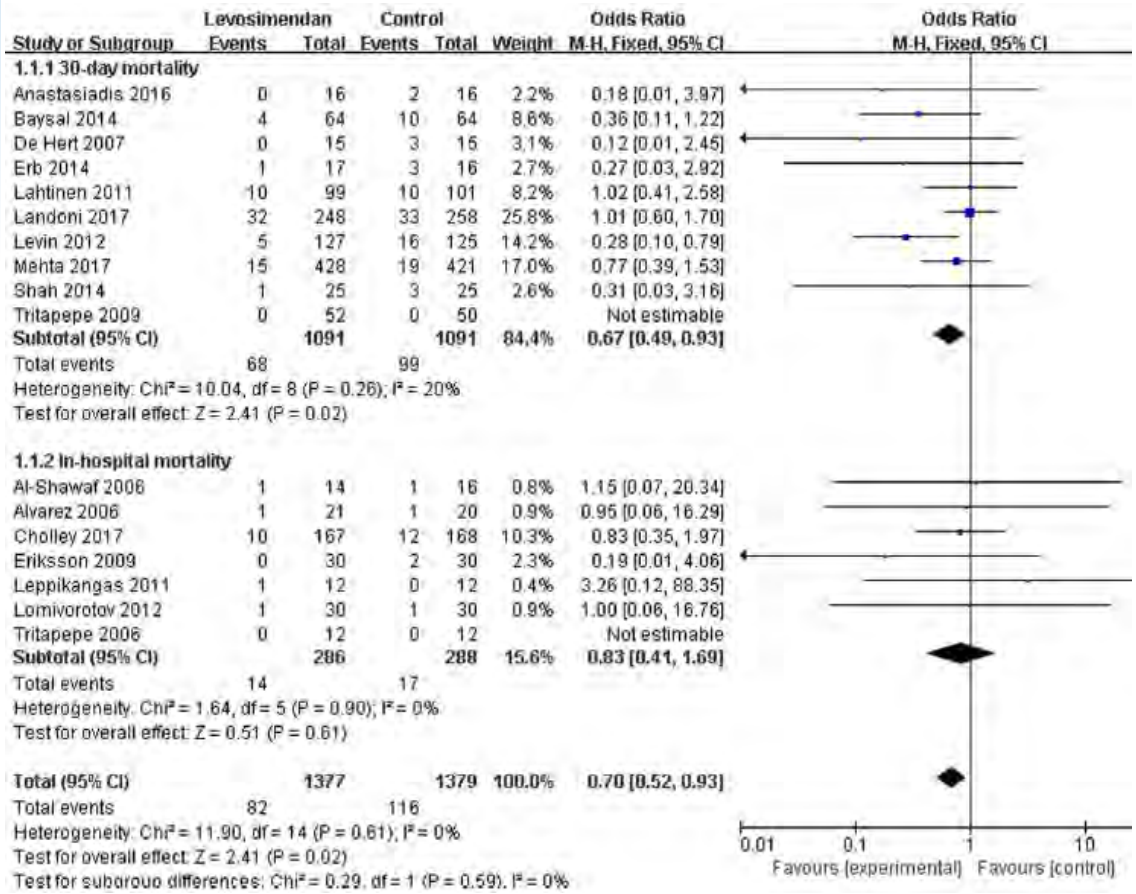
Fig 2. A Forest plot for the risk of in-hospital mortality comparing levosimendan versus control. CI, confidence intervals; df, degrees of freedom; OR, odds ratio pooled estimates of postoperative mortality.

Journal of Cardiothoracic and Vascular Anesthesia, Vol 24, No 1 (February), 2010: pp 51-57

Effect of levosimendan on prognosis in adult patients undergoing cardiac surgery: a meta-analysis of randomized controlled trials

Chen *et al. Critical Care* (2017) 21:253

Qi-Hong Chen[1†], Rui-Qiang Zheng[1†], Hua Lin[1], Jun Shao[1], Jiang-quan Yu[1] and Hua-Ling Wang[1,2*]



Study or Subgroup	Levosimendan Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 30-day mortality						
Anastasiadis 2016	0	16	2	16	2.2%	0.18 [0.01, 3.97]
Baysal 2014	4	64	10	64	8.6%	0.36 [0.11, 1.22]
De Hert 2007	0	15	3	15	3.1%	0.12 [0.01, 2.45]
Erb 2014	1	17	3	16	2.7%	0.27 [0.03, 2.92]
Lahtinen 2011	10	99	10	101	8.2%	1.02 [0.41, 2.58]
Landoni 2017	32	248	33	258	25.8%	1.01 [0.60, 1.70]
Levin 2012	5	127	16	125	14.2%	0.28 [0.10, 0.79]
Mehta 2017	15	428	19	421	17.0%	0.77 [0.39, 1.53]
Shah 2014	1	25	3	25	2.6%	0.31 [0.03, 3.16]
Tritapepe 2009	0	52	0	50		Not estimable
Subtotal (95% CI)		**1091**		**1091**	**84.4%**	**0.67 [0.49, 0.93]**
Total events	68		99			
Heterogeneity: Chi² = 10.04, df = 8 (P = 0.26); I² = 20%						
Test for overall effect: Z = 2.41 (P = 0.02)						
1.1.2 In-hospital mortality						
Al-Shawaf 2008	1	14	1	16	0.8%	1.15 [0.07, 20.34]
Alvarez 2006	1	21	1	20	0.9%	0.95 [0.06, 16.29]
Cholley 2017	10	167	12	168	10.3%	0.83 [0.35, 1.97]
Eriksson 2009	0	30	2	30	2.3%	0.19 [0.01, 4.06]
Leppikangas 2011	1	12	0	12	0.4%	3.26 [0.12, 88.35]
Lomivorotov 2012	1	30	1	30	0.9%	1.00 [0.06, 16.76]
Tritapepe 2006	0	12	0	12		Not estimable
Subtotal (95% CI)		**286**		**288**	**15.6%**	**0.83 [0.41, 1.69]**
Total events	14		17			
Heterogeneity: Chi² = 1.64, df = 5 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.51 (P = 0.61)						
Total (95% CI)		**1377**		**1379**	**100.0%**	**0.70 [0.52, 0.93]**
Total events	82		116			
Heterogeneity: Chi² = 11.90, df = 14 (P = 0.61); I² = 0%						
Test for overall effect: Z = 2.41 (P = 0.02)						
Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I² = 0%						

CRITICAL CARE

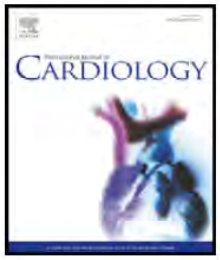
Conclusions: In patients undergoing cardiac surgery, the benefit of levosimendan in terms of survival was not shown in multicenter or in high-quality trials; however, levosimendan therapy was associated with reduced mortality in patients with preoperative ventricular systolic dysfunction.

International Journal of Cardiology 184 (2015) 323–336

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard



Review

Preoperative and perioperative use of levosimendan in cardiac surgery: European expert opinion

W. Toller [a,*], M. Heringlake [b], F. Guarracino [c], L. Algotsson [d], J. Alvarez [e], H. Argyriadou [f], T. Ben-Gal [g], V. Černý [h], B. Cholley [i,j], A. Eremenko [k], J.L. Guerrero-Orriach [l], K. Järvelä [m], N. Karanovic [n], M. Kivikko [o], P. Lahtinen [p], V. Lomivorotov [q], R.H. Mehta [r], Š. Mušič [s], P. Pollesello [o], S. Rex [t], H. Riha [u], A. Rudiger [v], M. Salmenperä [w], L. Szudi [x], L. Tritapepe [y], D. Wyncoll [z], A. Öwall [aa]

A panel of 27 experts from 18 countries has now reviewed the literature on the use of levosimendan in on-pump and off-pump coronary artery bypass grafting and in heart valve surgery. This panel discussed the published evidence in these various settings, and agreed to vote on a set of questions related to the cardioprotective effects of levosimendan when administered preoperatively, with the purpose of reaching a consensus on which patients could benefit from the preoperative use of Levosimendan.

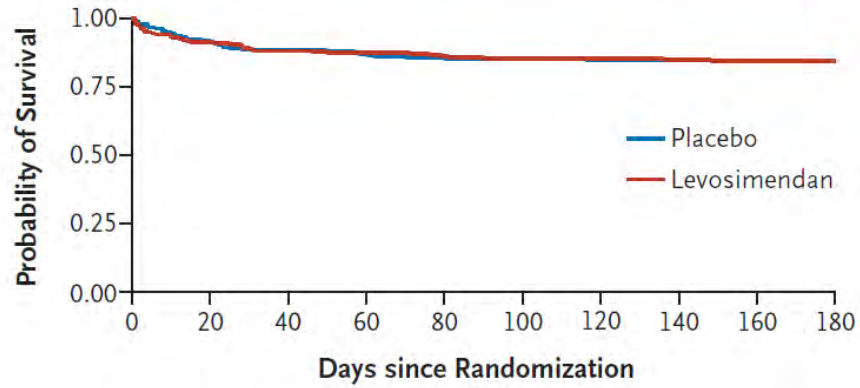
Levosimendan for Hemodynamic Support after Cardiac Surgery

G. Landoni, V.V. Lomivorotov, G. Alvaro, R. Lobreglio, A. Pisano, F. Guarracino, M.G. Calabrò, E.V. Grigoryev, V.V. Likhvantsev, M.F. Salgado-Filho, A. Bianchi, V.V. Pasyuga, M. Baiocchi, F. Pappalardo, F. Monaco, V.A. Boboshko, M.N. Abubakirov, B. Amantea, R. Lembo, L. Brazzi, L. Verniero, P. Bertini, A.M. Scandroglio, T. Bove, A. Belletti, M.G. Michienzi, D.L. Shukevich, T.S. Zabelina, R. Bellomo, and A. Zangrillo, for the CHEETAH Study Group*

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2017;376:2021-31.

Patients were included if they had perioperative cardiovascular dysfunction, which was defined as the presence of at least one of the following criteria: A preoperative left ventricular ejection fraction of less than 25%, preoperative support with an intraaortic balloon pump, or the need for support with an intraaortic balloon pump or high-dose inotropic support in order to be weaned from cardiopulmonary bypass or at any time within the first 24 hours after surgery.



No. at Risk										
Placebo	258	237	229	225	222	221	219	219	219	219
Levosimendan	248	227	219	217	214	212	212	211	210	210

In conclusion, in patients with perioperative left ventricular dysfunction requiring hemodynamic support after cardiac surgery, a low-dose infusion of levosimendan did not result in lower 30-day mortality than placebo nor did it positively affect any secondary-outcome measures as compared with placebo.

Effect of Levosimendan on Low Cardiac Output Syndrome in Patients With Low Ejection Fraction Undergoing Coronary Artery Bypass Grafting With Cardiopulmonary Bypass

The LICORN Randomized Clinical Trial

JAMA. 2017;318(6):548-556.

Bernard Cholley, MD, PhD; Thibaut Caruba, PharmD, PhD; Sandrine Grosjean, MD; Julien Amour, MD, PhD; Alexandre Ouattara, MD, PhD; Judith Villacorta, MD; Bertrand Miguet, MD; Patrick Guinet, MD; François Lévy, MD; Pierre Squara, MD; Nora Aït Hamou, MD; Aude Carillon, MD; Julie Boyer, MD; Marie-Fazia Boughenou, MD; Sebastien Rosier, MD; Emmanuel Robin, MD; Mihail Radutoiu, MD; Michel Durand, MD; Catherine Guidon, MD, PhD; Olivier Desebbe, MD; Anaïs Charles-Nelson, MSc; Philippe Menasché, MD, PhD; Bertrand Rozec, MD, PhD; Claude Girard, MD, PhD; Jean-Luc Fellahi, MD, PhD; Romain Pirracchio, MD, PhD; Gilles Chatellier, MD, PhD

CONCLUSIONES Y RELEVANCIA Entre los pacientes con FEVI baja (>40%), sometidos a CABG con CPB el levosimendan comparado con placebo no mostro una diferencia significativa en el objetivo primario subdividido en los tres puntos mencionado. Estos hallazgos no respaldan el uso de levosimendan para esta indicación

ORIGINAL ARTICLE

The NEW ENGLAND JOURNAL of MEDICINE

Levosimendan in Patients with Left Ventricular Dysfunction Undergoing Cardiac Surgery

R.H. Mehta, J.D. Leimberger, S. van Diepen, J. Meza, A. Wang, R. Jankowich, R.W. Harrison, D. Hay, S. Fremes, A. Duncan, E.G. Soltesz, J. Luber, S. Park, M. Argenziano, E. Murphy, R. Marcel, D. Kalavrouziotis, D. Nagpal, J. Bozinovski, W. Toller, M. Heringlake, S.G. Goodman, J.H. Levy, R.A. Harrington, K.J. Anstrom, and J.H. Alexander, for the LEVO-CTS Investigators*

N Engl J Med 2017;376:2032-42.

MÉTODOS. Evaluación de la eficacia y seguridad de levosimendan en pacientes con una FEVI ≤ 35% sometidos CPB. Los pacientes recibieron una dosis de 0.2 µg/Kg/min durante 1 hora, seguido de una dosis de 0.1 µg/kg/min durante 23 horas, o placebo, con la infusión comenzó antes de la cirugía. Los dos objetivos finales fueron:

- Fallecidos y necesidad de terapia de reemplazo renal en los 30 días.
- Infarto de miocardio perioperatorio
- Necesidad de asistencia mecánica hasta el día 5.

N Engl J Med 2017;376:2032-42.

The NEW ENGLAND JOURNAL of MEDICINE

Levosimendan in Patients with Left Ventricular Dysfunction Undergoing Cardiac Surgery

R.H. Mehta, J.D. Leimberger, S. van Diepen, J. Meza, A. Wang, R. Jankowich, R.W. Harrison, D. Hay, S. Fremes, A. Duncan, E.G. Soltesz, J. Luber, S. Park, M. Argenziano, E. Murphy, R. Marcel, D. Kalavrouziotis, D. Nagpal, J. Bozinovski, W. Toller, M. Heringlake, S.G. Goodman, J.H. Levy, R.A. Harrington, K.J. Anstrom, and J.H. Alexander, for the LEVO-CTS Investigators*

RESULTADOS. 849 pacientes recibieron levosimendan o placebo. El objetivo primario se identificó en 105 de 428 pacientes (24.5%) del grupo levosimendan y en 103 de 421 (24.5%) del grupo placebo.

CONCLUSIONES. El levosimendan no disminuyó la mortalidad, necesidad de terapia de reemplazo renal, infarto de miocardio perioperatorio, o uso de asistencia mecánica circulatoria que fue menor que la del grupo placebo entre los pacientes con FEVI reducida

The American Journal of Cardiology.

AJC 2007; 99: 146-7

AJC

Parisi J et al. Levosimendan for the treatment of Acute Heart Failure Syndromes: Time to Identify Subpopulations of Responding Patients

N Engl J Med 2017;376:2032-42.

The NEW ENGLAND JOURNAL of MEDICINE

Levosimendan in Patients with Left Ventricular Dysfunction Undergoing Cardiac Surgery

R.H. Mehta, J.D. Leimberger, S. van Diepen, J. Meza, A. Wang, R. Jankowich, R.W. Harrison, D. Hay, S. Fremes, A. Duncan, E.G. Soltesz, J. Luber, S. Park, M. Argenziano, E. Murphy, R. Marcel, D. Kalavrouziotis, D. Nagpal, J. Bozinovski, W. Toller, M. Heringlake, S.G. Goodman, J.H. Levy, R.A. Harrington, K.J. Anstrom, and J.H. Alexander, for the LEVO-CTS Investigators*

CONCLUSIONS

Prophylactic levosimendan did not result in a rate of the short-term composite end point of death, renal-replacement therapy, perioperative myocardial infarction, or use of a mechanical cardiac assist device that was lower than the rate with placebo among patients with a reduced left ventricular ejection fraction who were undergoing cardiac surgery with the use of cardiopulmonary bypass. (Funded by Tenax Therapeutics; LEVO-CTS ClinicalTrials.gov number, NCT02025621.)

http://www.tenaxthera.com/

TENAX THERAPEUTICS

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Tenax Therapeutics is focused on identifying, developing and commercializing products for the critical care market.

In the U.S. alone, more than five million hospitalized patients are treated in an intensive care setting annually according to the Society of Critical Medicine.

LEVO CTS
levosimendan in cardio thoracic surgery

The LEVO-CTS trial results were presented on

Sunday, March 19, 2017, at the

American College of Cardiology

66th Annual Scientific Session in Washington, D.C.

Primary Results Presentation

Focus on Critical Care

Given the high mortality, morbidity, and costs associated with the treatment of many intensive care patients, we believe that there is a substantial opportunity to add value for patients, physicians, hospitals, and ultimately shareholders.

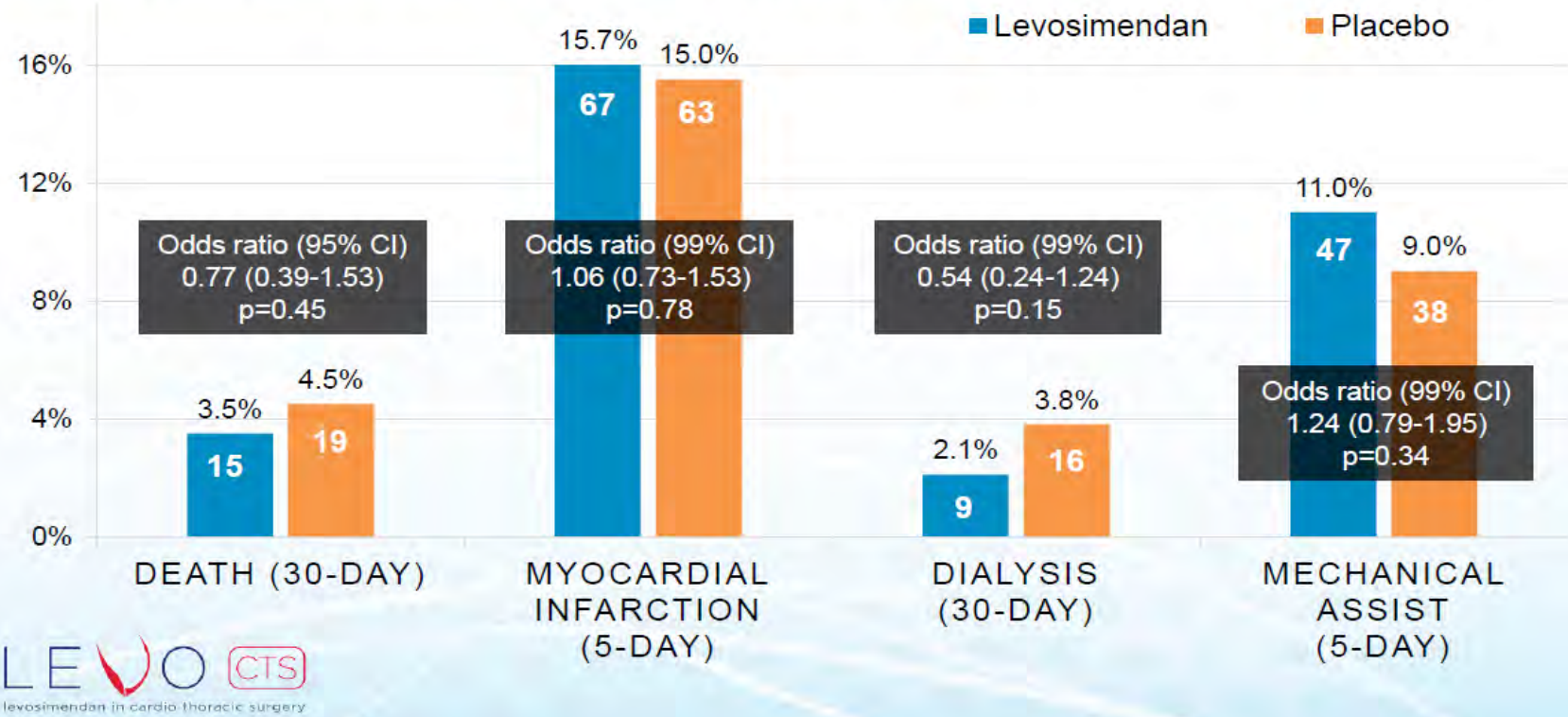
News

Tenax Therapeutics Provides Regulatory Update on Levosimendan

Tenax Meets with FDA to Discuss Positive Mortality Data and Potential Levosimendan NDA Submission

Tenax Therapeutics Announces Review of Strategic Alternatives and Business Update

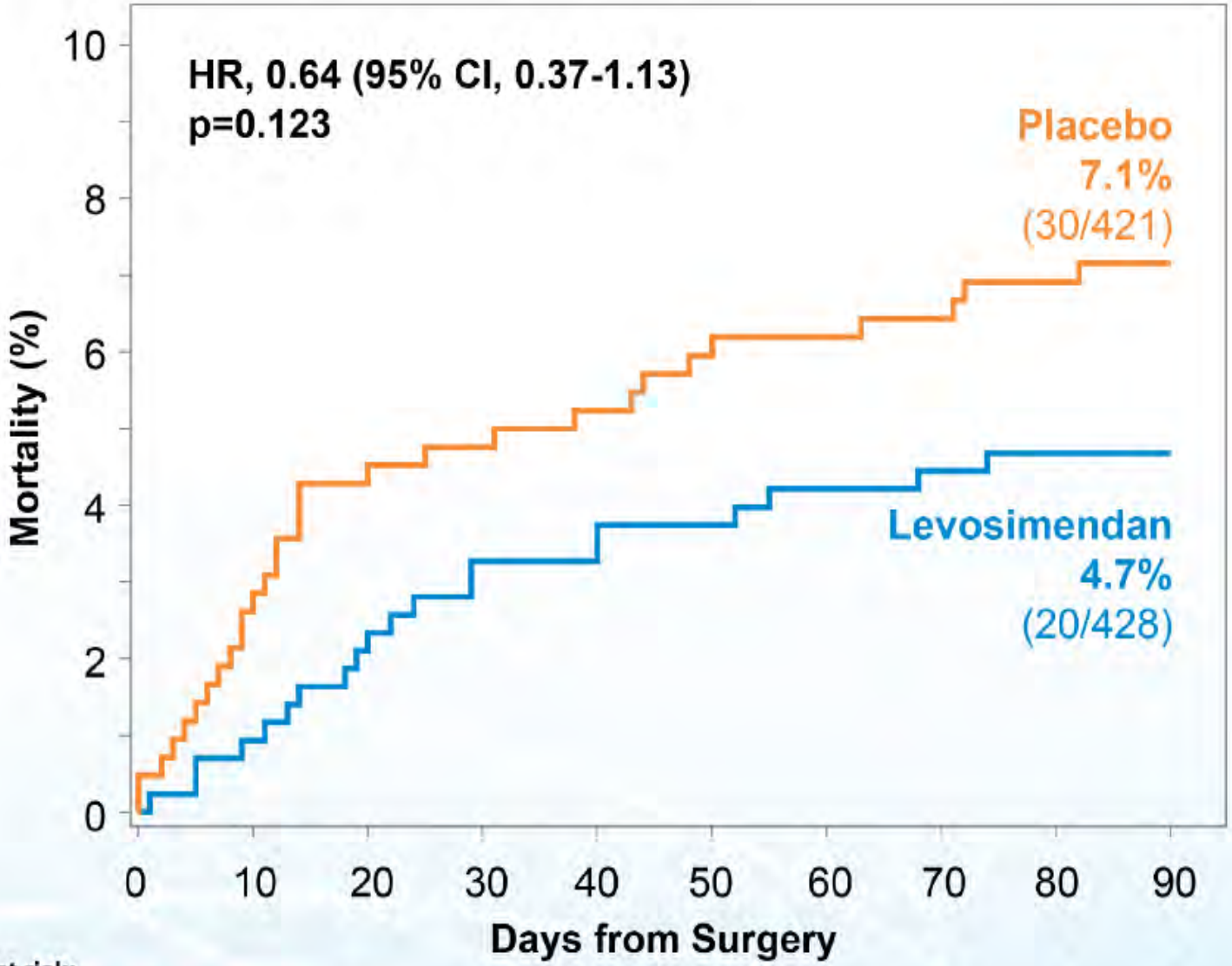
Individual Outcomes Components



LEVO CTS
levosimendan in cardio thoracic surgery

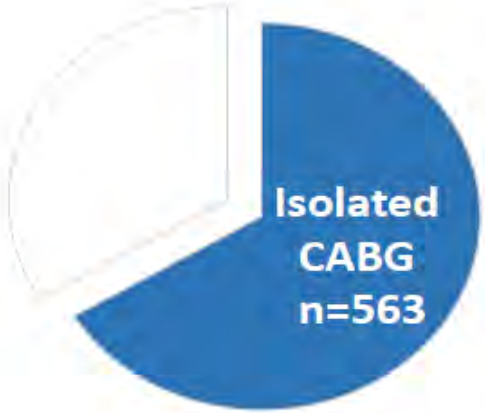
Cardiac Index	Mean (SD)	
Levosimendan (n=359)	2.86 (0.61)	p<0.0001
Placebo (n=340)	2.68 (0.65)	

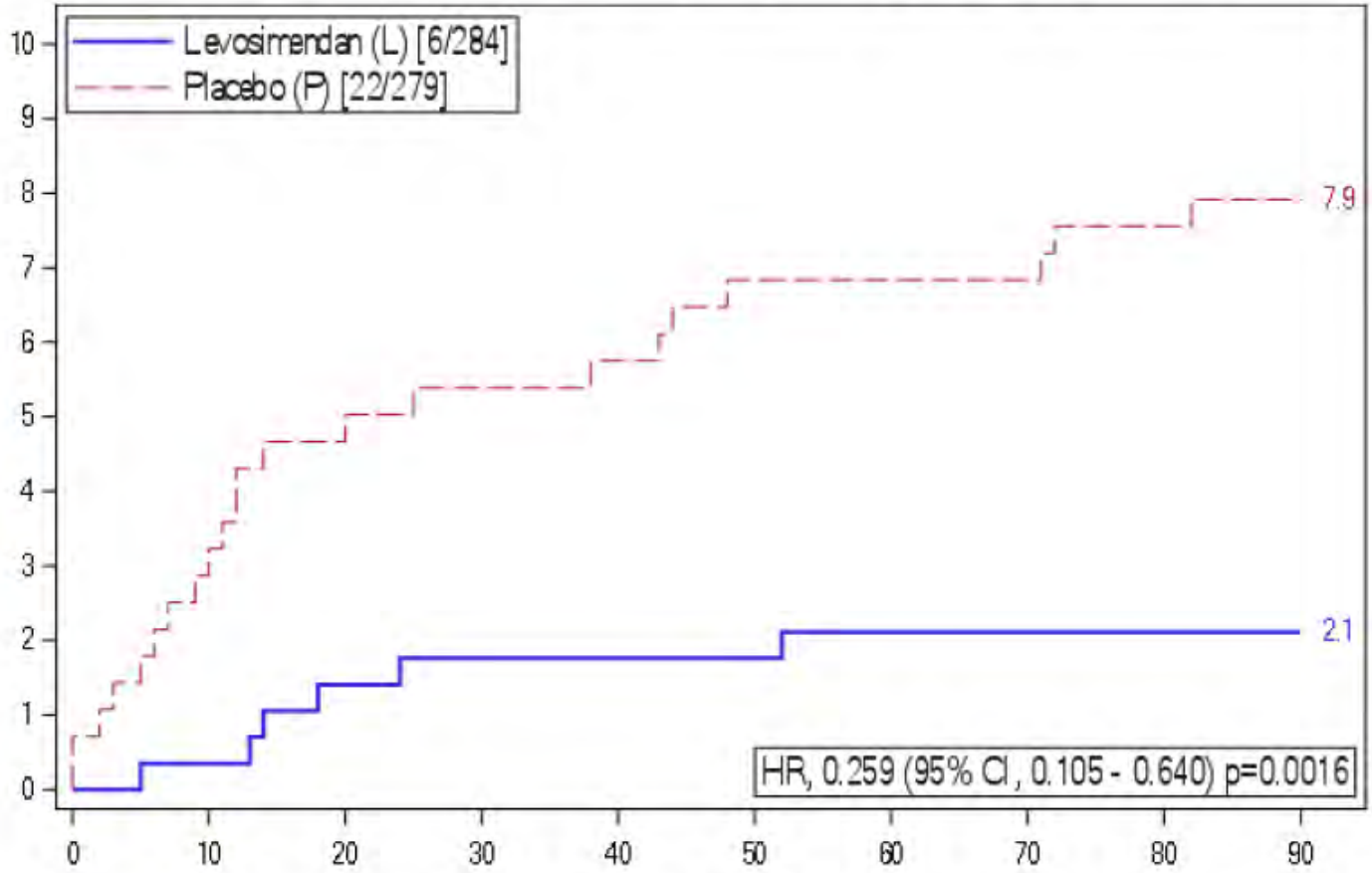
90-Day Mortality



LEVO CTS
levosimendan in cardio thoracic surgery

LEVO-CTS
90-Day Mortality in Isolated CABG Patients

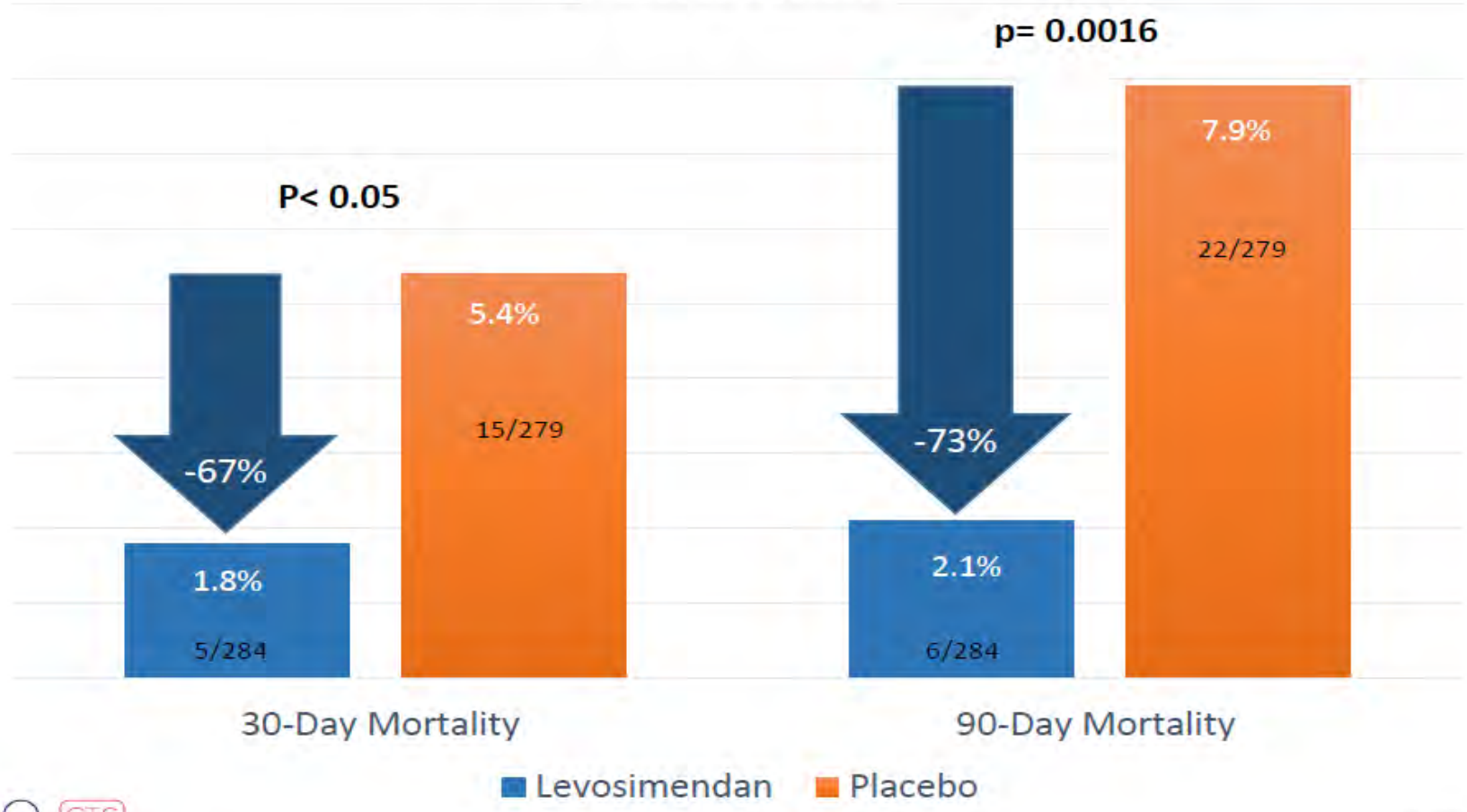




Kaplan-Meier plot of mortality to day 90 (Safety Population, As Treated) for patients with Isolated CABG

LEVO-CTS Isolated CABG Patients
Consistent Mortality Reduction at 30 & 90 Days

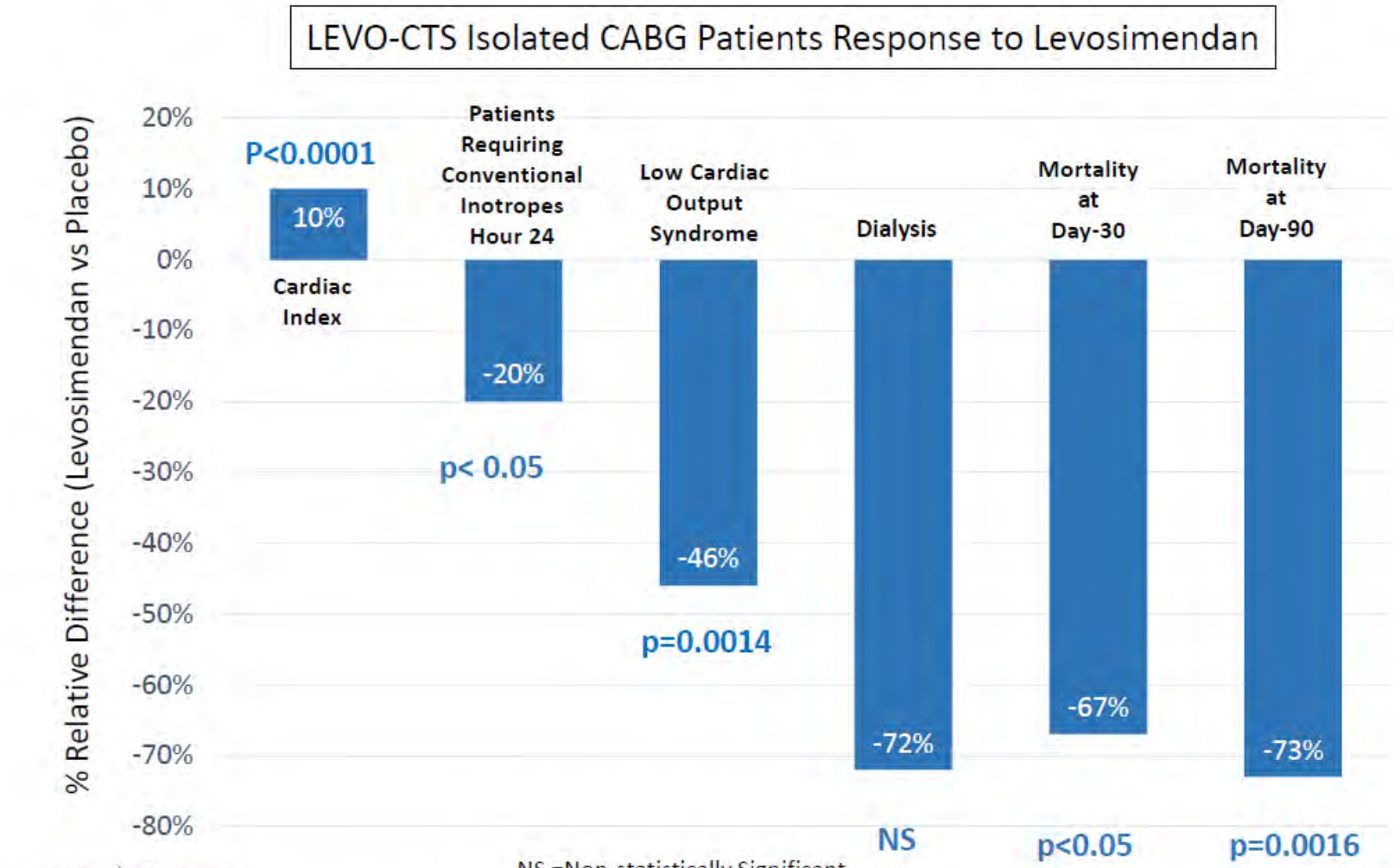
(n=563, as treated)



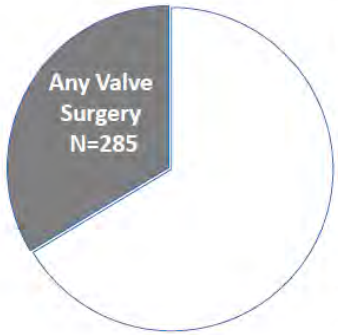
LEVO CTS
levosimendan in cardio thoracic surgery

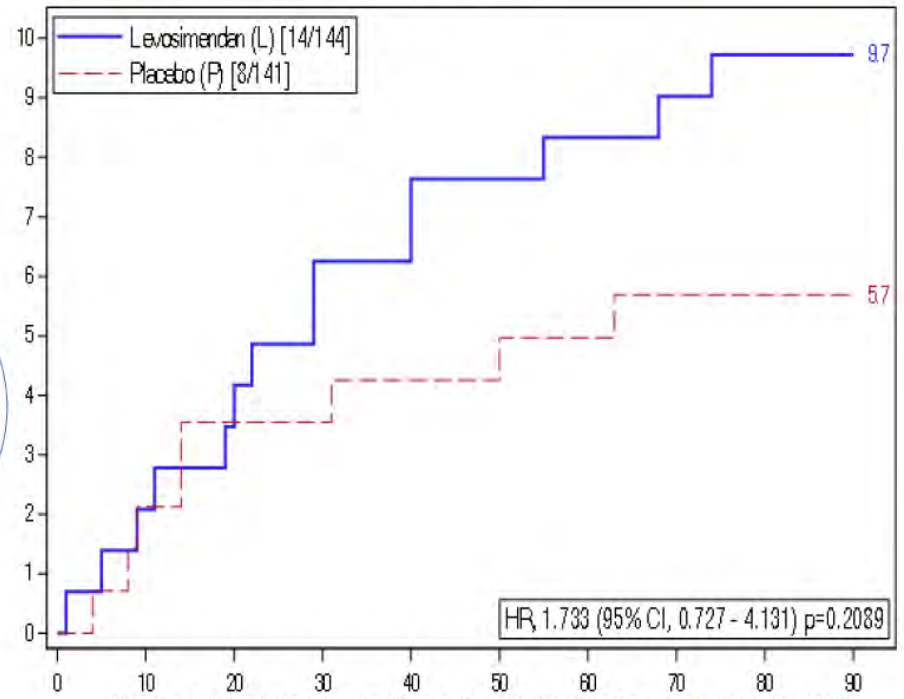
TENAX THERAPEUTICS

Consistent Response in Isolated CABG Patients



LEVO-CTS 90-Day Mortality in Valve Surgery Patients (with or without CABG)





Kaplan-Meier plot of mortality to day 90 (Safety Population, As Treated) for patients with Surgery Other than Isolated CABG

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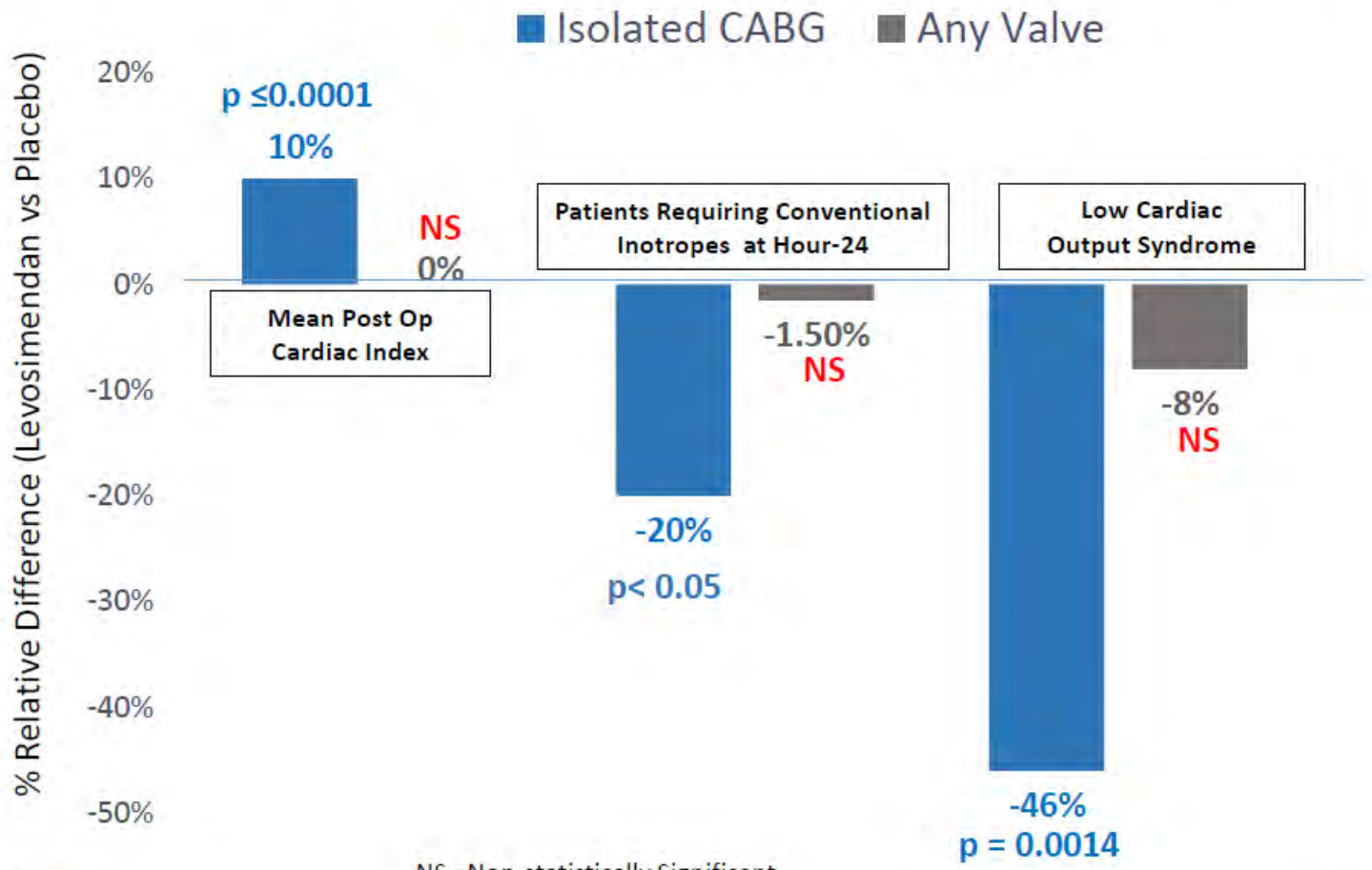
Variable	Levosimendan (N=428)	Placebo (N=421)
Type of surgery — no. (%)†		
CABG	283 (66.1)	280 (66.5)
Mitral valve	36 (8.4)	31 (7.4)
CABG and mitral valve	50 (11.7)	48 (11.4)
CABG and aortic valve	36 (8.4)	34 (8.1)
Mitral and aortic valves	10 (2.3)	14 (3.3)
CABG and mitral and aortic valves	10 (2.3)	10 (2.4)
Aortic valve	3 (0.7)	3 (0.7)

LEVO-CTS Reveals Divergent Hemodynamic Responses to Levosimendan - Varies by Surgery Type

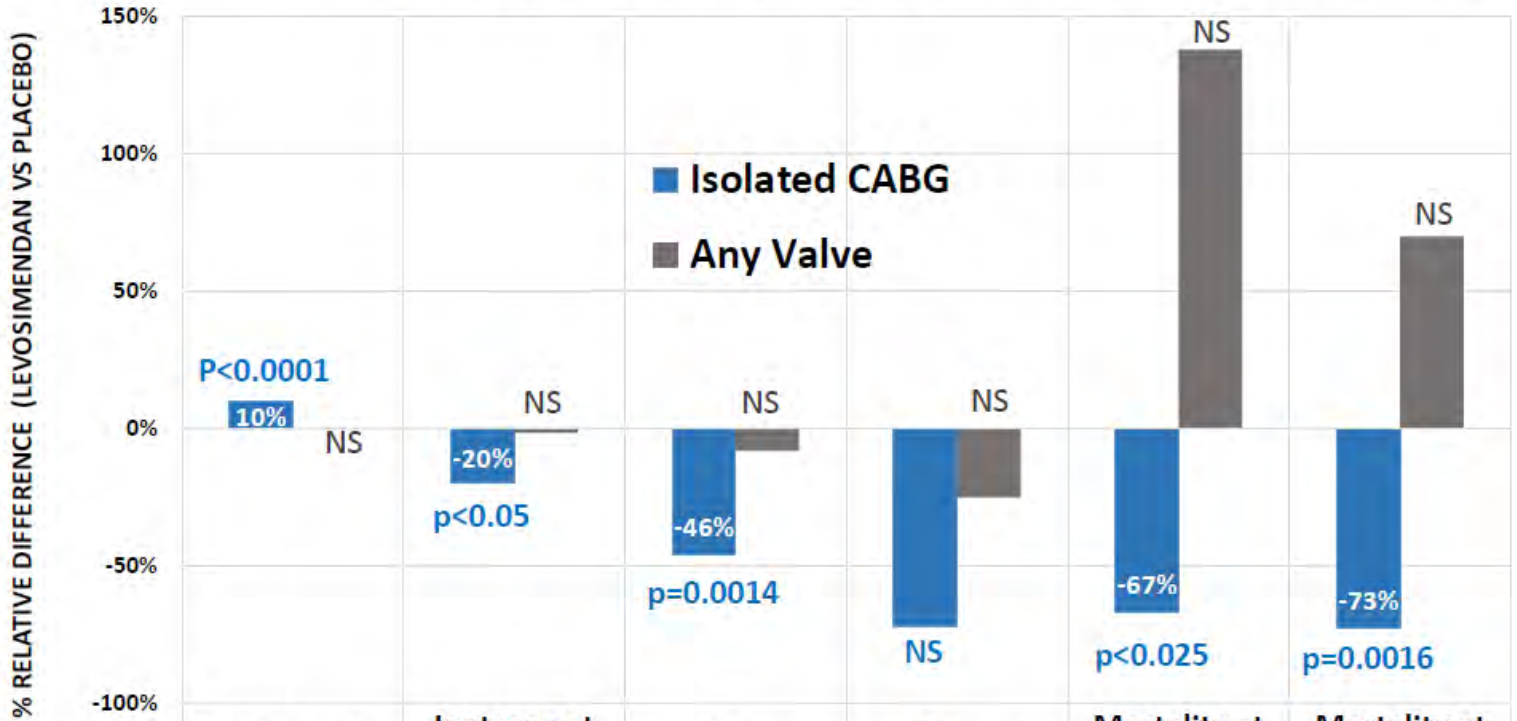


NS =Non-statistically Significant

Cardiac index based on N= 460, All other Variables based on n=563

18

Divergent Outcomes By Surgery Type Align with Divergent Hemodynamic Response



	Cardiac Index	Inotrope at Hour 24	LCOS	Dialysis	Mortality at Day-30	Mortality at Day-90
Isolated CABG	10%	-20%	-46%	-72%	-67%	-73%
Any Valve	0%	-1.50%	-8%	-25%	138%	70%

NS =Non-statistically Significant

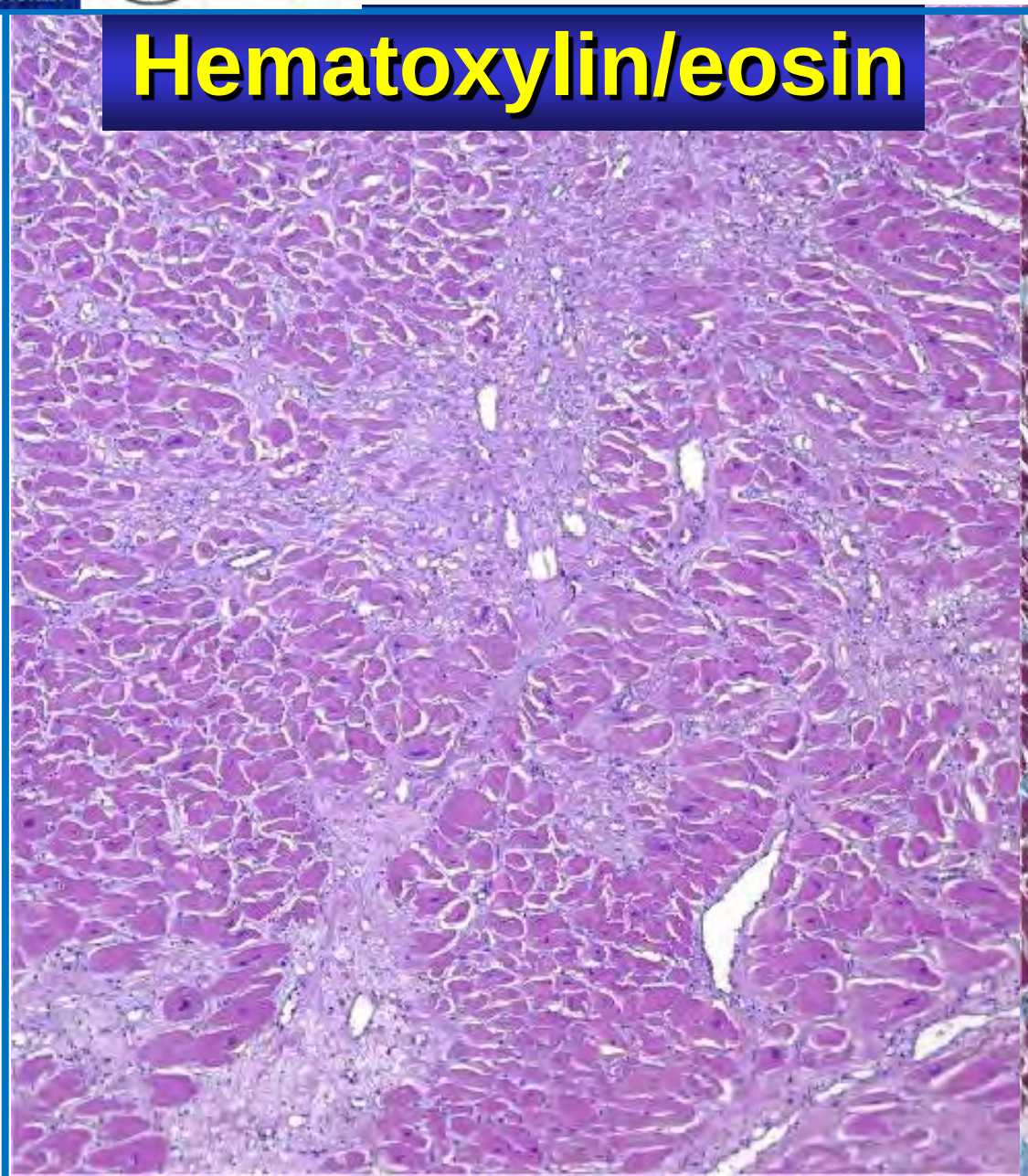
Cardiac index based on N= 460, All other Variables based on n=563

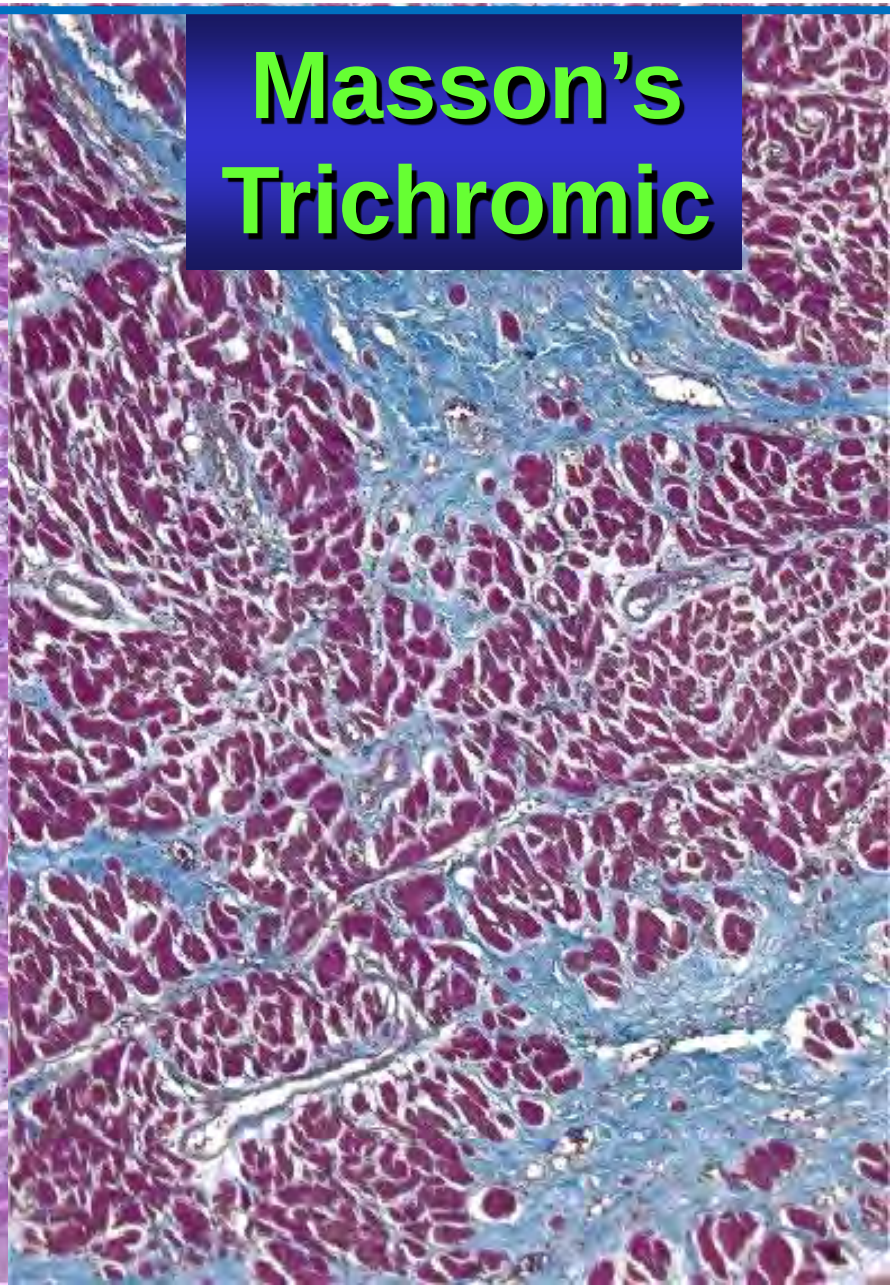
19

Pathophysiology May Provide Possible Explanation for Divergent Responses in Low EF Isolated CABG vs Valve Surgery Patients

Cardiac Dysfunction Characteristics	Low EF Isolated CABG Patients	Low EF Valve Surgery Patients
Etiology	Ischemic (usually reversible)	Structural and/or Ischemic (heterogenous population)
Pathophysiology	Ischemia/ Stunning/ Hibernating Myocardium	Myocyte disarray and irreversible fibrosis secondary to chronic wall stress, including some patients with ischemic component
Contractile Function	Cardiac Dysfunction Frequently **Reversible**	Cardiac Dysfunction Frequently **Irreversible**

1. Bonow RO, Maurer G, Lee KL, et al. Myocardial viability and survival in ischemic left ventricular dysfunction. *N Engl J Med* 2011;364:1617-1625.
2. Hein, Stefan, et al. "Progression from compensated hypertrophy to failure in the pressure-overloaded human heart." *Circulation* 107.7 (2003): 984-991.
3. Starling, Mark R., et al. "Impaired left ventricular contractile function in patients with long-term mitral regurgitation and normal ejection fraction." *Journal of the American College of Cardiology* 22.1 (1993): 239-250.


Hematoxylin/eosin


Masson's Trichromic

JOURNAL OF CARDIOVASCULAR MEDICINE

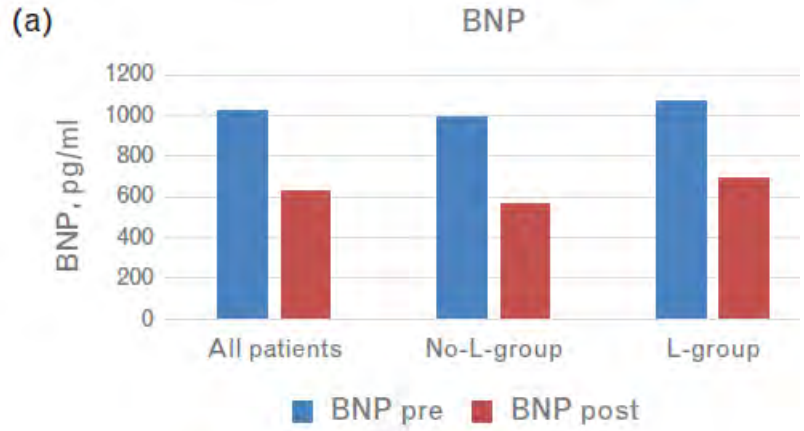
J Cardiovasc Med 2017

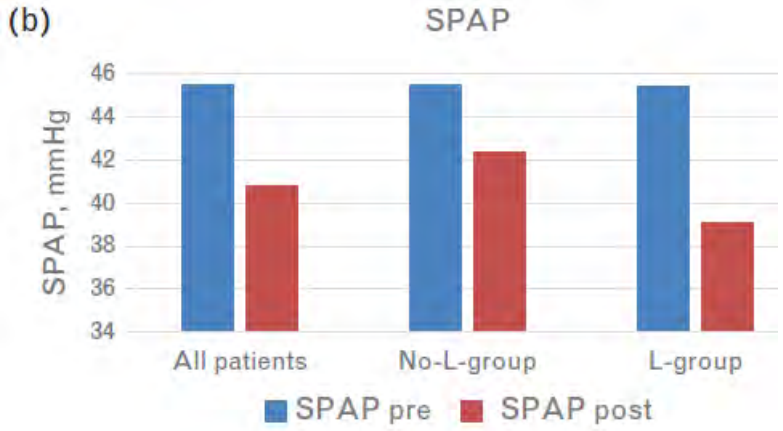
Effects of levosimendan in patients with severe functional mitral regurgitation undergoing MitraClip implantation

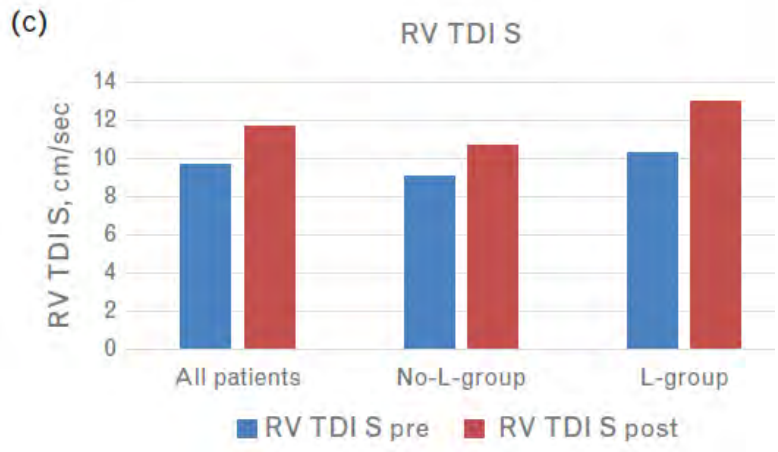
Cristina Giannini[a], Anna S. Petronio[a], Francesca Fiorelli[a], Riccardo Liga[a], Paolo Spontoni[a], Marco De Carlo[a], Emilia Marraccini[a], Andrea Pieroni[a] and Fabio Guarracino[b]

94 patients Mitral Regurgitation under (MitraClip System) were enrolled in a prospective registry. 27 patients receiving levosimendan.

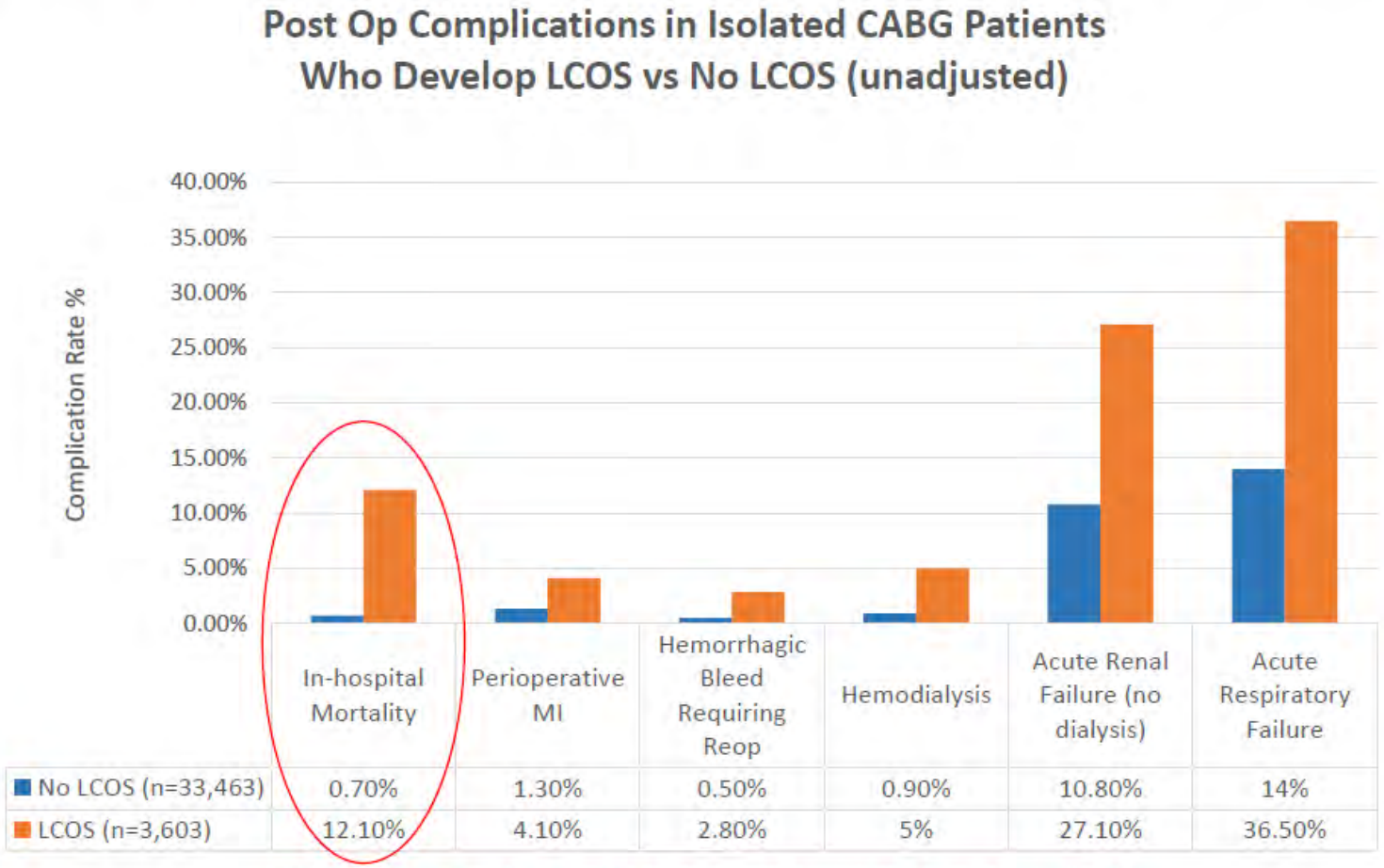
Prophylactic levosimendan did not affect longterm outcome. However, levosimendan as an adjunctive therapy to MitraClip implantation.







LCOS is Associated with Increased Mortality and Post Op Complications in Isolated CABG Patients



	In-hospital Mortality	Perioperative MI	Hemorrhagic Bleed Requiring Reop	Hemodialysis	Acute Renal Failure (no dialysis)	Acute Respiratory Failure
No LCOS (n=33,463)	0.70%	1.30%	0.50%	0.90%	10.80%	14%
LCOS (n=3,603)	12.10%	4.10%	2.80%	5%	27.10%	36.50%

Chi-square Test, p-value <0.0001 for in-hospital mortality and all complications

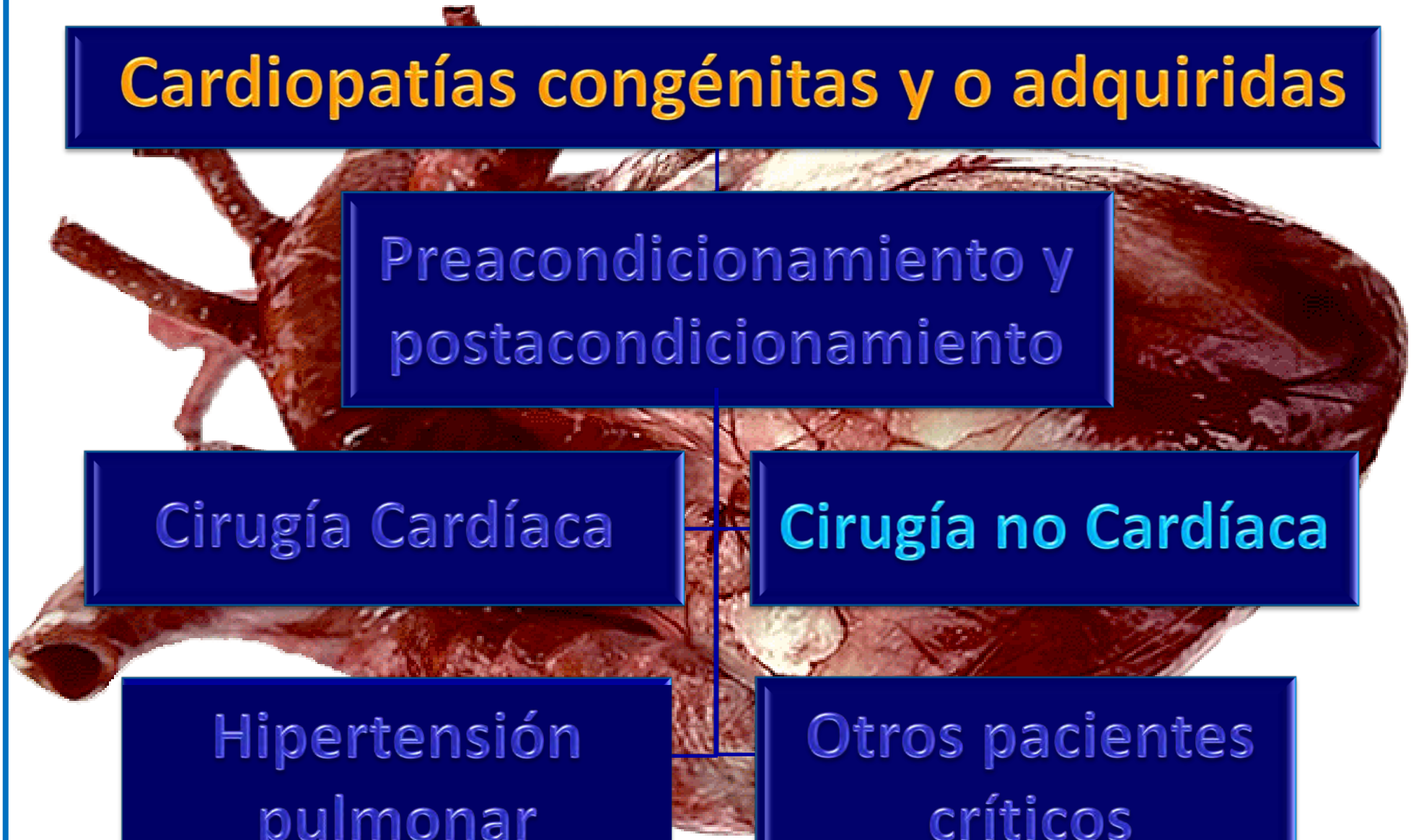
Source: Resource Utilization for Cardiovascular Surgery Patients at Risk for Development of Low Cardiac Output Syndrome, conducted by Premier, funded by Tenax

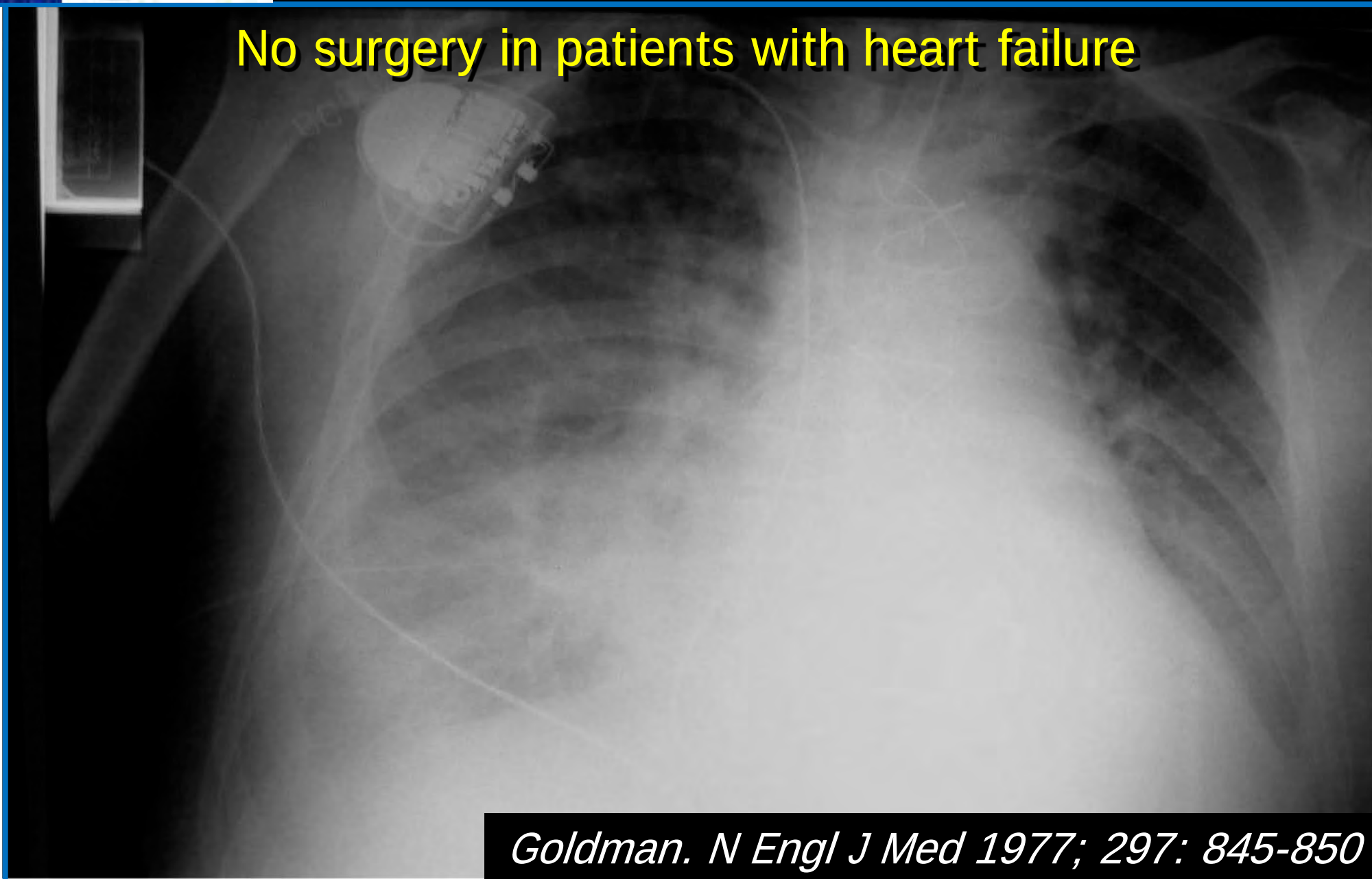
Conclusions

- Levosimendan, given prophylactically prior to cardiac surgery to patients with reduced left ventricular function, had no effect on the co-primary outcomes of…
  - death, dialysis, MI, or mechanical assist device use
  - death or mechanical assist device use

- Levosimendan is effective and safe as an inotrope to increase cardiac output in patients at risk for perioperative low cardiac output syndrome

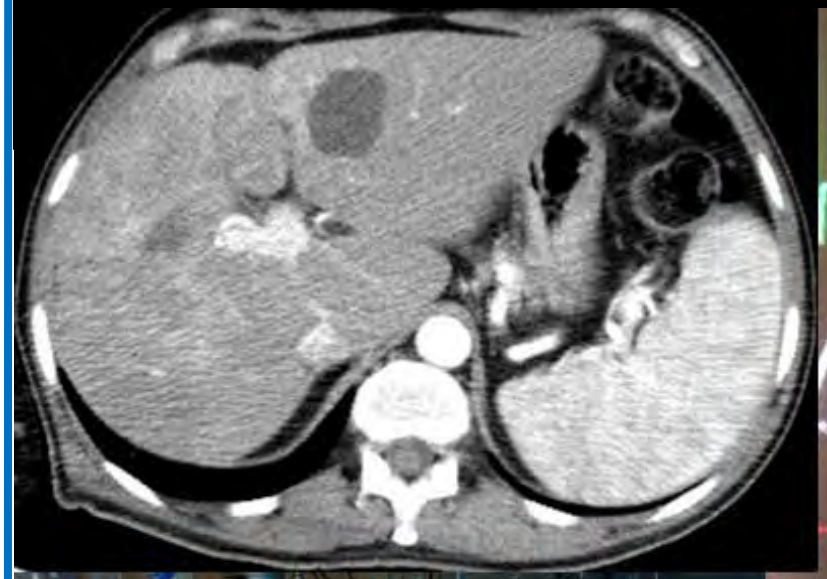
LEVO CTS
levosimendan in cardio thoracic surgery

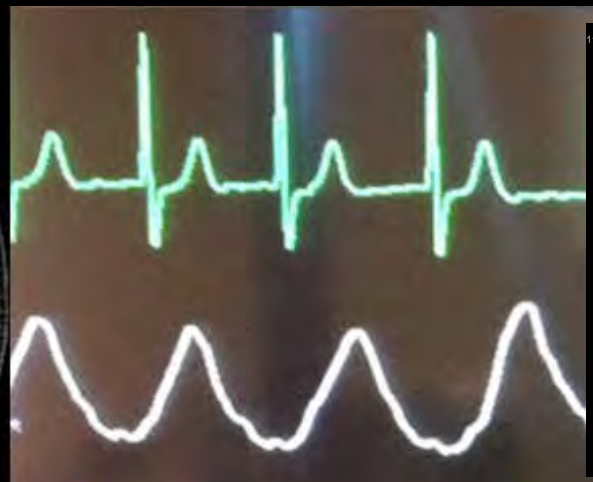

Cardiopatías congénitas y o adquiridas
Preacondicionamiento y postacondicionamiento
Cirugía Cardíaca
Cirugía no Cardíaca
Hipertensión pulmonar
Otros pacientes críticos

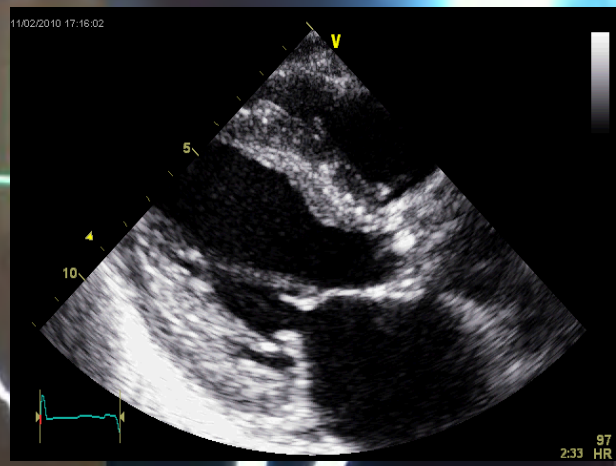


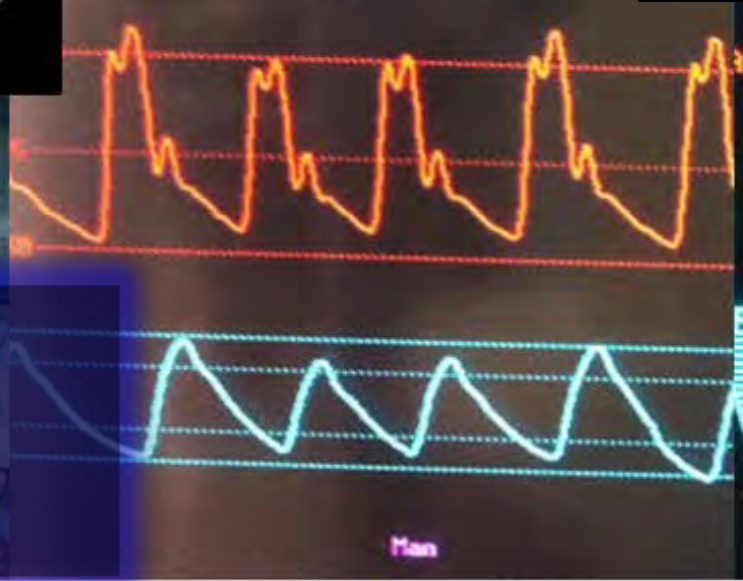
Goldman. N Engl J Med 1977; 297: 845-850

Male 78 years. Awaiting CABG + aortic valve replacement for severe aortic stenosis. LVEF preserved. Abdominal pain. Severe anemia. Hb = 6 g / dL. In abdominal scan, mass in colon with liver metastases



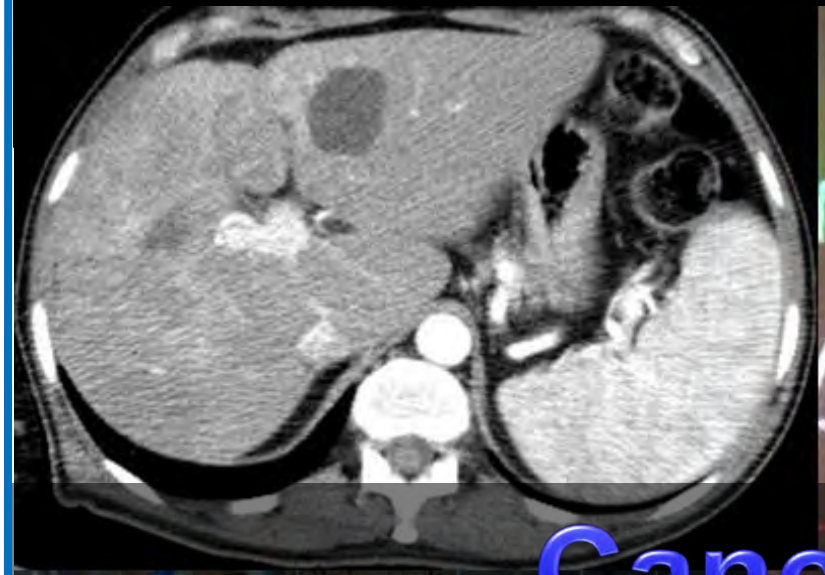


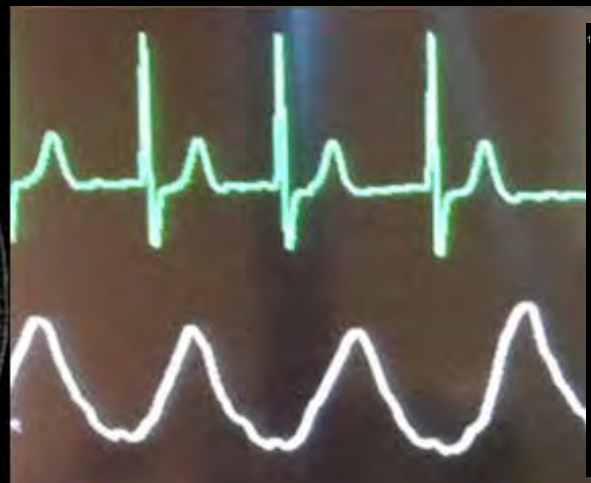


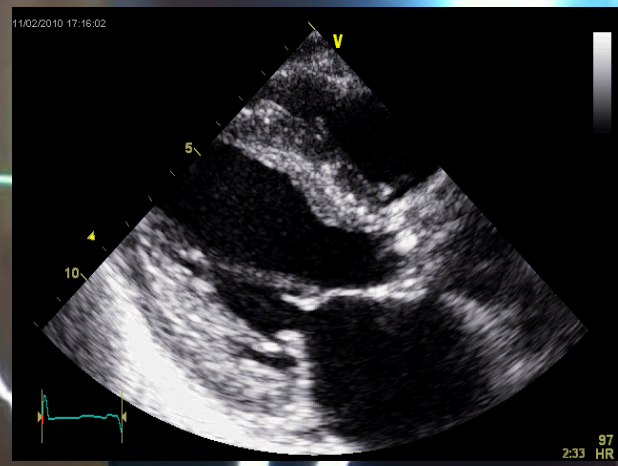


What do we do?
Cancer surgery?
Cardiac surgery?

Male 78 years. Awaiting CABG + aortic valve replacement for severe aortic stenosis. LVEF preserved. Abdominal pain. Severe anemia. Hb = 6 g / dL. In abdominal scan, mass in colon with liver metastases



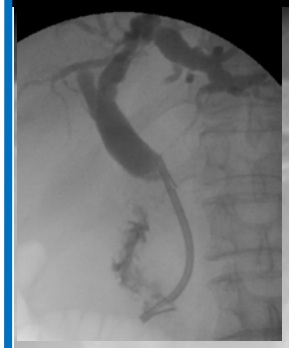


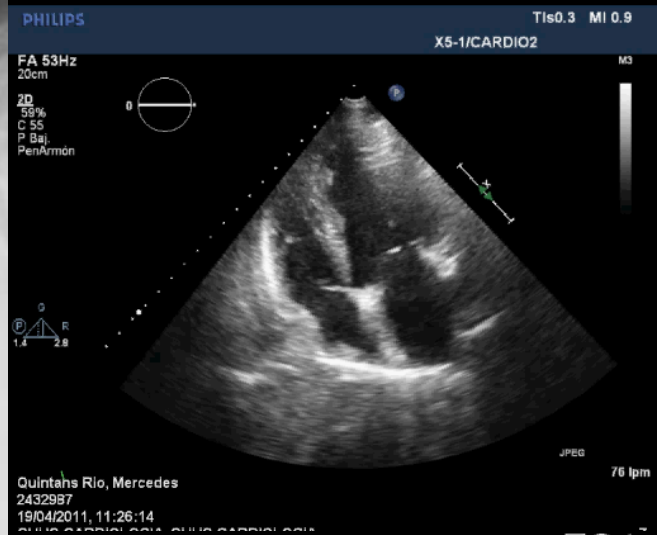


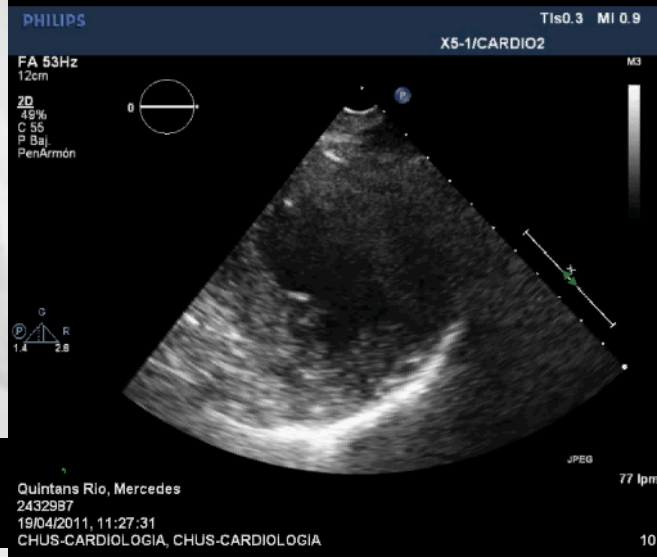
Cancer surgery

Levosimendan?

Woman. 69 years old. Cholangiocarcinoma. Congestive heart failure. LVEF = 30%







What do we do?

69 años. Colangiocarcinoma. Insuficiencia cardiaca congestiva. LVEF = 30%

Before surgery. Preconditioning

Acta Anaesthesiologica Scandinavica

Scandinavian Journal of Surgery 96: 121–124, 2007

MEDICAL SUPPORT AND SURGERY OF THE FAILING HEART: LEVOSIMENDAN

W. Toller[1], I. Knez[2]

[1] Department of Anesthesiology and Intensive Care Medicine, Medical University of Graz, Graz, Austria
[2] Department of Surgery, Division of Cardiac Surgery, Medical University of Graz, Graz, Austria

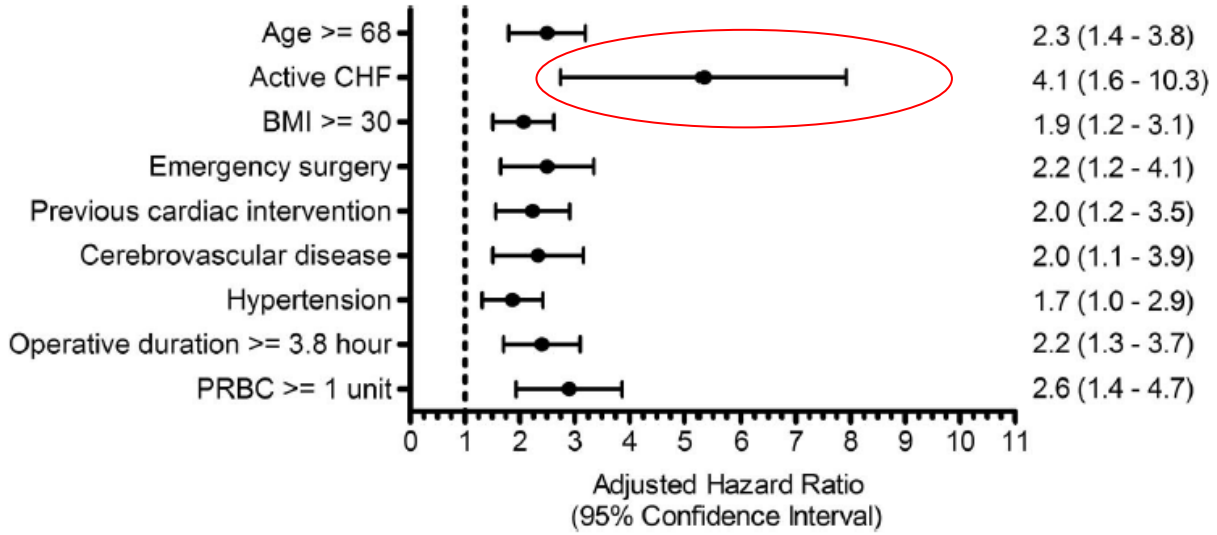
¡¡¡Preconditioning!!!

Levosimendan 0.1 ug / kg / min without a loading dose 12 hour befor surgery. We modified infusion rate depending patiente response

Anesthesiology 2009; 110:58–66

Preoperative and Intraoperative Predictors of Cardiac Adverse Events after General, Vascular, and Urological Surgery

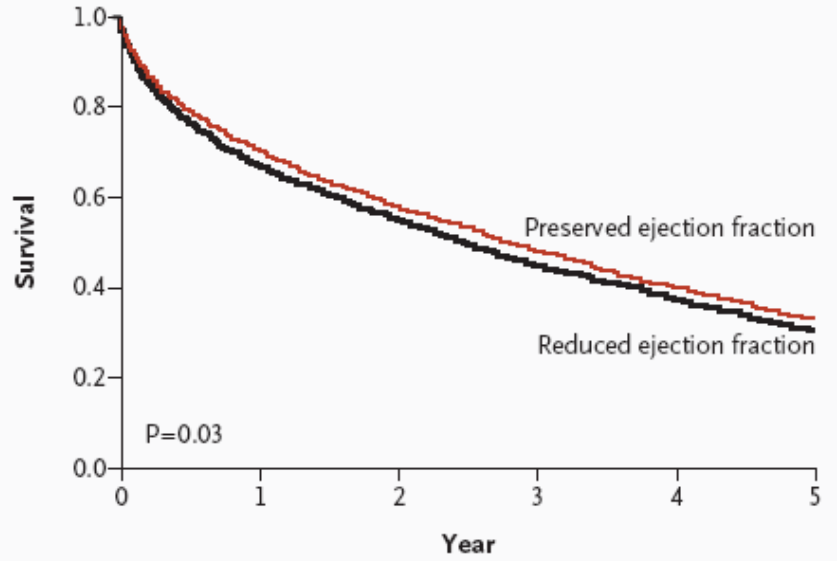
Sachin Kheterpal, M.D., M.B.A., Michael O'Reilly, M.D.,† Michael J. Englesbe, M.D.,‡ Andrew L. Rosenberg, M.D.,**



Active congestive heart failure	Congestive heart failure is the inability of the heart to pump a sufficient quantity of blood to meet the metabolic needs of the body or can do so only at increased ventricular filling pressure. Only newly diagnosed congestive heart failure within the previous 30 days or a diagnosis of chronic congestive heart failure with new signs or symptoms in the 30 days prior to surgery fulfills this definition. Common manifestations are abnormal limitation in exercise tolerance due to dyspnea or fatigue, orthopnea (dyspnea on lying supine), paroxysmal nocturnal dyspnea (awakening from sleep with dyspnea), increased jugular venous pressure, pulmonary rales on physical examination, cardiomegaly, and pulmonary vascular engorgement. Should be noted in the medical record as congestive heart failure or pulmonary edema.

Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction

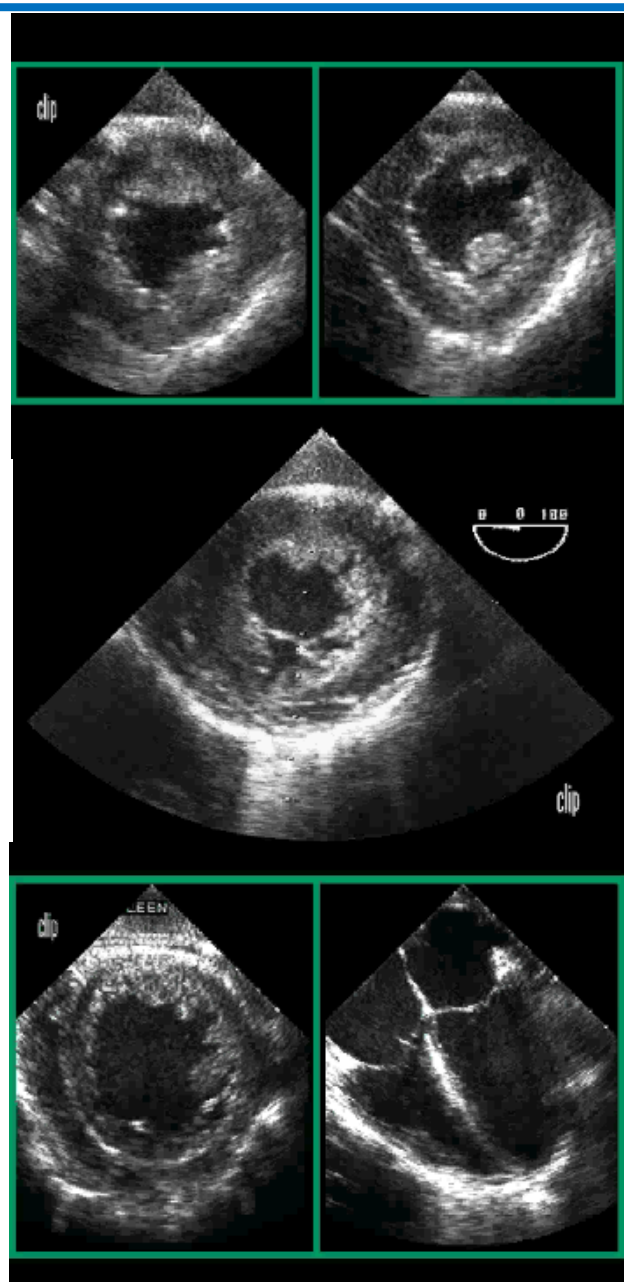
Theophilus E. Owan, M.D., David O. Hodge, M.S., Regina M. Herges, B.S.,



No. at Risk						
Reduced ejection fraction	2424	1637	1350	1049	813	604
Preserved ejection fraction	2166	1539	1270	1001	758	574

Figure 2. Kaplan–Meier Survival Curves for Patients with Heart Failure and Preserved or Reduced Ejection Fraction.

N Engl J Med 2006;355:251-9.

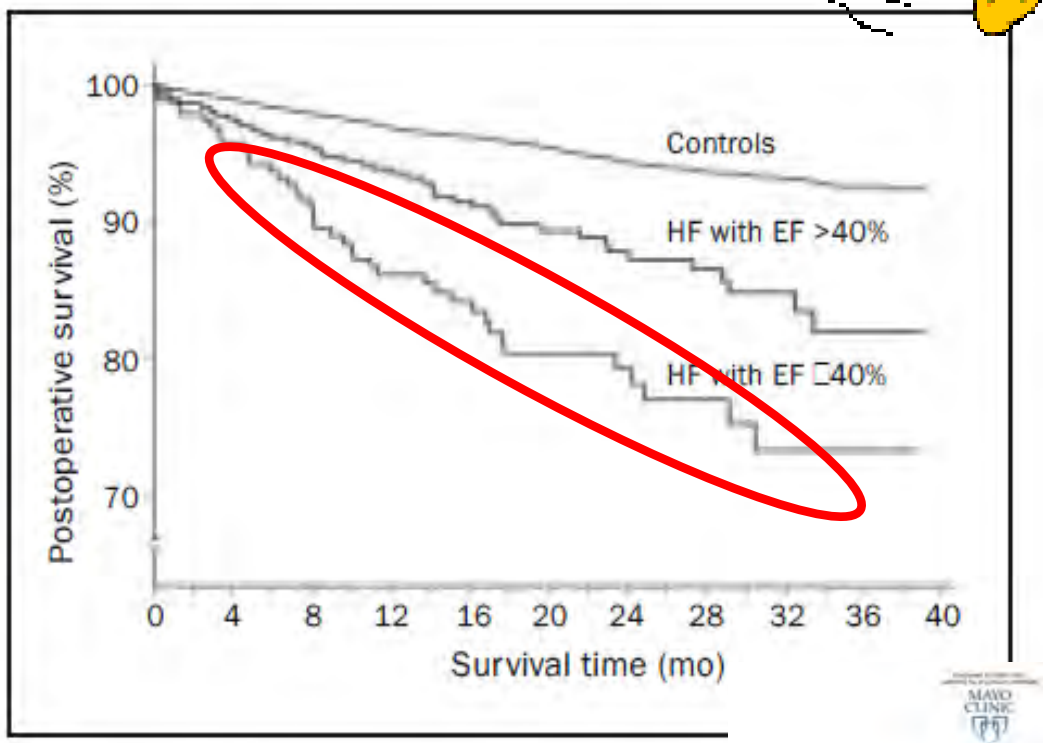


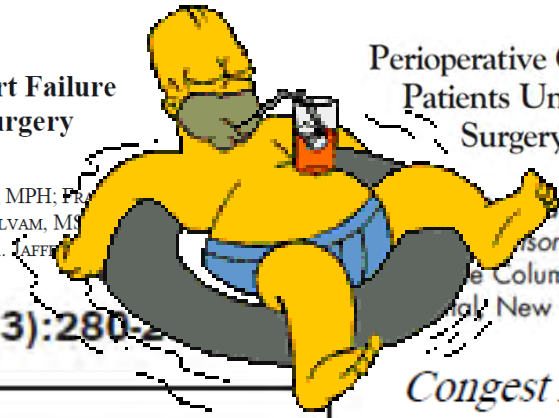
ORIGINAL ARTICLE

Outcomes of Patients With Stable Heart Failure Undergoing Elective Noncardiac Surgery

Ye Olivia Xu-Cai, MD; Daniel J. Brotman, MD; Christopher O. Phillips, MD, MPH; Pr
W. H. Wilson Tang, MD; Christopher M. Whinney, MD; Ashok Panneerselvam, MS
Mario Garcia, MD; Gary S. Francis, MD; and Amir K. Jaffe

***Mayo Clin Proc.* 2008;83(3):280-**

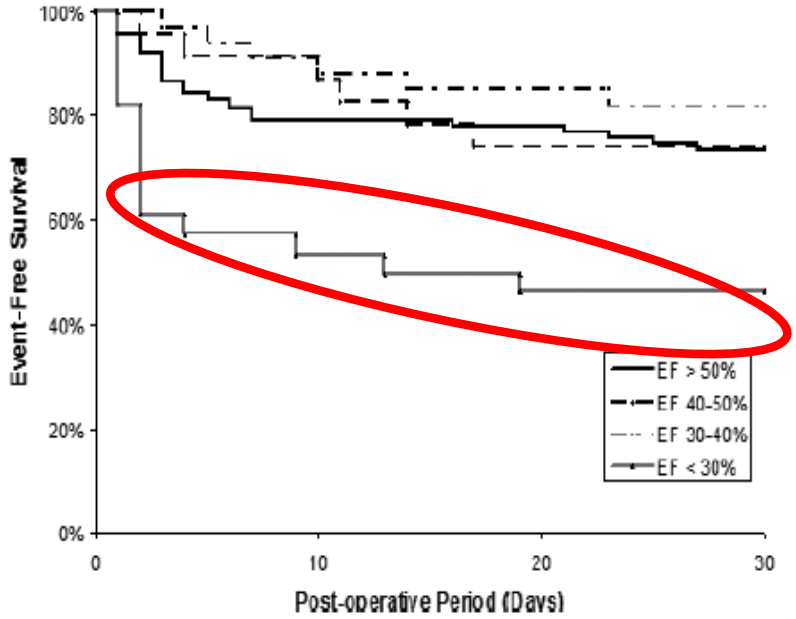




Perioperative Outcome and Long-Term Mortality for Heart Failure Patients Undergoing Intermediate- and High-Risk Noncardiac Surgery: Impact of Left Ventricular Ejection Fraction

ly, MD; Carol A. Waksmonski, MD; Robert K. Altman, MD;
son, MD; Alex Reyentovich, MD; Mathew S. Maurer, MD
e Columbia University Medical Center and New York Presbyterian
al, New York, NY

Congest Heart Fail. 2010 March ; 16(2): 45–49.



The Netherlands Journal of Medicine

APRIL 2008, VOL. 66, NO. 4

154

Preoperative levosimendan in heart failure patients undergoing noncardiac surgery

S. Katsaragakis[1], A. Kapralou[1], H. Markogiannakis[1*], G. Kofinas[2], E-M. Theodoraki[3], A. Larentzakis[1], E. Menenakos[1], D. Theodorou[1]

Table 2. *Haemodynamic data during levosimendan infusion*

Variable	Value 0 min	Value 10 min	Value 24 hrs	p value (0 *vs* 10 min)	p value (0 min *vs* 24 hrs)
Heart rate (beats/min)	75 ± 9.2	85 ± 8.4	89 ± 7.6	NS	0.05
Systolic arterial pressure (mmHg)	154 ± 17.5	150.5 ± 22.9	149 ± 15.6	NS	NS
Diastolic arterial pressure (mmHg)	73 ± 6.2	72 ± 9.4	71 ± 10.9	NS	NS
Mean arterial pressure (mmHg)	99 ± 9.3	97.5 ± 13.4	96 ± 11	NS	NS
Pulmonary artery pressure (mmHg)	19.5 ± 7.8	19 ± 7.2	20 ± 5.2	NS	NS
Pulmonary wedge pressure (mmHg)	10 ± 5.9	10 ± 6.3	11 ± 4.1	NS	NS
Cardiac output (l/min)	4.2 ± 0.5	5.1 ± 0.7	6.7 ± 0.8	0.01	0.01
Systemic vascular resistance (dyn. sec/cm^5)	1710.5 ± 223.2	1342 ± 264.6	970.5 ± 212.3	0.01	0.01

Table 3. *Comparison between echocardiographic measurements before levosimendan administration (day 0) and on the 7th postinfusion day (day 7)*[1]

Variable	Day 0	Day 7	p value
Left ventricular ejection fraction (%)	21 ± 4.2	32 ± 7.8	<0.01
Velocity time integral (cm)	21.2 ± 3.6	23.5 ± 3.2	<0.01
Velocity time integral x heart rate (cm/min)	1396.7 ± 418.3	2168.9 ± 235.1	<0.01
Pre-ejection period (msec)	90 ± 24.5	70 ± 22.2	0.04
Ejection time (msec)	270 ± 30.4	260 ± 34.4	0.04
Pre-ejection period/ejection time	0.3 ± 0.1	0.2 ± 0.1	0.04
V_{max} (m/sec)	1.2 ± 0.1	1.4 ± 0.1	<0.01
V_{min} (m/sec)	0.8 ± 0.1	0.9 ± 0.1	<0.01
P_{max} (mmHg)	6.1 ± 1.6	8 ± 1.1	<0.01
P_{min} (mmHg)	3 ± 0.5	4.3 ± 0.8	<0.01

To evaluate the effects of prophylactic preoperative levosimendan administration on left ventricular function in HF patients undergoing noncardiac surgery.

Conclusion: Prophylactic preoperative levosimendan treatment may be safe and efficient for perioperative optimisation of heart failure patients undergoing noncardiac surgery.

Prophylactic Preoperative Levosimendan Administration in Heart Failure Patients Undergoing Elective Non-Cardiac Surgery: A Preliminary Report

HJC

Hellenic J Cardiol 2009; 50: 185-192

Stilianos Katsaragakis, Athina Kapralou, Panagiotis Drimousis, Haridimos Markogiannakis, Andreas Larentzakis, George Kofinas, Panagiotis Misthos, Konstantinos Filis, Dimitrios Theodorou

Introduction: Preoperative optimization of cardiac failure (CF) patients undergoing non-cardiac surgery is of utmost importance. Levosimendan is a promising adjunct in our therapeutic repertoire for the treatment of CF; however, it has not been evaluated in CF patients undergoing non-cardiac surgery. Our objective was to evaluate the safety and efficacy of prophylactic preoperative levosimendan administration in these patients.

Methods: CF patients with ejection fraction <35% undergoing elective non-cardiac (abdominal) surgery during a 6-month-period were included in this prospective study. All patients, admitted to the Surgical Intensive Care Unit (SICU) one day preoperatively for levosimendan administration, received a bolus infusion (2.4 μg/kg) for 10 min followed by a 24-hour continuous infusion (0.1 μg/kg/min) at the end of which they were operated. Patients were under continuous hemodynamic monitoring in the SICU during levosimendan infusion and for 24 h post-infusion. Hemodynamic parameters, including heart rate, arterial pressure and pulmonary artery catheter data, were recorded before treatment, 10 min after drug initiation, and at 3-hour intervals to 24 h post-infusion. Echocardiography was performed before infusion and on the 7th post-infusion day.

Results: Nine patients were enrolled. Cardiac index (0-48 h, 95% CI: -2.790-0.432, p<0.001) and stroke volume index (0-48 h, 95% CI: -32.53-0.91, p=0.01) increased significantly at 24 h after drug initiation and remained increased for 24 h post-infusion. Systemic vascular resistance index decreased at 10 min and remained reduced during the whole observation period (0-48 h, 95% CI: 875.64-2378.14, p<0.001). Ejection fraction was significantly increased on the 7th post-infusion day (32.65 ± 7.32 vs. 20.89 ± 6.24, p<0.05). No adverse reactions, complications or deaths occurred during 30 days' follow up.

Conclusion: Prophylactic preoperative levosimendan treatment may be safe and efficient for the perioperative optimization of heart failure patients undergoing non-cardiac surgery.

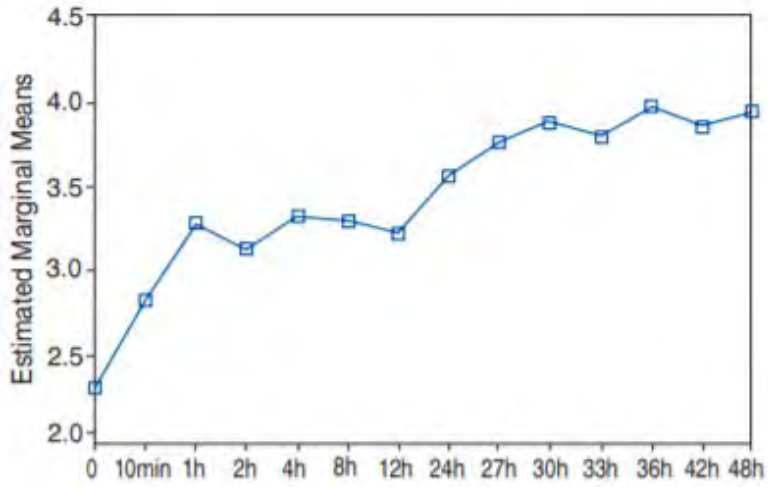


Figure 1. Changes in cardiac index (CIx) during and after levosi-

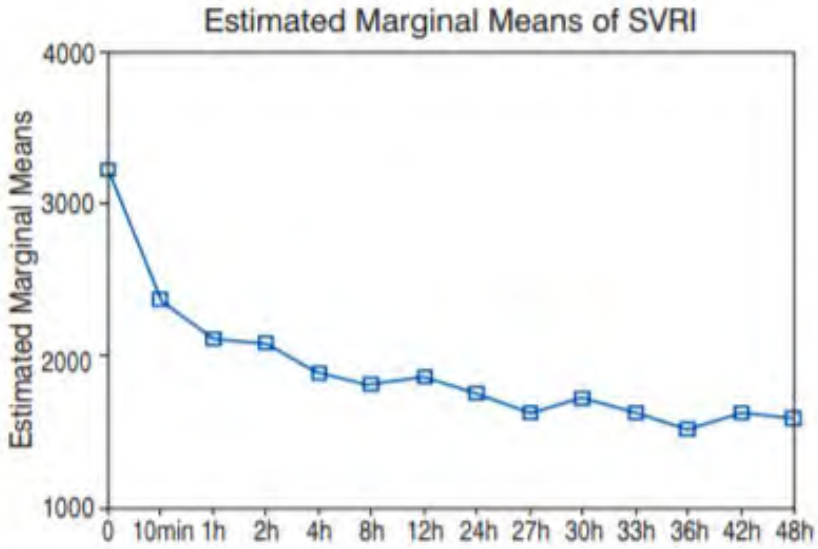


Figure 3. Changes in systemic vascular resistance index (SVRI) during and after infusion.

European Journal of Anaesthesiology 2008; 1–7

doi: 10.1017/S0265021508004080

Original Article

Levosimendan infusion improves haemodynamics in elderly heart failure patients undergoing urgent hip fracture repair

M. Ponschab*, N. Hochmair*, N. Ghazwinian*, T. Mueller†, W. Plöchl¶

Inclusión

To evaluate patients before being included into the study, we used two cardiac scoring systems that try to define the risk of severe cardiac complications in patients undergoing operative non-cardiac procedures. One was the Cardiac Risk Index by Goldman [17]; the other one was the Revised Cardiac Risk Index, published by Lee in 1999 [18]. Exclusion criteria were age under 18 yr, acute myocardial infarction on admission, heart failure due to hypertrophic cardiomyopathy (CMP), severe aortic valve stenosis, sustained ventricular tachycardia or ventricular fibrillation, a heart rate (HR) more than 120 beats min^{-1}, and a systolic blood pressure (BP) beyond 80 mmHg.

Exclusión

Anesteziol Reanimatol 2016; 61: 411-7

Preoperative Prevention of Heart Failure in Noncardiac Surgery

V. V. Likhvantsev[1,2], Yu. V. Ubasev[3], Yu. V. Skripkin[1,2],
T. S. Zabelina[1], V. A. Sungurov[3], V. V. Lomivorotov[4], D. N. Marchenko[5]

Congestive heart failure is consistently associated with adverse outcomes, and is characterized by a twofold increase in mortality in non-cardiac surgery. In this regard, developing the methods aimed to prevent and treat acute heart failure (AHF) in the intraoperative period remain a challenging problem.

Objective. To evaluate the efficacy of preoperative levosimendan infusion in reduction both mortality and duration of treatment of elderly patients with reduced left ventricular ejection fraction in non-cardiac surgery.

Material and Methods. Design: Multicenter blind randomized placebo-controlled study. Patients: 81 patients operated on abdominal organs. The main endpoint of the study: The length of stay in the Intensive Care Unit (ICU) and at the hospital were chosen as the primary endpoints. The secondary endpoints of the study were 30-day and annual mortality, the rate of acute myocardial infarction and stroke.

Results. Levosimendan infusion at a rate of 0,05 μg/kg/min – 0,1 μg/kg/min to patients with low left ventricular ejection fraction just before the surgery reduced the length of stay in ICU for 2 days and required hospital stay for 3 days. NT-proBNP showed the best ratio of sensitivity/specificity in predicting 30-day mortality in cumulative group: AUC=0,86 (90,77 to 0,93), $P<0,0001$. From other indicators the most informative were the Inotropes scoring, no change or decrease of a left ventricular ejection fraction, and cardiac index.

Conclusion. To reduce perioperative mortality, the intravenous infusion of levosimendan at a rate of 0,05–0,1 μg/kg/min in elderly patients with low left ventricular ejection fraction is recommened as a preoperative preparation the day before the alleged non-cardiac surgery.

Anesteziol Reanimatol 2016; 61: 411-7

Preoperative Prevention of Heart Failure in Noncardiac Surgery

Table 3. Postoperative mortality and the incidence of complications (myocardial infarction and stroke) in compared groups.

Indicators	Values of indicators in patients groups		*P*
	Control	Levosimendan	
30-day mortality	2/40 (5%)	1/41 (2.4%)	1.0
Annual mortality	4/40 (10%)	2/41 (4.9%)	0.36
Myocardial infarction within 30 days p/o	4/40 (10%)	1/41 (2.4%)	0.36
Stroke within 30 days p/o	2/40 (5%)	1/41 (2.4%)	1.0

Table 4. Some indicators of current perioperative period in compared groups.

Indicators	Values of indicators in patients groups		*P*
	Control	Levosimendan	
Inotropes	33/40 (82,5%)	18/41 (43,9%)	0,001
Inotropes score	7 (5; 8)	0 (0; 5)	0,00001
ICU, days	3 (2; 4)	1 (1; 2)	0,00001
Days inpatient	10 (9; 11)	7 (7; 8)	0,00000

Rev Esp Anestesiol Reanim. 2015;62(7):359–419

Revista Española de Anestesiología y Reanimación

www.elsevier.es/redar

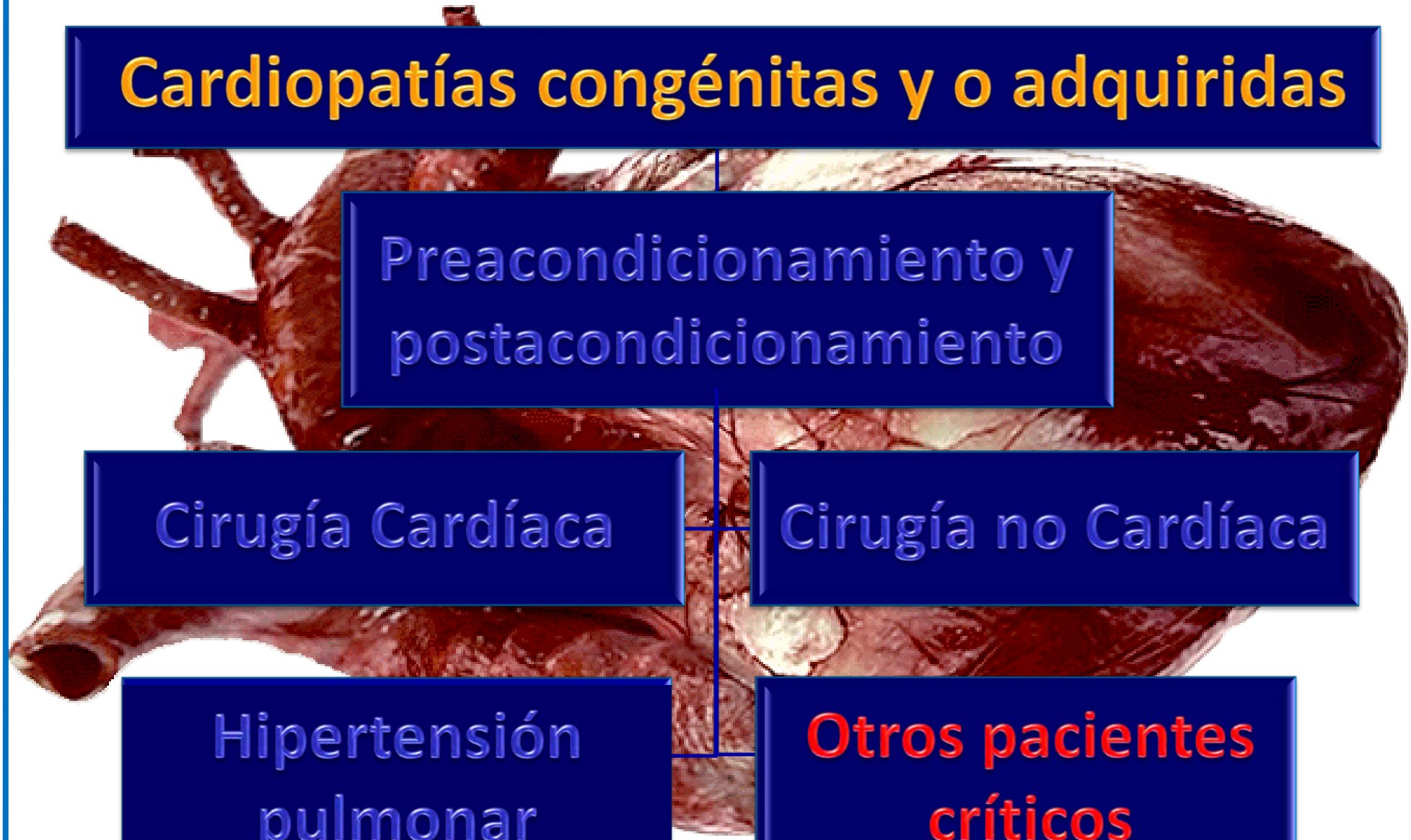
ELSEVIER

CONSENSUS STATEMENT

Clinical Practice Guideline (CPG). Recommendations on strategy for reducing risk of heart failure patients requiring noncardiac surgery

Reducing risk of heart failure patients in noncardiac surgery☆,☆☆

J. Alvarez Escudero[a], J.M. Calvo Vecino[a,b,*], S. Veiras[c], R. García[d], A. González[e], Working Group of the CPG**


Cardiopatías congénitas y o adquiridas
Preacondicionamiento y postacondicionamiento
Cirugía Cardíaca
Cirugía no Cardíaca
Hipertensión pulmonar
Otros pacientes críticos

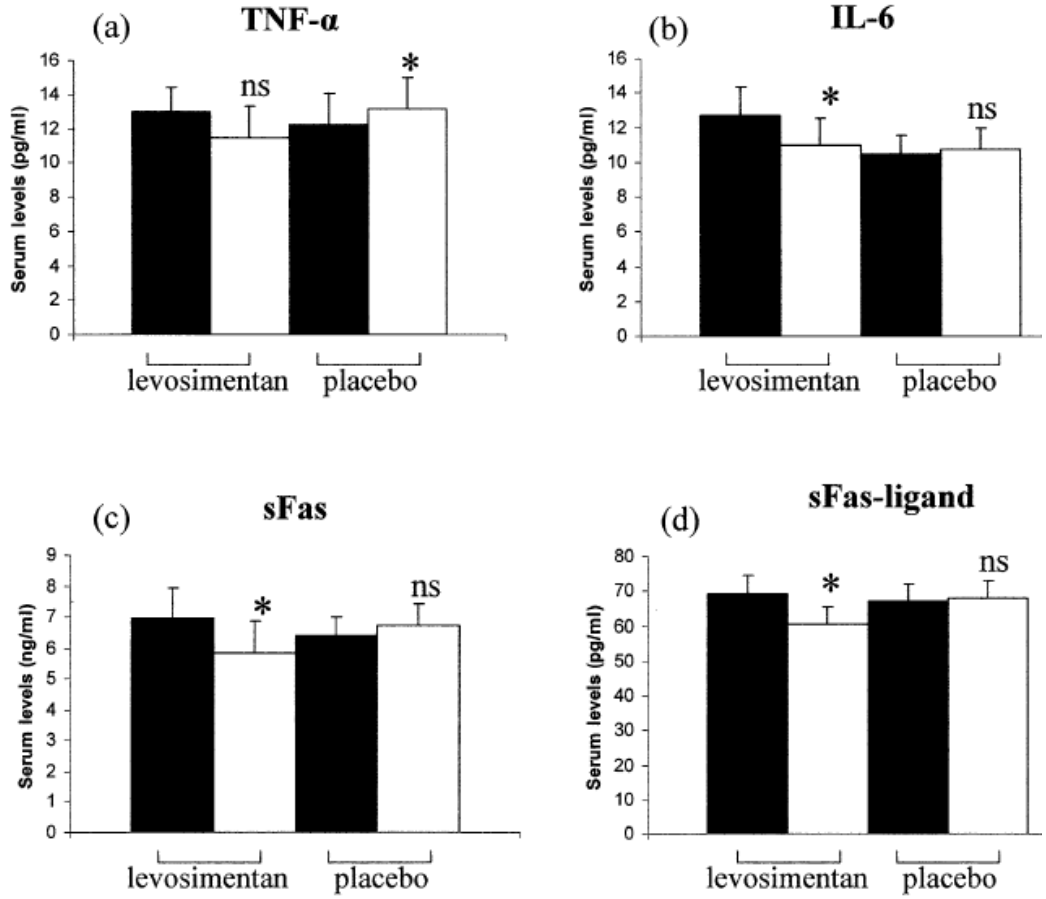
Effects of *Levosimendan* on Circulating Pro-inflammatory Cytokines and Soluble Apoptosis Mediators in Patients With Decompensated Advanced Heart Failure

John T. Parissis, MD, Stamatis Adamopoulos, MD, Charalambos Antoniades, MD
George Kostakis, MD, Antonios Ri
Efstathios Iliodromitis, MD, a

This randomized, placebo-controlled trial showed that levosimendan administration causes a significant reduction of circulating proinflammatory cytokine interleukin-6 and soluble apoptosis mediators, such as soluble Fas and Fas ligand in patients with decompensated heart failure. These immunomodulatory effects may lead to improvement of symptoms and echocardiographic markers of cardiac contractile performance in these patients.

(Am J Cardiol 2004;93:1309–1312)

The American Journal of Cardiology

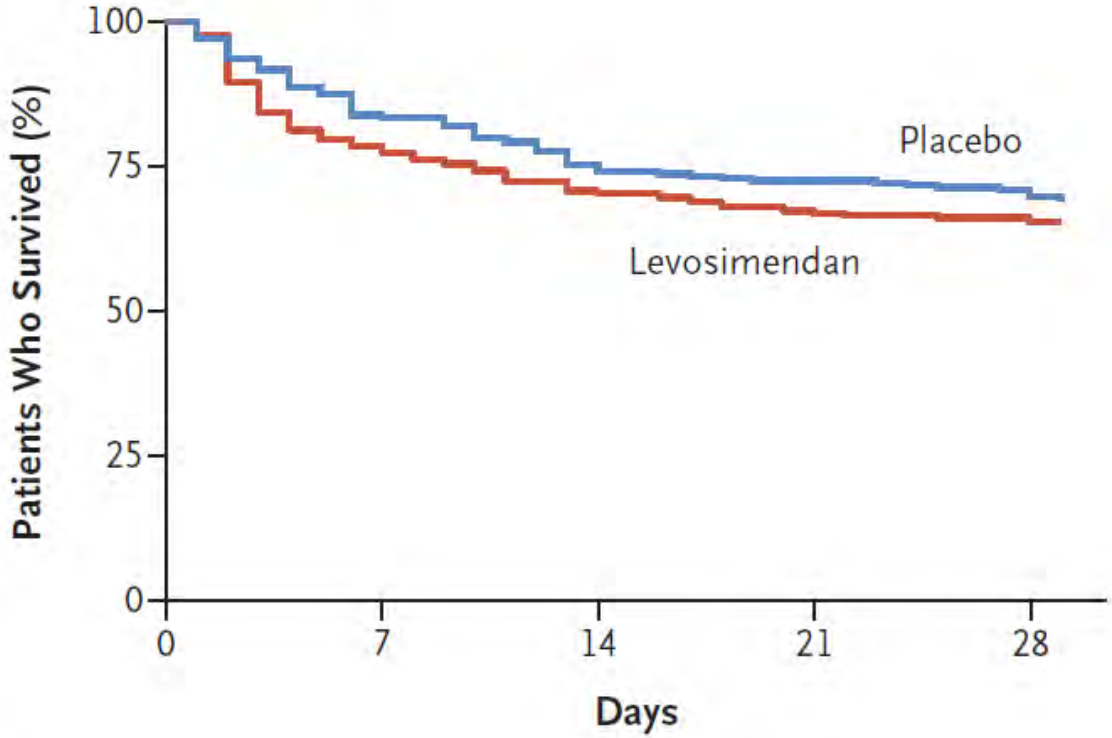


Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis

A.C. Gordon, G.D. Perkins, M. Singer, D.F. McAuley, R.M.L. Orme, S. Santhakumaran, A.J. Mason, M. Cross, F. Al-Beidh, J. Best-Lane, D. Brealey, C.L. Nutt, J.J. McNamee, H. Reschreiter, A. Breen, K.D. Liu, and D. Ashby

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2016;375:1638-48.



No. at Risk					
Levosimendan	258	203	183	174	171
Placebo	257	216	194	186	182

The addition of levosimendan to standard treatment in adults with sepsis was not associated with less severe organ dysfunction or lower mortality.

Anaesthesia and Intensive Care

Anaesth Intensive Care 2013; 41: 719-27

A comparison of doubutamine and levosimendan n hepatic blood flow in patients with a low cardiac output state after cardiac surgery: a randomised controlled study

J. ALVAREZ*. A. BALUJA†. S. SELAS‡. P. OTERO§. M. RIAL**. S. VEIRAS**. V. CARUEZO**. M. TABOADA††. I. RODRIGUEZ‡‡. J. CASTROAGUDIN§§. S. TOME***. A. RODRIGUEZ†††. J. RODRIGUEZ‡‡‡

Department Anesthesia and Surgical ICU, University Hospital, University of Santiago de Compostela, Spain.

SUMMARY

Liver dysfunction, d
but whether one inc
compared the syste
low cardiac output
were randomised to
an infusion of 0.2 μg
the study. The syste
than dobutamine (d
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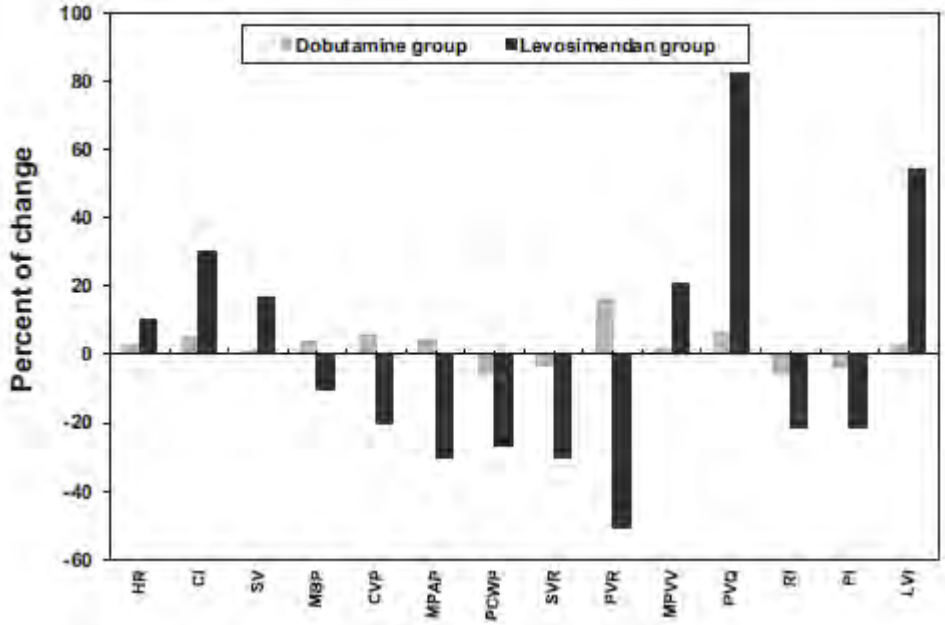

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Key Words: levosimen

J Card Surg. 2008; 23: 251-3

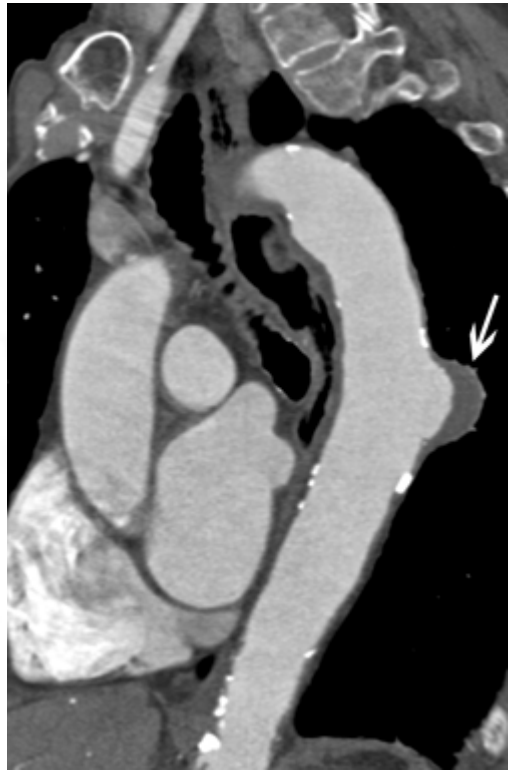
JOURNAL OF CARDIAC SURGERY

DEVOTED TO THE PRACTICES OF ADULT AND CONGENITAL HEART SURGERY, HEART/LUNG TRANSPLANTATION, AND MECHANICAL ASSISTANCE CIRCULATION

Levosimendan for Ischemic Preconditioning in Thoracic Aortic Aneurysm Repair

Ozgur Ersoy M.D., A. Baran Budak M.D., Ufuk Mungan M.D., Ufuk Tutun M.D., A. Ihsan Parlar M.D., Ferit Cicekcioglu M.D., A. Tulga Ulus M.D., S. Fehmi Katircioglu M.D.

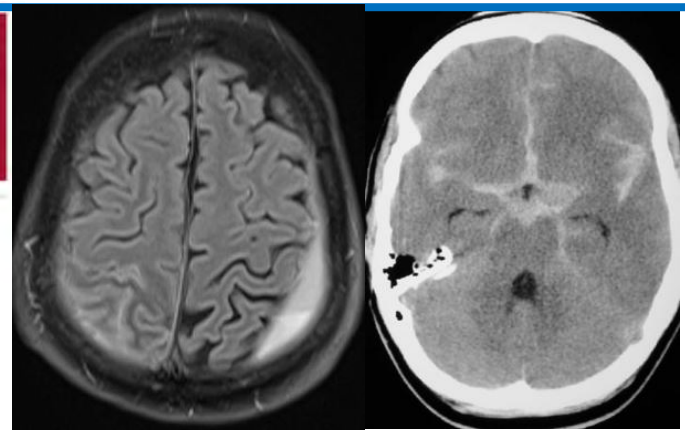
Abstract *Background and Aim:* Postoperative neurologic deficit is the most devastating complication after surgical thoracic aorta repair. Cerebrospinal fluid drainage and some medications are used for spinal cord protection during and after the operation. *Methods:* A 25-year-old patient applied to our clinic with a traumatic descending aortic aneurysm. We performed a surgical repair for the aneurysm but could not achieve to place a lumbar catheter to provide cerebrospinal fluid drainage. Levosimendan was chosen for spinal cord ischemic preconditioning because of its vasodilatory effects. *Results:* Postoperative course was uneventful. Hemodynamic and neurologic complication was not observed, and the patient was discharged from the hospital in the postoperative 5th day. *Conclusions:* Levosimendan can be used for preconditioning and spinal cord protection from ischemic injury during descending aorta repair. We clearly benefit from the vasodilator peculiarity of the drug for improving spinal cord perfusion.



The American Journal of Emergency Medicine
Volume 34, Issue 2, February 2016, Pages 298-306

Role of levosimendan in the management of subarachnoid hemorrhage

Varvarousi G, Xanthos T, Sarafidou P et al.



Aneurysmal subarachnoid hemorrhage (aSAH) is one of the leading causes of neurologic disability accounting for dismal long term survival rates. aSAH leads to a sudden increase in intracranial pressure and a massive sympathetic discharge. Excessive sympathetic stimulation leads to catecholamine mediated myocardial dysfunction and hemodynamic instability which may critically hamper brain perfusion and oxygenation. In the setting of acute aSAH, administration of vasoactive drugs aims at stabilizing impaired hemodynamics. However, studies have shown that conventional treatment with vasoactive drugs that lead to Ca^{+2} overload and increase myocardial oxygen consumption, fail to restore hemodynamics and decrease cerebral blood flow. Levosimendan is a non-adrenergic inotropic Ca^{+2} sensitizer with not only beneficial hemodynamic properties but also pleiotropic effects, contributing to its cardioprotective and neuroprotective role. Although there have been limited data available regarding the use of levosimendan in patients with aSAH, current evidence suggests that levosimendan may have a role in the setting of post-aSAH cardiomyopathy and decreased cerebral blood flow both in the emergency departments and in intensive care units. The purpose of this review is to provide an overview of studies of levosimendan therapy for aSAH, and describe current knowledge about the effects of levosimendan in the management of aSAH.

Research

Open Access

Levosimendan may improve survival in patients requiring mechanical assist devices for post-cardiotomy heart failure

Jan-Peter Braun[1], Dominik Jasulaitis[2], Maryam Moshirzadeh[2], Ulrich R Doepfmer[1], Marc Kastrup[1], Christian von Heymann[1], Pascal M Dohmen[3], Wolfgang Konertz[4] and Claudia Spies[5]

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Berlin, Germany
[2]Medical Doctor, Department of A
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[4]Professor of Cardiovascular Surg
Charité – University Medicine Ber
[5]Professor of Anesthesiology, Dir
University Hospital, Charité – Uni

Corresponding author: Jan-Peter

Received: 12 Aug 2005 Revisior

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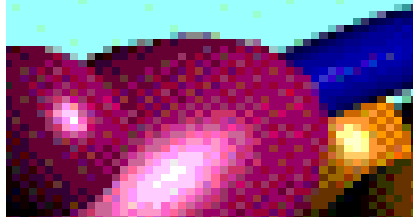
Postconditioning?



Levosimendan Versus an Intra-Aortic Balloon Pump in High-Risk Cardiac Patients

Vladimir V. Lomivorotov, MD, PhD, Vladimir A. Boboshko, MD, Sergey M. Efremov, MD, PhD, Igor A. Kornilov, MD, PhD, Alexandr M. Chernyavskiy, MD, PhD, Vladimir N. Lomivorotov, MD, PhD, Lubov G. Knazkova, MD, PhD, and Alexander M. Karaskov, MD, PhD

Objective: To test the hypothesis that levosimendan is more effective than preventive intra-aortic balloon pump (IABP) support in cardiac surgical ventricular ejection fraction to decr levels (primary endpoint) and imp namics.

Design: Prospective randomized t

Setting: Tertiary cardiothoracic re

(12 μg/kg for 10 minutes) after anesthesia induction. Hemodynamic and biochemical data and rate of complications

Levosimendan Versus Intra-aortic Balloon Pump in High-Risk Cardiac Surgery Patients

Luca Severi, MD,* Angela Lappa, MD,* Giovanni Landoni, MD,† Lucio Di Pirro, MD,* Sacha Jerome Luzzi, MD,* Patrizia Caravetta, MD,* Pierluigi Cipullo, MD,* and Antonio Menichetti, MD*

Objective: Patients with severe left ventricular dysfunction receive inotropic and mechanical circulatory support with an intra-aortic balloon pump (IABP) during the perioperative phase of cardiac surgery. The authors performed the first comparison of levosimendan versus an IABP in patients with poor left ventricular function undergoing cardiac surgery.

Design: A case-matched study.

Setting: A teaching hospital.

Participants: Twenty-two heart failure patients scheduled surgery

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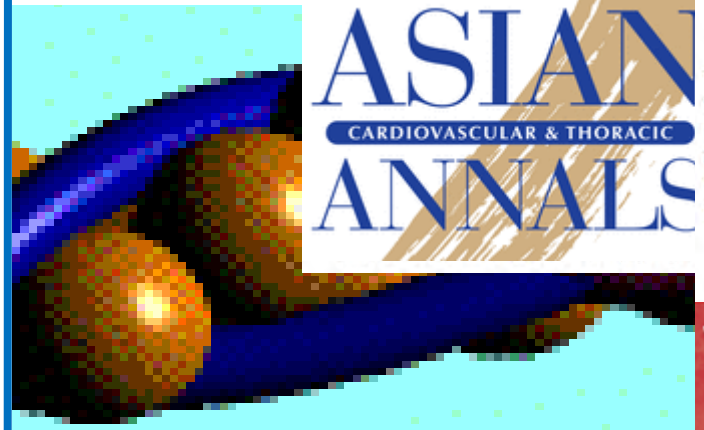
graphic data were collected together with the time on mechanical ventilation and 30-day mortality.

Measurements and Main Results: The length of intensive care unit stay was reduced in patients receiving levosimendan (median, 2.5; range, 1-3 days) compared with those receiving an IABP (median, 5; range, 3-6 days; $p = 0.01$). No deaths occurred in the levosimendan group; 1 patient died in the intra-aortic balloon pump group.

Conclusions: Patients receiving levosimendan had a shorter duration of intensive care stay than peers who received a preoperative IABP. The findings of this pilot study should be investigated further in a large randomized controlled study.

KEY WORDS: cardiac surgery, levosimendan, intra-aortic balloon pump, intensive care unit



ASIAN CARDIOVASCULAR & THORACIC ANNALS

Journal of Cardiothoracic and Vascular Anesthesia

BJA British Journal of Anaesthesia

British Journal of Anaesthesia, 117 (1): 52–8 (2016)

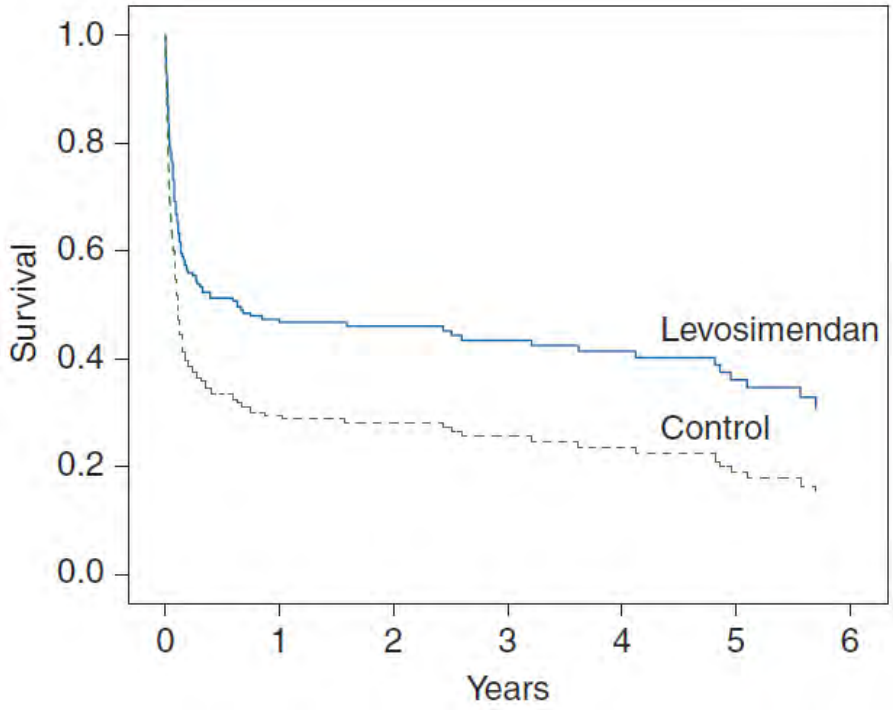
Beneficial effects of levosimendan on survival in patients undergoing extracorporeal membrane oxygenation after cardiovascular surgery

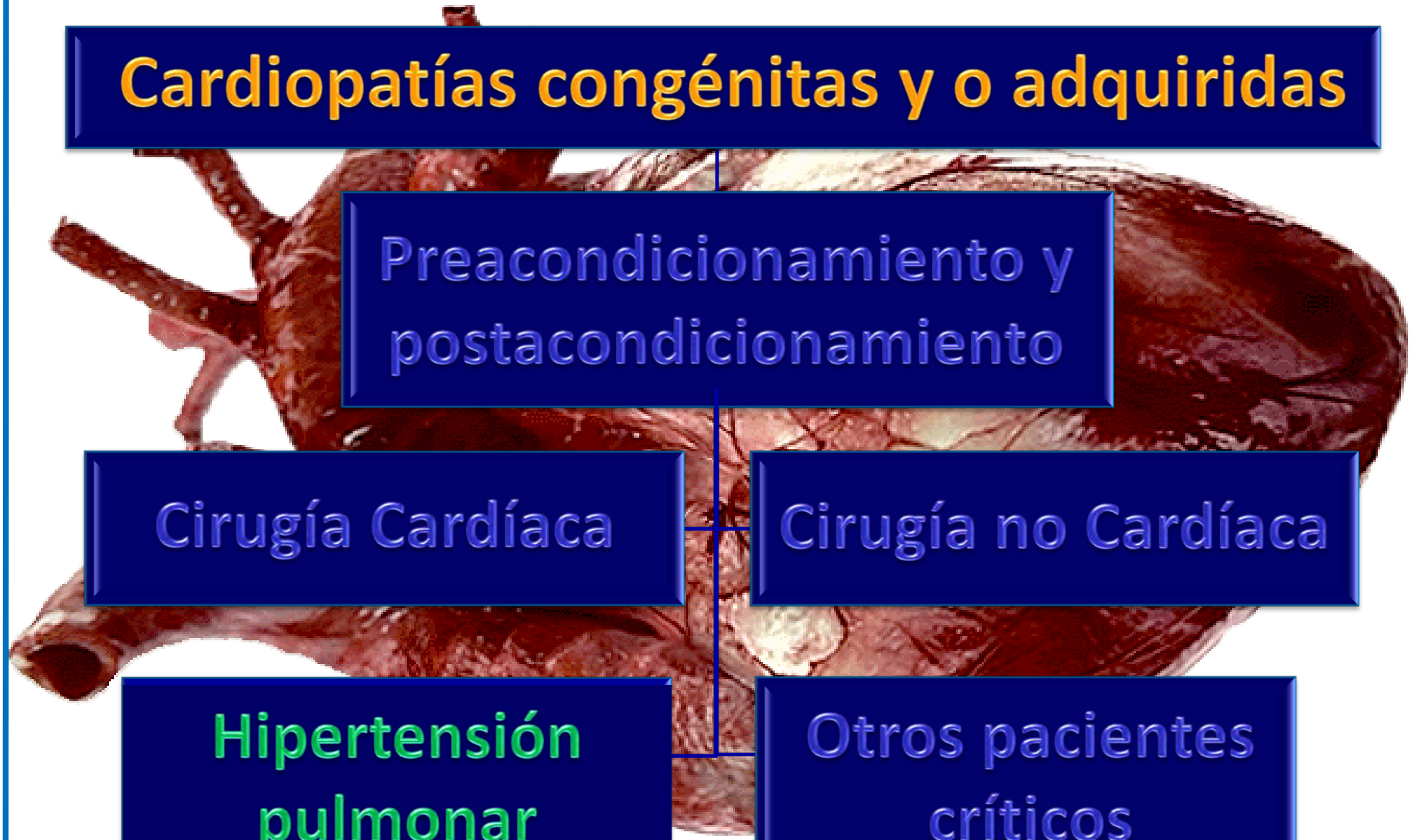
K. Distelmaier[1], C. Roth[1], L. Schrutka[1], C. Binder[1], B. Steinlechner[2], G. Heinz[1], I. M. Lang[1], G. Maurer[1], H. Koinig[3], A. Niessner[1], M. Hülsmann[1], W. Speidl[1] and G. Goliasch[1,*]

Methods: We enrolled a total of 240 patients undergoing veno-arterial ECMO therapy after cardiovascular surgery.

Results: During a median follow-up period of 37 months (interquartile range 19–67 months), 65% of patients died. Seventy-five per cent of patients received levosimendan treatment within the first 24 h after initiation of ECMO therapy.

Conclusions: These data suggest an association between levosimendan treatment and improved short- and long-term survival in patients undergoing ECMO support after cardiovascular surgery.




Cardiopatías congénitas y o adquiridas
Preacondicionamiento y postacondicionamiento
Cirugía Cardíaca
Cirugía no Cardíaca
Hipertensión pulmonar
Otros pacientes críticos

Pulmonary Circulation

Pulmonary Circulation 2018; 8: 1-7

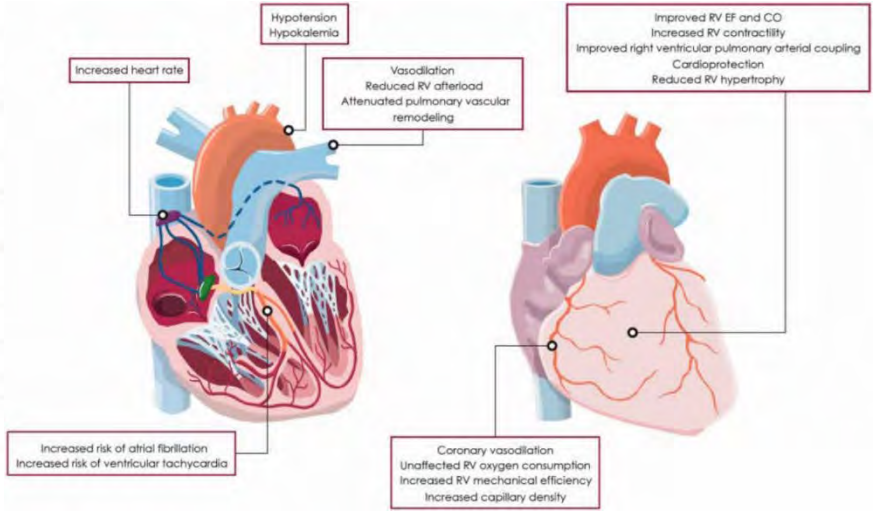
Pulmonary Circulation

Levosimendan in pulmonary hypertension and right heart failure

Mona Sahlholdt Hansen, Asger Andersen and Jens Erik Nielsen-Kudsk

Conclusions

The present literature on levosimendan in PH, despite limited in its extent, suggests that levosimendan is potentially favorable in treating PH and associated RV failure resulting from different etiologies such as PAH, LHD, and CHD. The existing literature does not provide adequate evidence to currently recommend the use of levosimendan in PH and associated RV failure. Larger, well-designed and sufficiently powered clinical trials should be carried out to evaluate the clinical efficacy and safety of levosimendan in this important group of patients with a high morbidity and mortality.



J Med Econ. 2008;11(3):415-29. JME

The costs of treating acute heart failure: an economic analysis of the SURVIVE trial

Gregory de Lissovoy , PhD MPH, Kathy Fraeman , SM, Jeff Salon , MD, Tatia Chay Woodward , MS MPH & Raimund Sterz , MD PhD

Conclusion: At an acquisition cost of €600 per vial, there is at least 50% likelihood that levosimendan is cost effective relative to dobutamine if willingness to pay is equal to or greater than €15,000 per life year gained.

J Cardiovasc Pharmacol 2011; 58 Journal of Cardiovascular Pharmacology

Cost-effectiveness of Levosimendan in Patients With Acute Heart Failure

Francesco Fedele, MD, Alessandra D'Ambrosi, MD, Noemi Bruno, MD, Carmen Caira, MD, Bruno Brasolin, MD, and Massimo Mancone, MD

Our view of these findings therefore is that the use of levosimendan slightly increased costs during the first hospitalization but that over the course of 12 months of follow-up reductions in rehospitalization plausibly attributable to levosimendan led to net reductions in the total direct medical costs in our cohort of patients with AHF.

J Med Econ. 2016;19(5):506-14. JME

Cost-benefits of incorporating levosimendan into cardiac surgery practice: German base case

Silvy Mardiguian, Matti Kivikko, Matthias Heringlake, Caitlin Smare, Evelina Bertranou, Marjo Apajasalo &

Conclusions:

The use of levosimendan in patients undergoing cardiac surgery who require inotropic support appears to be cost-saving. The results of the analysis provide a strong rationale to run local clinical studies with pharmacoeconomic end-points which would allow a much more precise computation of the benefits of levosimendan.

Eur J Health Econ 2010;11:185-93. The European Journal of Health Economics

Hospital costs for treatment of acute heart failure: economic analysis of the REVIVE II study

Greg de Lissovoy, Kathy Fraeman, John R. Teerlink, John Mullahy, Jeff Salon, Raimund Sterz, Amy Durtschi, Robert J. Padley

Conclusions

In the REVIVE II trial, patients treated with levo had shorter LOS and lower cost for the initial hospital admission relative to patients treated with SOC. Based on sub-group analysis of patients administered per the current label, levo appears cost-effective relative to SOC.

Adv Thera 2012; 29: 1037-50 Advances in therapy

Economic Evaluation of Levosimendan Versus Dobutamine for the Treatment of Acute Heart Failure in Italy

Carlo Lucioni · Alessandra D'Ambrosi · Silvio Mazzi · Piero Pollesello · Marjo Apajasalo · Francesco Fedele

Results: Based on the reference study, a cost analysis from the hospital perspective was carried out. The incremental cost of treatment with levosimendan (€697) was equivalent to the incremental savings (€694), the latter being obtained from the reduction in LOS (€508) and rehospitalization rate (€186).