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Long-term outcome of perioperative low cardiac output syndrome in cardiac surgery: 1-year results of a multicenter randomized trial

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1. Introduction

Perioperative myocardial dysfunction (also referred to as low cardiac output syndrome (LCOS) or perioperative acute heart failure) occurs frequently after cardiac surgery, and is a well-described risk factor for short-term morbidity and mortality [1,2]. Overall in-hospital mortality is reported to be around 20%, but in the most severe form it may be as high as 40% [3,4]. Long-term data on outcome of these very high-risk patients are currently lacking.

Inotropes are a cornerstone of treatment of perioperative myocardial dysfunction [5]. Among the different inotropic drugs, levosimendan has been suggested in meta-analyses to reduce mortality of patients with myocardial dysfunction, especially in the cardiac surgery setting [6,7]. Accordingly, we designed and conducted a multicenter, randomized, placebo-controlled trial (mRCT) to investigate whether levosimendan administration in cardiac surgery patients with perioperative myocardial dysfunction could reduce mortality (the Levosimendan to Reduce Mortality in High Risk Cardiac Surgery Patients. A Multicentre Randomized Controlled Trial [CHEETAH]) [8]. Short-term results of the CHEETAH trial has been previously published, showing no difference between levosimendan and placebo in terms of mortality. [9]. However, survival benefits can become evident only at extended follow-up as documented in similar settings (e.g. a previous trial on early revascularization for patients with cardiogenic shock following acute myocardial infarction) [10-12], and 1-year mortality is currently reported in major cardiogenic shock mRCTs [13-16]. Accordingly, we decided to include 1-year mortality among pre-specified secondary outcomes of the CHEETAH trial [8]. Moreover, predictors of long-term survival in patients with perioperative myocardial dysfunction have never been investigated.

The aims of the present investigation are to assess overall long-term mortality in cardiac surgery patients requiring hemodynamic support, to investigate whether levosimendan administration could improve 1-year survival in this high-risk subset of patients, and to identify early predictors of long-term mortality.

2. Materials and methods

This is a pre-specified secondary outcome analysis of a multicenter, randomized, double-blind, placebo-controlled trial performed in 14 centers in three countries. The trial was approved by Ethics Committee of all participating centers and registered on ClinicalTrials.gov (Registration no. NCT00994825). Details on the CHEETAH study design, procedure, and statistical analysis have been extensively described previously [8,9].

All patients scheduled for cardiac surgery were assessed for eligibility, and provided written informed consent before surgery. Patients subsequently meeting inclusion criteria either in the operating room (OR) or in the intensive care unit (ICU) were then randomized. Patients were included if they developed perioperative myocardial dysfunction, defined as preoperative left ventricular ejection fraction (LVEF) < 25%, preoperative need for intra-aortic balloon pump (IABP), need for high-dose inotropic drugs (defined as vasoactive-inotropic score ≥ 10) or IABP during weaning from cardiopulmonary by-

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pass (CPB) or within 24 h from surgery. Exclusion criteria were enrolment in another randomized trial, a previous adverse response to levosimendan or receipt of levosimendan in the previous 30 days, previous kidney or liver transplantation, liver cirrhosis, emergency operation, a decision to use extracorporeal membrane oxygenation (ECMO) already made, or the presence of a do-not-resuscitate order.

Patients were randomized (using a computer-generated, permuted block sequence stratified by center) in a 1:1 ratio to receive levosimendan or placebo, in addition to standard inotropic care. Allocated group was concealed in sealed, opaque, sequentially-numbered envelopes. Attending physicians, study investigators, and outcome assessors were blinded to treatment allocation. Levosimendan was administered as continuous infusion without loading dose, starting at a dose of 0.05 μg/kg/min. Dose could be then decreased to 0.025 μg/kg/min or increased up to 0.2 μg/kg/min at discretion of the attending physician, and continued for up to 48 h or until ICU discharge.

Primary outcome of the CHEETAH study was 30-day mortality. However, data on 1-year mortality were also collected as per study protocol [8]. All patients were followed-up until hospital discharge. A telephone follow-up was performed by blinded investigators at 1 year from randomization. In case of difficulties in follow-up by telephone, the following methods were used to ascertain 1-year vital status: sending a letter to the patient's home address; checking hospital records and surgical databases; contacting the patient's general practitioner; and contacting the city municipality. Causes of death were classified according to previously validated criteria [17].

2.1. Statistical analysis

Details on sample size calculation and statistical analysis have been described in details previously [8,9].

All analyses comparing levosimendan and placebo were performed according to the intention-to-treat principle, and no imputation for missing data was applied.

Data are presented as means ± standard deviation (SD) when the variables were normally distributed or as medians and interquartile ranges (IQR) for non-normally distributed variables. Dichotomous data were compared by 2-tailed χ^2 tests with the Yates correction or Fisher's exact tests when appropriate. The primary analysis was not adjusted for covariates. Continuous measurements were compared using the Mann-Whitney *U* test.

Logistic regression model using stepwise selection was used to identify predictors of 1-year mortality. Baseline and pre-randomization clinical data and center information were entered into the model if they had a univariate *p*-value of less than 0.10. Treatment group (levosimendan versus placebo) was forced into the multivariate model. In the multiple logistic regression analyses, clinical factors or potential confounding variables were expressed as odds ratio (OR) with 95% confidence interval (CI).

The trial was interrupted for futility after the second interim analysis, performed after enrolment of 50% of planned sample size. Details on sample size calculation, together with interim analysis and trial interruption, have been previously published [8,9].

All reported *p*-values are 2-sided. Data were stored electronically and analyzed with Stata (Stata Statistical Software: release 15, StataCorp LP, College Station, Texas).

3. Results

Between November 2009 and April 2016, a total of 4725 patients provided written informed consent. Among these, 506 patients were enrolled and randomized, with 248 assigned to levosimendan and 258 assigned to placebo. All patients completed 30-day follow-up, while one-year follow-up data were available for 505 patients (99.8%), who were included in the intention-to-treat analysis (Fig. 1).

Baseline and intraoperative characteristics of patients have been previously reported and are described in Supplementary Tables 1 and 2 [9]. The study drug was administered at a mean dose of 0.066 ± 0.031 μg/kg/min in the levosimendan group, with a volume equivalent to a in the placebo group ($P = .002$). The cumulative dose was 10.5 ± 4.05 mg in the levosimendan group and 9.9 ± 3.44 mg in the placebo group ($p = .12$). Hemodynamic parameters and doses of vasoactive drugs over the first three days of treatment are presented in the Supplementary Appendix.

Overall, 1-year mortality was 17.4%. (88/505). Mortality data at different time-points are reported in Table 1. There were no differences in ICU, hospital, or 30-days mortality, as previously reported [9]. At 1-year follow-up, a total of 41 patients (16.5%) died in the levosimendan group, while 47 (18.3%) died in the placebo group (absolute risk difference – 1.8; 95% CI -8.4 to 4.9; $P = .60$) (Table 1). There were no significant differences in survival rate over time as assessed by the Kaplan-Meier survival plots (hazard ratio 1.10; 95% CI 0.73 to 1.78; $P = .64$) (Fig. 2). Causes of death are presented in the Supplementary Appendix.

Results of univariate analysis of association between baseline variables and 1-year mortality are reported in Supplementary Table 3. Results of the multiple logistic regression analysis are shown in Table 2: female sex, history of chronic obstructive pulmonary disease (COPD), previous myocardial infarction, high baseline serum creatinine, low baseline hematocrit, low mean arterial pressure (MAP) at randomization, and duration of CPB were independently associated with increased risk of 1-year mortality, while chronic therapy with angiotensin-converting enzyme (ACE) inhibitors and mitral valve surgery were associated with a reduced risk.

4. Discussion

4.1. Key findings

The most important finding of the CHEETAH trial is that levosimendan administration in cardiac surgery patients who require postoperative hemodynamic support is not associated with improved 30-days and 1-year outcomes. Furthermore, multiple logistic regression analysis allowed to identify, for the first time, several risk factors associated with worse long-term outcome in this patient population.

Relationship to previous studies.

To the best of our knowledge, this is the first study reporting long-term outcome of patients requiring high-dose hemodynamic support in cardiac surgery. Short-term mortality for postoperative LCOS ranges from 12.5% to about 30%, depending on definition and procedures included [3,18-21]. Notably, mortality varies widely depending on severity of LCOS, as mortality rates may be lower than 5% for postoperative myocardial stunning [4], but rise up to more than 30% when over cardiogenic shock develops [3,4] and may reach 70% when mechanical circulatory support with ECMO is required [22].

Short-term [30-days] overall mortality rate in our study was 12.9%, which increased to 17.4% at 1-year, with no difference between the levosimendan and the placebo group. Previous studies performed in the setting of cardiogenic shock following acute myocardial infarction showed similar trends, with a steep decrease in survival in the first 30-days, and a relative stabilization of survival rates in the following months [10-16].

In the Intra-Aortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial, patients with cardiogenic shock following acute myocardial infarction were randomized to receive hemodynamic support with a IABP or standard treatment [13]. Similarly to our trial, IABP-SHOCK II investigators found no difference in both 30-days [13] and 1-year mortality between patients receiving IABP and patients receiving standard treatment without IABP [14]. Conversely, the SHOCK (SHould we emergently revascularize Occluded Coronaries for cardiogenic shock) trial showed an increased 1-year [11] and 6-year survival [12] in patients with cardiogenic shock receiving early revascularization as compared with medical management alone, despite no mortality difference at 30-days [10]. Finally, the CULPRIT-SHOCK (Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock) trial randomized patients with cardiogenic shock following acute myocardial infarction to PCI of the culprit lesion only or multivessel PCI. This trial found a short-term survival benefit [15] that disappeared at 1-year [16].

Our study allowed us to identify several baseline characteristics associated with 1-year mortality. These include female sex, history of

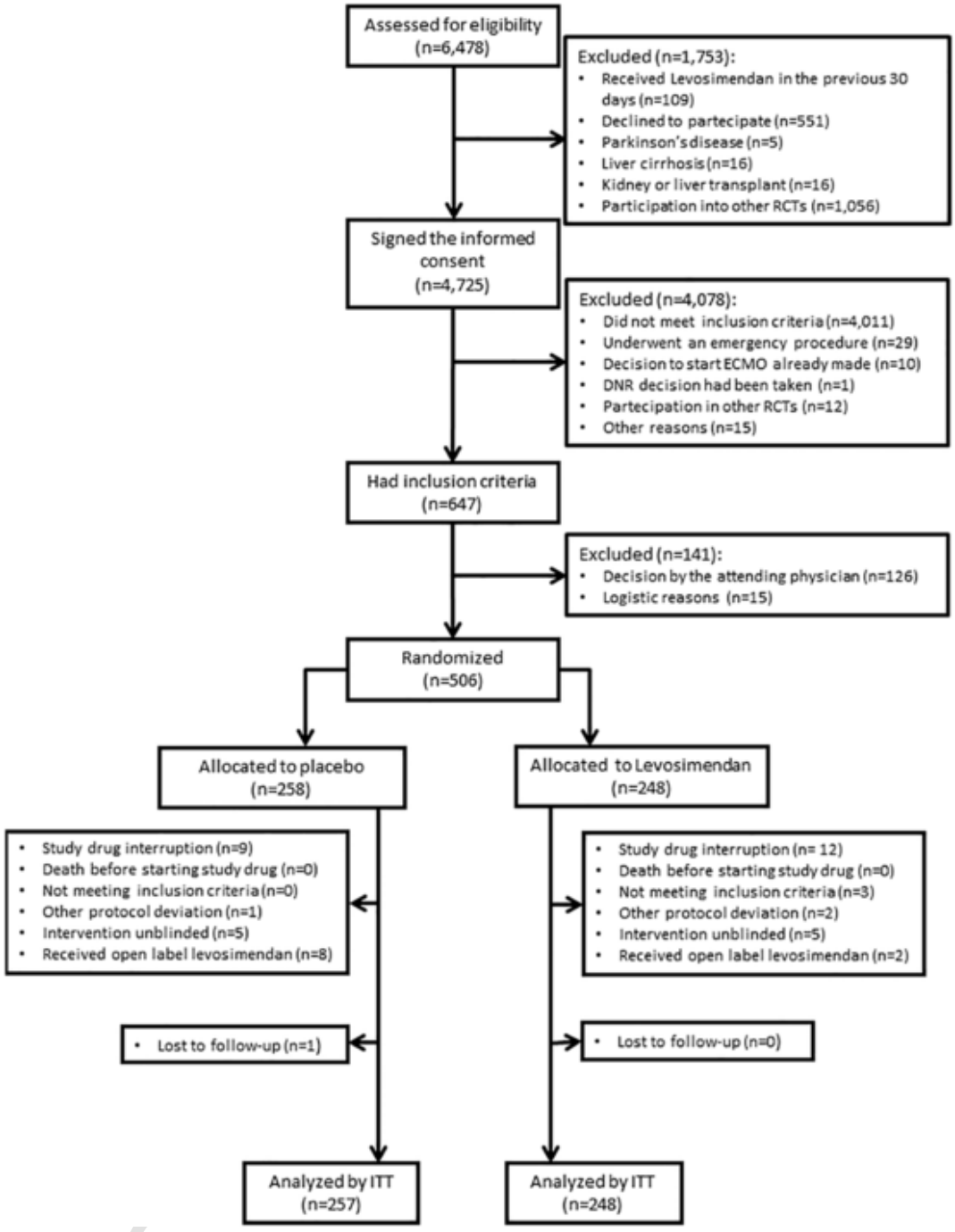

Fig. 1. Study flow-chart. DNR: do-not-resuscitate; ECMO: extracorporeal membrane oxygenation; ITT: intention-to-treat. Modified from Landoni et al. (9).

ous myocardial infarction, baseline serum creatinine, baseline hematocrit, MAP at randomization, duration of CPB, chronic therapy with ACE inhibitors and mitral valve surgery. Most of these factors are unmodifiable, baseline characteristics. For most of them, the association with worse long-term outcome is not surprising. Chronic lung and kidney disease, preoperative anemia, history of myocardial infarction, female sex, and prolonged duration of CPB are well known risk factors for postoperative mortality [23-27]. Of note, preoperative anemia is the only baseline modifiable risk factor, and studies investigating whether optimization of preoperative red cells mass improves outcome are ongoing. Interestingly, age and left ventricular ejection fraction were not associated with increased 1-year mortality risk in our study. In addition, chronic therapy with ACE inhibitors and mitral valve surgery were identified as potential protective factors. Preoperative administration of ACE inhibitors in cardiac surgery remains a controversial issue, with some studies reporting improved outcome and increased myocardial protection, and others suggesting an increased risk for perioperative hypotension and adverse renal outcome [28,29]. The favorable effect observed in our study may be related to the cardioprotective effect of ACE inhibitors [30] or may simply be a marker of optimized preoperative therapy. We did not collect data on preoperative discontinuation of chronic medication, therefore we are unable to draw conclusions on the beneficial effect of withholding ACE inhibitors in the 24 h preceding cardiac surgery.

Identification of mitral valve surgery as a protective mechanism is also unexpected and should be taken with caution, as mitral valve surgery is generally associated with a worse outcome compared with other cardiac surgical procedures. Mitral valve surgery is associated with a high risk of postoperative LCOS due to afterload mismatch [31,32]. However, the associated depres-

Table 1
Mortality at different time-points.

Outcome	Levosimendan (N = 248)		Placebo (N = 258)		Difference (95% CI)	P value
	Value	No. with missing data	Value	No. with missing data		
ICU mortality – no. (%)	24 (9.7%)	0	19 (7.4%)	0	2.3 (−2.6 to 7.2)	0.35
Hospital mortality – no. (%)	31 (12.5%)	0	31 (12.0%)	0	0.5 (−5.2 to 6.2)	0.87
30-day mortality – no. (%)	32 (12.9%)	0	33 (12.8%)	0	0.1 (−5.7 to 5.9)	0.97
1-year mortality – no. (%)	41 (16.5%)	0	47 (18.3%)	1	−1.8 (−8.4 to 4.9)	0.60

CI: confidence interval; ICU: intensive care unit.

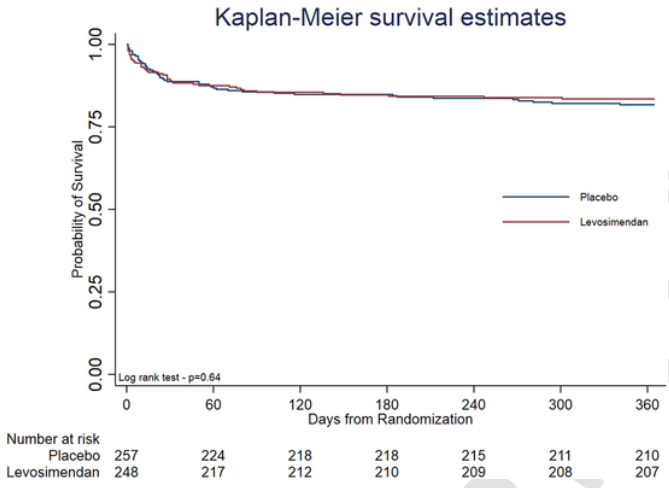

Fig. 2. Kaplan–Meier survival estimates of all-cause 1-year mortality.

Table 2
Predictors of 1-year mortality among baseline characteristics at the multiple logistic regression analysis.

Variable	OR	95% CI	P value
Randomization to levosimendan	0.97	0.57 to 1.68	0.93
History of COPD	3.61	1.79 to 7.27	<0.001
Duration of CPB [a]	1.01	1.00 to 1.01	<0.001
Baseline hematocrit [b]	0.94	0.91 to 0.97	<0.001
Female sex	2.26	1.28 to 3.99	0.01
History of myocardial infarction	2.19	1.22 to 3.94	0.01
Chronic ACE-inhibitors therapy	0.50	0.28 to 0.88	0.02
MAP at randomization [c]	0.98	0.96 to 0.99	0.02
Baseline serum creatinine [d]	1.60	1.02 to 2.53	0.04
Mitral valve surgery	0.56	0.32 to 0.99	0.049

ACE = angiotensin-converting enzyme; CPB = cardiopulmonary bypass; CI = confidence interval; COPD = chronic obstructive pulmonary disease; MAP = mean arterial pressure; OR = odds ratio.

[a] For one minute increase.
[b] For one percentage point increase.
[c] For one mmHg increase.
[d] For one mg/dL increase.

sion in myocardial function is generally transient and recovers spontaneously, requiring only short-term circulatory support. On the contrary, development of LCOS after coronary artery bypass grafting (CABG), aortic valve or aortic surgery may be related to different mechanisms (e.g. poor myocardial protection, myocardial ischemia) leading to a more severe degree of heart injury that potentially affect long-term prognosis. Notably, more than 50% of patients enrolled in our study underwent combined procedures including double- or triple-valve surgery, aortic-valve surgery, or CABG + valve surgery, while previous studies on LCOS or need for inotropic support generally focused on a specific procedure (isolated CABG, isolated aortic valve, or isolated mitral valve surgery).

Significance of study findings.

Overall, evidences from previous RCTs suggest that treatments addressing the primary cause of the disease (i.e. revascularization for coronary artery disease) have a disease-modifying effect that become evident once the acute condition has been stabilized. Conversely, supportive treatments such as levosimendan and IABP are unable to provide survival benefits neither at short-term nor at long-term.

This is a common finding in other critical care settings, where mRCTs comparing different vasopressors or inotropes have generally failed to show significant survival benefits [33].

Indeed, available guidelines only provide general recommendations with low level of evidence for the choice of different inotropes in various settings [5,34-38].

Our study demonstrates that the treatment of patients already being supported with high-dose catecholamines after cardiac surgery with (relatively) low-doses of levosimendan does not provide a long-term mortality benefit as compared with placebo.

Our findings do not confirm results of meta-analyses of RCTs suggested a mortality reduction associated with levosimendan administration both overall and in the specific cardiac surgery subpopulation [6,7]. However, meta-analyses should be considered hypothesis-generating, with high-quality mRCTs carrying the highest level of evidence. Notably, recent meta-analyses on levosimendan use found no beneficial effect on mortality with levosimendan when only low-risk-of-bias studies where analyzed [39,40].

Strengths and limitations of the study.

The CHEETAH trial was a pragmatic, international mRCT, thereby designed to carry the highest degree of external validity and level of evidence [41,42]. At the same time, we cannot exclude that a more strict protocol for hemodynamic management and earlier administration of levosimendan (i.e. preoperative or intraoperative) would have yielded different results, although both the LICORN and LEVO-CTS demonstrated that also preoperative administration do not confer additional benefit. Yet, all major RCTs on levosimendan use failed to demonstrate significant benefits in terms of mortality regardless of the clinical setting [43-46]. Similarly, higher doses might have exerted a more pronounced hemodynamic effect. However, this usually come at expense of higher catecholamines doses and higher incidence of side effects [46]. Due to the pragmatic nature of the study, choice of hemodynamic monitoring and concomitant treatment was at discretion of attending clinicians. Even if we can not exclude that few patients with primary vasoplegic, hypovolemic or obstructive shock might have been enrolled, this possibility is highly unlikely. Only 1.6% of patients were receiving norepinephrine only at randomization, mean cardiac index at randomization (i.e. after fluid status optimization and under full inotropic support) was 2.2 L/min/m^2, and most of the patients were still on inotropes on day 3 following randomization. All of these data are consistent with the clinical picture of myocardial dysfunction. Most patients were treated with high-dose ß-adrenergic agonists, that in some early studies have been shown to blunt the inotropic effect of levosimendan [47]. However, while designing the study, we believed that avoiding completely use of catecholamines would have been unfeasible and unethical. Similarly, use of levosimendan has been shown to be more effective than dobutamine in patients receiving chronic beta-blocker therapy, but pre-specified subgroup analyses showed no significant subgroup interaction [9]. At univariate analyses, several variables had a p-value <.1 for mortality. As per convention, a logistic regression should include not more

than one variable per 10 events, therefore sample size and event rate may not be appropriate to allow firm conclusions. Finally, we limited our 1-year follow-up to mortality data, while we did not collect data on long-term quality of life, ventricular function, or renal outcome.

Future studies and perspectives.

Despite negative results, several investigators believe that there might be room for future trials on levosimendan use. The most promising settings remain the preoperative optimization of patients with severely reduced LVEF undergoing CABG [48] and intermittent levosimendan administration in patients with advanced chronic heart failure with the aim of improving quality of life and reducing hospitalizations for acute decompensations [49].

5. Conclusions

In this international mRCT, levosimendan administration in cardiac surgery patients with perioperative LCOS did not result in improved 1-year survival. Overall, 1-year mortality of patients with LCOS was 17.4%. Independent risk factors for 1-year mortality are non-modifiable and include: female sex, history of COPD, previous myocardial infarction, baseline serum creatinine, baseline hematocrit, MAP at randomization, and duration of CPB.

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Levosimendan was provided free of charge by the manufacturer (Orion) to centers that recruited patients in Italy.

The funders and Orion had no role in trial design, data collection and analysis, writing of the manuscript, or the decision to submit the manuscript for publication.

Declaration of Competing Interest

Dr. Fabio Guarracino received speaker fees from Amomed, Baxter, Edwards, Masimo and Orion.

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Trial protocol

The trial protocol has been previously published (see Zangrillo et al. [8], and Landoni et al. [9]).

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Data analysis and interpretation: A. Zangrillo, V.V. Lomivorotov, A. Belletti, R. Lembo, A. Yavorovskiy, G. Landoni,

Manuscript drafting: A. Zangrillo, A. Belletti, E.V. Fominskiy.

Manuscript review: V.V. Lomivorotov, A. Pisano, M.G. Calabrò, L. Brazzi, E.V. Grigoryev, F. Guarracino, F. Monaco, E. Garofalo, M. Crivellari, V.V. Likhvantsev, G. Paternoster, V.V. Pasyuga, A. Oriani, R. Lembo, A. Bianchi, A.M. Scandroglio, M.N. Abubakirov, N. Di Tomasso, A. Yavorovskiy, G. Landoni.

All Authors approved the final version of the manuscript submitted for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2020.04.005.

References

[1] V V Lomivorotov, S M Efremov, M Y Kirov, E V Fominskiy, A M Karaskov Low-cardiac-output syndrome after cardiac surgery. J Cardiothorac Vasc Anesth 2017;31:291–308. doi:10.1053/j.jvca.2016.05.029.

[2] J L Pérez Vela, J C Martín Benítez, M Carrasco González, M A de la Cal López, R Hinojosa Pérez, V Sagredo Meneses, et al. Grupo de Trabajo de Cuidados Intensivos Cardiológicos y RCP de SEMICYUC, con el aval científico de la SEMICYUC. [Clinical practice guide for the management of low cardiac output syndrome in the postoperative period of heart surgery]. Med Intensiva 2012;36(4):e1-44. doi:10.1016/j.medin.2012.02.007.

[3] J L Pérez Vela, J J Jiménez Rivera, MÁ Alcalá Llorente, B González de Marcos, H Torrado, C García Laborda, et al. Low cardiac output syndrome in the postoperative period of cardiac surgery. Profile, differences in clinical course and prognosis. The ESBAGA study. Med Intensiva 2018;42:159–167. doi:10.1016/j.medin.2017.05.009.

[4] A Rudiger, F Businger, M Streit, E R Schmid, M Maggiorini, F Follath Presentation and outcome of critically ill medical and cardiac-surgery patients with acute heart failure. Swiss Med Wkly 2009;139:110–116. smw-12446.

[5] A Mebazaa, A A Pitsis, A Rudiger, W Toller, D Longrois, S E Ricksten, et al. Clinical review: practical recommendations on the management of perioperative heart failure in cardiac surgery. Crit Care 2010;14:201. doi:10.1186/cc8153.

[6] G Landoni, G Biondi-Zoccai, M Greco, T Greco, E Bignami, A Morelli, et al. Effects of levosimendan on mortality and hospitalization. A meta-analysis of randomized controlled studies. Crit Care Med 2012;40:634–646. doi:10.1097/CCM.0b013e318232962a.

[7] R W Harrison, V Hasselblad, R H Mehta, R Levin, R A Harrington, J H Alexander Effect of levosimendan on survival and adverse events after cardiac surgery: a meta-analysis. J Cardiothorac Vasc Anesth 2013;27:1224–1232. doi:10.1053/j.jvca.2013.03.027.

[8] A Zangrillo, G Alvaro, A Pisano, F Guarracino, R Lobreglio, N Bradic, et al. A randomized controlled trial of levosimendan to reduce mortality in high-risk cardiac surgery patients (CHEETAH): rationale and design. Am Heart J 2016;177:66–73. doi:10.1016/j.ahj.2016.03.021.

[9] G Landoni, V V Lomivorotov, G Alvaro, R Lobreglio, A Pisano, F Guarracino, et al. Levosimendan for hemodynamic support after cardiac surgery. N Engl J Med 2017;376:2021–2031. doi:10.1056/NEJMoa1616325.

[10] J S Hochman, L A Sleeper, J G Webb, T A Sanborn, H D White, J D Talley, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should we emergently revascularize occluded coronaries for cardiogenic shock. N Engl J Med 1999;341:625–634. doi:10.1056/NEJM199908263410901.

[11] J S Hochman, L A Sleeper, H D White, V Dzavik, S C Wong, V Menon, et al. Should we emergently revascularize occluded coronaries for cardiogenic shock. One-year survival following early revascularization for cardiogenic shock. JAMA 2001;285:190–192. doi:10.1001/jama.285.2.190.

[12] J S Hochman, L A Sleeper, J G Webb, V Dzavik, C E Buller, SHOCK Investigators, et al. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. JAMA 2006;295:2511–2515. doi:10.1001/jama.295.21.2511.

[13] H Thiele, U Zeymer, F J Neumann, M Ferenc, H G Olbrich, J Hausleiter, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med 2012;367:1287–1296. doi:10.1056/NEJMoa1208410.

[14] H Thiele, U Zeymer, F J Neumann, M Ferenc, H G Olbrich, J Hausleiter, et al. Intraaortic Balloon Pump in cardiogenic shock II (IABP-SHOCK II) trial Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. Lancet 2013;382:1638–1645. doi:10.1016/S0140-6736(13)61783-3.

[15] H Thiele, I Akin, M Sandri, G Fuernau, S de Waha, R Meyer-Saraei, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. N Engl J Med 2017;377:2419–2432. doi:10.1056/NEJMoa1710261.

[16] H Thiele, I Akin, M Sandri, S de Waha-Thiele, R Meyer-Saraei, G Fuernau, et al. One-year outcomes after PCI strategies in cardiogenic shock. N Engl J Med 2018;379:1699–1710. doi:10.1056/NEJMoa1808788.

[17] E Ridgeon, R Bellomo, J Myburgh, M Saxena, M Weatherall, R Jahan, et al. Validation of a classification system for causes of death in critical care: an assessment of inter-rater reliability. Crit Care Resusc 2016;18:50–54.

[18] C Ellenberger, T Sologashvili, M Cikirikcioglu, G Verdon, J Diaper, T Cassina, et al. Risk factors of postcardiotomy ventricular dysfunction in moderate-to-high risk patients undergoing open-heart surgery. Ann Card Anaesth 2017;20:287–296. doi:10.4103/aca.ACA_60_17.

[19] M Maganti, M Badiwala, A Sheikh, H Scully, C Feindel, T E David, et al. Predictors of low cardiac output syndrome after isolated mitral valve surgery. J Thorac Cardiovasc Surg 2010;140:790–796. doi:10.1016/j.jtcvs.2009.11.022.

[20] M D Maganti, V Rao, M A Borger, J Ivanov, T E David Predictors of low cardiac output syndrome after isolated aortic valve surgery. Circulation 2005;112(9 Suppl):I448–I452. doi:10.1161/CIRCULATIONAHA.104.526087.

[22] F Biancari, A Perrotti, M Dalén, M Guerrieri, A Fiore, D Reichart, et al. Meta-analysis of the outcome after postcardiotomy venoarterial extracorporeal membrane oxygenation in adult patients. J Cardiothorac Vasc Anesth 2018;32:1175–1182. doi:10.1053/j.jvca.2017.08.048.
[23] H Z Saleh, K Mohan, M Shaw, O Al-Rawi, H Elsayed, M Walshaw, et al. Impact of chronic obstructive pulmonary disease severity on surgical outcomes in patients undergoing non-emergent coronary artery bypass grafting. Eur J Cardiothorac Surg 2012;42:108–113. discussion 113 https://doi.org/10.1093/ejcts/ezr271.
[24] W A Cooper, S M O'Brien, V H Thourani, R A Guyton, C R Bridges, L A Szczech, et al. Impact of renal dysfunction on outcomes of coronary artery bypass surgery: results from the Society of Thoracic Surgeons National Adult Cardiac Database. Circulation 2006;113:1063–1070. doi:10.1161/CIRCULATIONAHA.105.580084.
[25] M Ranucci, U Di Dedda, S Castelvecchio, L Menicanti, A Frigiola, G Pelissero, et al. Impact of preoperative anemia on outcome in adult cardiac surgery: a propensity-matched analysis. Ann Thorac Surg 2012;94:1134–1141. doi:10.1016/j.athoracsur.2012.04.042.
[26] M D McEvoy, R Gupta, E J Koepke, A Feldheiser, F Michard, D Levett, et al. Perioperative Quality Initiative consensus statement on postoperative blood pressure, risk and outcomes for elective surgery. Br J Anaesth 2019;122:575–586. doi:10.1016/j.bja.2019.01.019.
[27] M Alam, V V Lee, M A Elayda, S A Shahzad, E Y Yang, V Nambi, et al. Association of gender with morbidity and mortality after isolated coronary artery bypass grafting. A propensity score matched analysis. Int J Cardiol 2013;167:180–184. doi:10.1016/j.ijcard.2011.12.047.
[28] M Bhatia, H Arora, P A Kumar Pro: ACE inhibitors should be continued perioperatively and prior to cardiovascular operations. J Cardiothorac Vasc Anesth 2016;30:816–819. doi:10.1053/j.jvca.2016.04.003.
[29] A Disque, J Neelankavil Con: ACE inhibitors should be stopped prior to cardiovascular surgery. J Cardiothorac Vasc Anesth 2016;30:820–822. doi:10.1053/j.jvca.2016.01.016.
[30] U Benedetto, G Melina, F Capuano, C Comito, R Bianchini, C Simon, et al. Preoperative angiotensin-converting enzyme inhibitors protect myocardium from ischemia during coronary artery bypass graft surgery. J Cardiovasc Med (Hagerstown) 2008;9:1098–1103. doi:10.2459/JCM.0b013e32830a6daf.
[31] J Ross Jr. Afterload mismatch in aortic and mitral valve disease: implications for surgical therapy. J Am Coll Cardiol 1985;5:811–826. doi:10.1016/s0735-1097(85)80418-6.
[32] D H Harpole Jr., S A Gall Jr., W G Wolfe, J S Rankin, R H Jones Effects of valve replacement on ventricular mechanics in mitral regurgitation and aortic stenosis. Ann Thorac Surg 1996;62:756–761. doi:10.1016/s0003-4975(96)00378-5.
[33] D Annane, L Ouanes-Besbes, D de Backer, B Du, A C Gordon, et al. A global perspective on vasoactive agents in shock. Intensive Care Med 2018;44:833–846. doi:10.1007/s00134-018-5242-5.
[34] M H Møller, C Claudius, E Junttila, M Haney, A Oscarsson-Tibblin, A Haavind, et al. Scandinavian SSAI clinical practice guideline on choice of first-line vasopressor for patients with acute circulatory failure. Acta Anaesthesiol Scand 2016;60:1347–1366. doi:10.1111/aas.12780.
[35] M H Møller, A Granholm, E Junttila, M Haney, A Oscarsson-Tibblin, A Haavind, et al. Scandinavian SSAI clinical practice guideline on choice of inotropic agent for patients with acute circulatory failure. Acta Anaesthesiol Scand 2018;62:420–450. doi:10.1111/aas.13089.
[36] A Mebazaa, A Combes, S van Diepen, A Hollinger, J N Katz, G Landoni, et al. Management of cardiogenic shock complicating myocardial infarction. Intensive Care Med 2018;44:760–773. doi:10.1007/s00134-018-5214-9.
[37] A Rhodes, L E Evans, W Alhazzani, M M Levy, M Antonelli, R Ferrer, et al. Surviving Sepsis Campaign: international guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med 2017;43:304–377. doi:10.1007/s00134-017-4683-6.
[38] S van Diepen, J N Katz, N M Albert, T D Henry, A K Jacobs, N K Kapur, et al. Contemporary management of cardiogenic shock: a scientific statement from the American heart association. Circulation 2017;136:e232–e268. doi:10.1161/CIR.0000000000000525.
[39] A Putzu, S Clivio, A Belletti, T Cassina Perioperative levosimendan in cardiac surgery: a systematic review with meta-analysis and trial sequential analysis. Int J Cardiol 2018;251:22–31. doi:10.1016/j.ijcard.2017.10.077.
[40] G Koster, J Wetterslev, C Gluud, J G Zijlstra, T W Scheeren, I C van der Horst, et al. Effects of levosimendan for low cardiac output syndrome in critically ill patients: systematic review with meta-analysis and trial sequential analysis. Intensive Care Med 2015;41:203–221. doi:10.1007/s00134-014-3604-1.
[41] M Baiardo Redaelli, G Landoni, S Di Sanzo, S Frassoni, C Sartini, L Cabrini, et al. Interventions affecting mortality in critically ill and perioperative patients: a systematic review of contemporary trials. J Crit Care 2017;41:107–111. doi:10.1016/j.jcrc.2017.05.005.
[42] G Landoni, M Pieri, P J Young, R Bellomo Why do multicenter randomized controlled trials not confirm the positive findings of single center randomized controlled trials in acute care? Minerva Anestesiol 2019;85:194–200. doi:10.23736/S0375-9393.18.13070-7.
[43] R H Mehta, J D Leimberger, S van Diepen, J Meza, A Wang, R Jankowich, et al. Levosimendan in patients with left ventricular dysfunction undergoing cardiac surgery. N Engl J Med 2017;376:2032–2042. doi:10.1056/NEJMoa1616218.
[44] A Mebazaa, M S Nieminen, M Packer, A Cohen-Solal, F X Kleber, S J Pocock, et al. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. JAMA 2007;297:1883–1891. doi:10.1001/jama.297.17.1883.
[45] M Packer, W Colucci, L Fisher, B M Massie, J R Teerlink, J Young, et al. Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. JACC Heart Fail 2013;1:103–111. doi:10.1016/j.jchf.2012.12.004.
[48] S van Diepen, R H Mehta, J D Leimberger, S G Goodman, S Fremes, R Jankowich, et al. Levosimendan in patients with reduced left ventricular function undergoing isolated coronary or valve surgery. J Thorac Cardiovasc Surg 2019. doi:10.1016/j.jtcvs.2019.06.020. In press.
[49] G Pölzl, J Altenberger, L Baholli, P Beltrán, A Borbély, J Comin-Colet, et al. Repetitive use of levosimendan in advanced heart failure: need for stronger evidence in a field in dire need of a useful therapy. Int J Cardiol 2017;243:389–395. doi:10.1016/j.ijcard.2017.05.081.