

**Clinical Study Protocol: 10 /18.07.17**

**Thiamine supplementation in high risk cardiac surgery patients  
(APPLY trial)**

**Sponsor:** Meshalkin Research Institution of Pathology of Circulation  
Russia. Novosibirsk. Rechkunovskaya 15. 7 (383)347-60-66

**Sponsor Contact:** Lomivorotov V.V. MD. PHD

Revision Number: 4.0

Issue Date: July 18. 2017

# ThiAmine SuPPLementation in High Risk Cardiac SurgerY Patients (APPLY trial)

## Background

Over the past decade, there has been a significant decline in cardiac surgery-associated mortality, despite an increase in procedural complexity. Although the average perioperative mortality currently is 1% to 2%, the rate of major complications remains high. Advanced age, congestive heart failure, redo surgery and some other factors contribute to increased morbidity and mortality in patients undergoing surgery under cardiopulmonary bypass.

Although low-cardiac-output syndrome is considered to be the most common and the most serious complication leading to multiple organ dysfunction syndrome after cardiac surgery, recent trials have elucidated that sepsis-associated organ dysfunction often occurs in the adequate perfusion settings [1, 2]. It seems that mitochondrial dysfunction (inability to utilize oxygen for aerobic metabolism even in the presence of adequate oxygen delivery) plays an important role in this phenomenon. In clinical practice, plasma levels of lactate and mixed venous oxygen saturation are used as surrogate markers of tissue metabolism. For example, increased lactate production in anaerobic state is associated with morbidity and mortality in different clinical settings [3, 4, 5].

In normal physiological state, pyruvate steps in into the mitochondria by the enzyme pyruvate dehydrogenase and further undergoes pyruvate decarboxylation to acetylcoenzyme which forwarded to tricarboxylic acid [TCA] cycle (Fig. 1).

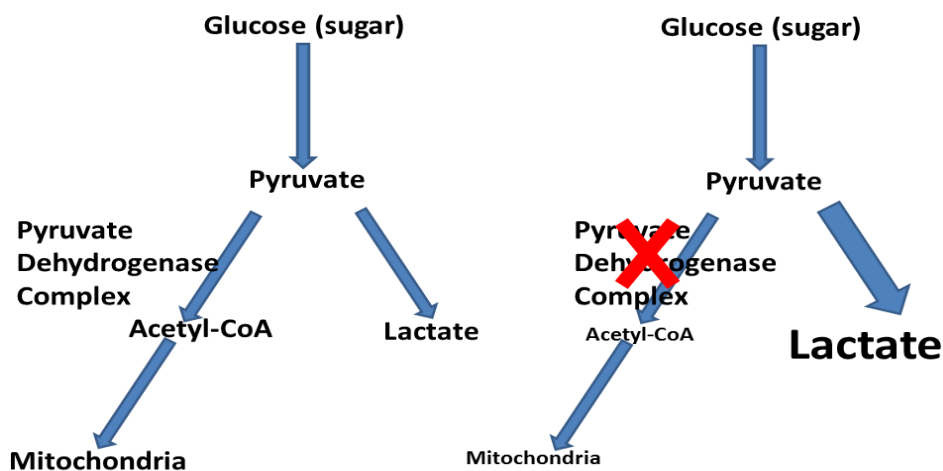


Fig. 1 Pyruvate Dehydrogenase Complex (PDC).

If by any reason the level or activity of PDH is decreased, the metabolism will turn to anaerobic way, producing lactate.

Thiamine has a pivotal role and is an essential cofactor for pyruvate dehydrogenase activity. Widely known wet beri-beri is developed due to thiamine deficiency and characterized by vasodilatory shock and despaired oxygen extraction leading to kidney, heart and central nervous system dysfunction. Thiamine deficiency is often underestimated and even in primary absence of vitamin B1 deficiency, high-consumptive state of many critical illness and cardiac surgery itself can lead to its lack [6,7,8]. Wiesen et al. reported that in patients on chronic dialysis and patients with AKI requiring RRT thiamine deficiency is a usual finding [9]. In cross-sectional observational study it has been shown that up to 33% of patients with a diagnosis of congestive heart failure (CHF) had thiamine deficiency due to chronic loop diuretic use [10]. Seligmann et al. reported that 96% of patients (21 of 23) with heart failure receiving loop diuretic therapy (daily dose: 80–240 mg furosemide) developed thiamine deficiency [11]. In prospective observational trial Donnino et al. showed that plasma thiamine levels were decreased after CABG surgery [6].

In a secondary analysis of a randomized, double-blind, placebo-controlled trial conducted in septic patients, thiamine supplementation showed highly-promising renal protective effect. Need for RRT was 8 patients (21%) in placebo group and 1 patient (3%) in thiamine group ( $p=0.04$ ) [12].

On the other hand Andersen et al. was unable to show any benefit of thiamine supplementation in patients undergoing CABG surgery [13]. Although, postoperative oxygen consumption was significantly increased among patients receiving thiamine.

Nevertheless, existing evidence suggests that thiamine supplementation might be an attractive strategy in counteracting organ dysfunction and thus morbidity and mortality in high-risk cardiac surgical patients.

### **Study design**

The **APPLY** trial (ThiAmine SuPPLementation in High Risk Cardiac SurgerY patients) is a single-center randomized double-blind placebo-controlled pilot clinical trial comparing thiamine supplementation with placebo on top of standard care in patients undergoing combined valve + CABG procedures under CPB. The aim of this study is to determine the best research endpoint that allows estimation of thiamine usage in clinical practice. Based on the results of recent data from RCT's and on physiological rationale for thiamine we consider several research outcomes. Major end points will include recruitment rate, compliance with the protocol, need and dosage of inotropic support during 48 hours (will be measured with 4 hours

intervals), creatinine level (during 1-3 POD), peak lactate level (lactate will be measured every 4 hours after surgery), cardiovascular and renal system SOFA score (will be measured every 6 hour postoperatively) on POD 1-3. A full list of outcome measures is shown in Table 1.

Table 1. Trial end points

<p><b>Primary end-points:</b></p> <p><b>1. Recruitment rate.</b> Recruitment of trial patients: successful recruitment is defined as 2 patients per week on average.</p> <p><b>2. Compliance with the protocol.</b> Successful compliance with protocol is defined as <math>\geq 90\%</math> of prescribed intervention being administered across all patients.</p> <p><b>Secondary end-points:</b></p> <p><b>1. Vasoinotropic score.</b> <b>Dosage of vasoinotropic agents and total vasopressor/norepinephrine equivalent dose</b></p> <p>The need for inotropic agent and dosage of all administered agents will be measured every 4 hours during the first 72 hours (or until ICU discharge). As the first line for vasoinotropic therapy we will use norepinephrine infusion. As the second line, dopamine will be used. Other vasoinotropic agents added to the therapy will be converted to norepinephrine equivalents and total vasopressor/norepinephrine equivalent dose will be calculated (Supplementary appendix A). Inotropic therapy will be guided by cardiac output measurement by pre-pulmonary Swan-Ganz catheter (the mean value from a triple measurement is used for each time-point for CO).</p> <p><b>2. Peak lactate level after CPB weaning to 48 hours</b> Lactate levels will be derived from blood gases during first 48 hours with 4 hours intervals.</p> <p><b>3. The value of postoperative peak serum creatinine (sCr) concentration during 3 postoperative days.</b> Will be measured every 12 hours for 3 days, postoperatively.</p>
---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

**4. The incidence of acute kidney injury (AKI) according to “Kidney Disease: Improving Global Outcomes (KDIGO) criteria” during ICU stay.**

Increase in sCr by  $\geq 26.5 \mu\text{mol/L}$  (0.3 g/dL) within 48 hours or increase in sCr to  $\geq 1.5$  times baseline, which is known or presumed to have occurred within the prior 7 days.

**5. The daily incidence of cardiovascular and renal dysfunction according to Sequential Organ Failure Assessment (SOFA) score during 48 hours postoperatively.**

The score is calculated, excluding respiratory and hepatic system scores every 6 hours during 48 hours (Supplementary Appendix B). CVS SOFA will be scored every 6 hours for 48 hours along with lactate levels.

**6. Rates of postoperative complications.**

Reintubation, need for noninvasive respiratory support, pneumothorax, postoperative delirium, postoperative stroke, postoperative myocardial damage, wound infection.

**7. Incidence of treatment-emergent adverse events**

The safety of high dose IV thiamine supplementation will be evaluated by comparison of adverse, serious adverse events and routinely assessed biochemical parameters (i.e. complete blood count, coagulation parameters, standard biochemistry, etc.).

**8. Availability of data needed.**

We expect that loss of follow up will not exceed 5% and data loss less than 10%.

**9. 7-day all-cause mortality** (or mortality at any time during the first hospitalization).

**10. 30-day all-cause mortality**

The trial has a simple, pragmatic design with allocation concealment, blinding, and minimization of ascertainment bias and loss to follow-up, and will be analyzed on an intention-to-treat basis. The APPLY trial will enroll 40 participants in E. Meshalkin National Medical Research Center (Novosibirsk, Russia) with an anticipated recruitment period of 4 months. We will follow up patients until 30 days

by phone or till hospital discharge if this occurs later. Adult patients who required cardiac surgery with CPB and fulfilled the other eligibility criteria will be allocated at random to receive Thiamine or equivalent volume of placebo during surgery. A complete list of inclusion and exclusion criteria is provided in Table 2.

Table 2. Trial eligibility criteria

<b>Inclusion criteria</b> Valve surgery + CABG that required cardiac surgery with CPB Aged 18 years or older Signed informed consent
<b>Exclusion criteria</b> Emergency surgery Chronic kidney disease of G4-G5 categories according to KDIGO criteria (at least one of the following present for > 3 months: glomerular filtration rate $\leq$ 29 ml/min/1.73 m <sup>2</sup> , history of kidney transplantation) Known allergy to thiamine Pregnancy Current enrollment into another RCT (in the last 30 days) Previous enrollment and randomisation into the APPLY trial Administration of thiamine in the previous 30 day

### **Participants**

Patients admitted to the cardiac surgery department will be assessed by study personnel. Patients will be eligible for enrollment if they fulfill all of the inclusion criteria and none of the exclusion criteria (Table 2). Participants will be allocated to the treatment arm using a randomly generated sequence. Randomization will be in 2 group with 20 patients in each. Allocation concealment will be maintained by using sequentially numbered, sealed, opaque envelopes containing the numeric code of the study arm to which the participant has been assigned. The randomization code will be documented in the participant's notes and the case report form (CRF) and provided to the anaesthesiological nurse with access to the unblinding code for preparation of the intervention.

### **Study treatment**

Participants will be randomly assigned to receive either 200 mg of Thiamine dissolved in 100 ml of normal saline through intravenous injection or same amount of placebo (100 ml of normal saline) at following time point:

1. After anesthesia induction
2. After separation from CPB

3. On the evening of the day of surgery (22:00)
4. on POD 1 twice a day at 8:00 and 22:00
5. on POD 2 twice a day at 8:00 and 22:00 (if patient is still in ICU)
6. on POD 3 twice a day at 8:00 and 22:00 (if patient is still in ICU)

All aspects of patient management other than the specific study-related procedures will be at the discretion of the treating clinician.

Anaesthesia induction and maintenance protocols are similar for all patients and consist of doses of midazolam, sevoflurane, fentanyl, pipecuronium bromide, and propofol, adjusted for weight. Intra- and postoperatively, volume-controlled mechanical ventilation is provided at  $FiO_2$  0.5, tidal volume 6-8 mL/kg, respiratory rate 12–14 breaths/min, and positive end-expiratory pressure 5 cmH<sub>2</sub>O (Perseus a 500, Primus, Evita XL; Dräger, Germany). The radial artery is catheterized with a 20G catheter (B Braun, Germany). A pulmonary artery catheter (7.5F, five-lumen, Corodyn TDI, B Braun) via the right internal jugular vein through an introducer (Intradyn 8F, B Braun), and a triple-lumen central venous catheter (Certofix, B Braun) are placed. Cardiopulmonary bypass is performed in nonpulsatile mode (LivaNova PLC, Sorin Group Stockert S5) with a perfusion index of 2.4–2.8 L/min/m<sup>2</sup>. For CPB, standard cannulation of the ascending aorta, and the upper and lower vena cava is performed. Before connecting to extracorporeal circulation, the patients are heparinised with 3 mg/kg of sodium heparin, maintaining an activated coagulation time > 480 s during bypass. The circuit is primed with 1000 mL of balanced crystalloid solution, 200 mL of 15% mannitol, and 150 mL of 5 % sodium hydrocarbonate. Aminocaproic acid (20 g as a continuous infusion) is used in all patients. The nasopharyngeal temperature is maintained at 33–34.0°C, and mean arterial pressure (MAP) is maintained between 70–80 mmHg by administering phenylephrine when necessary. At the end of CPB, heparinization is reversed using protamine sulphate in a ratio of 1:1. For myocardial protection, 2000 mL of ice-cold (4–6°C) cardioplegic solution (Custodiol) is antegradely used for 2-hour period of ischaemia with supplementation (1000 mL) when necessary. The initial dose of defibrillation for the termination of ventricular fibrillation, ventricular and supraventricular tachycardia after aortic declamping is 30-50 Joules. The ultrafiltration protocol, if necessary, used during CPB is identical in all patients. Steroids are not used in the present study. None of the patients receive aprotinin. Packed red blood cells are administered when haemoglobin level decreased to less than 8 g/dL. Fresh frozen plasma is transfused when there is ongoing bleeding (150 mL/h of blood loss over 2 h) based on pathological coagulation parameters.

The surgical approach is through a conventional median sternotomy. Preoperatively cefuroxime is used to reduce surgical site infection.

Inotropic therapy will be guided by cardiac output measurement by pre-pulmonary Swan-Ganz catheter (Supplementary appendix C). Postoperatively, all patients will be transferred to ICU.

Patients are transferred from the ICU to the ward after they meet the following criteria: fully oriented, saturation level of oxygen in arterial blood > 90% on room air, no episodes of severe arrhythmias (see above), bleeding < 50 mL/h, diuresis > 0.5 mL/kg/h, no need for inotrope/vasopressor support, and no signs of ischaemia on electrocardiograph. Patients are discharged from hospital when they fit the following criteria: haemodynamic stability, independence of ambulation and feeding, afebrile with no obvious infections, normal voiding and bowel movements, pain control on oral medications, and exercise tolerance.

### **Recruitment rate.**

In our center, we accomplish more than 2 000 cardiac surgeries with CBP in adults and such a complex patients who meet the inclusion criteria (combined valve surgery + CABG) encounter 2-3 patients per week. Thus, we estimate study start up activities to take 2 month. To enroll 40 patients we will require approximately 5-8 months (1-2 patients/week).

### **Blinding**

Study treatment will be blinded using identical syringes. An unblinded research nurse will draw up the study medication, and the treating anaesthesiologist will deliver the infusion

### **Discontinuation of study treatment**

Participants will not receive further study treatment after the last dose given at the ICU admission. Participants experiencing a suspected or confirmed immediate hypersensitivity reaction temporally related to the delivery of the study intervention will have immediate interruption of the study treatment.

### **Statistical considerations**

All analyses will be conducted on an intention-to-treat basis. Differences in outcome variables will be compared using the t test, repeated measures analysis of variances, and  $\chi^2$  test, as appropriate, if normally distributed, and using non-parametric equivalents if not normally distributed. Analysis will be conducted using Stata version 10.2 (StataCorp) and a two-sided P of 0.05 will be considered to be statistically significant. Continuous measures will be compared by analysis of variance (ANOVA) or the Mann-Whitney U test when appropriate; 95% confidence



interval estimate for the mean/median difference will be performed. All statistical analyses will be blinded.

### **Data management**

All data will be collected by trained staff using a paper source document developed by the management committee. Data will then be entered into a secure, password-protected electronic database. Participants will be followed up to the 30th day after randomization or till hospital discharge if this occurs later. A “postoperative day” in the ICU will be defined as commencing at 8 a.m. The study data to be collected are shown in Table 3.

Table 3. Data to be collected

<p><b>Baseline</b></p> <ol style="list-style-type: none"><li>1. Demographic data: age, gender, body mass index.</li><li>2. Severity of illness: left ventricular ejection fraction, previous cardiac surgery, ongoing cardiogenic shock, New York Heart Association class, EuroCORE II,</li><li>3. Concurrent medical conditions and comorbidities: previous myocardial infarction, hypertension, carotid stenosis, previous stroke, angina severity, unstable angina, diabetes mellitus, atrial fibrillation, ventricular extrasystole, chronic obstructive pulmonary disease, peripheral vascular disease, chronic kidney disease.</li><li>4. Smoking status.</li><li>5. Cardiac catheterization in the last 48 h.</li><li>6. Preoperative Medication: <math>\beta</math>-blockers, angiotensin-converting-enzyme inhibitors/angiotensin II–receptor <math>\alpha</math> antagonists, platelet inhibitors, anticoagulants, statins, antiarrhythmics, diuretics, and nitrates.</li><li>7. Serum creatinine at hospital admission.</li></ol>
<p><b>Operating room, ICU and hospital stay</b></p> <ol style="list-style-type: none"><li>1. The rate and dose of inotropic and vasopressor support.</li><li>2. Peak lactate level after CPB weaning to 48 hour postoperatively. Lactate levels will be derived from blood gases during 48 hours with 4 hours intervals.</li><li>3. Serum creatinine during 3 postoperative days</li><li>4. SOFA score daily in the ICU, but CVS SOFA every 6 hours for 48 hours postoperatively.</li><li>5. All-cause 7-day and 30-day mortality.</li></ol>

6. The rate of postoperative complications: reintubation, need for noninvasive respiratory support, pneumothorax, postoperative delirium, postoperative stroke, postoperative myocardial damage, wound infection.

**Follow-up at the 30th day**

1. All-cause mortality on 30 day after randomization or mortality at any time during the first hospitalization

**Protocol compliance.**

Successful compliance with protocol is defined as  $\geq 90\%$  of prescribed intervention being administered across all patients.

The Principal Investigator undertakes to conduct the trial in compliance with the protocol and with approval given by the Ethic Committee (EC). Necessity for any changes revealing through trial process will be negotiated with EC and will be only implemented after written approval by EC. In situation where is urgent rewire required due to potential hazard for trial participants, study will be stopped by Principal Investigator, collect and document all data's and after thorough revision all division will mirrored in the protocol and CRF. Edited protocol will anew reported and approved in EC.

**Safety monitoring**

The safety of high dose IV thiamine supplementation will be evaluated by comparison of adverse, serious adverse events and routinely assessed biochemical parameters (i.e. complete blood count, coagulation parameters, standard biochemistry, etc.). Serious adverse events (SAEs) will be reported according to the Good Clinical Practice guidelines and the requirements of the institution in which the study will take place. The Ethics committee will receive notification of all SAEs. No interim analysis is planned; however, the Ethics committee will reserve the right to request an interim analysis on the basis of SAEs. In keeping with the advice of Cook et al, events that are part of the natural history/progression of the primary disease process or expected complications of critical illness (e.g. those reported in the CRF) will not be reported as SAEs in this trial unless thought to be causally related to the study intervention or otherwise specified in the CRF.

## **Ethics issues**

The study will not proceed at the site until approval has been gained from the Ethics committee. Prospective informed consent will be sought from eligible patients who retain capacity.

## **Funding and support**

The study will be supported by E. Meshalkin National Medical Research Center.

## **Registration**

The APPLY trial after receiving the Ethics committee approval will be registered on ClinicalTrials.gov.

## **References**

1. Legrand M, Dupuis C, Simon C, et al. Association between systemic hemodynamics and septic acute kidney injury in critically ill patients: a retrospective observational study. *Critical care* 2013; 17(6):R278.
2. Maiden MJ, Otto S, Brealey JK, Finnis ME, Chapman MJ, Kuchel TR, Nash CH, Edwards J, Bellomo R. Structure and Function of the Kidney in Septic Shock. A Prospective Controlled Experimental Study. *Am J Respir Crit Care Med* 2016; 15;194(6):692-700
3. Filho, Roberto Rabello et al. "Blood Lactate Levels Cutoff and Mortality Prediction in Sepsis—Time for a Reappraisal? A Retrospective Cohort Study." *Shock (Augusta, Ga.)* 46.5 (2016): 480–485.
4. Kruse O, Grunnet N, Barfod C. Blood lactate as a predictor for in-hospital mortality in patients admitted acutely to hospital: a systematic review. *Scand J Trauma Resusc Emerg Med* 2011;19:74.
5. Andersen LW, Holmberg MJ, Doherty M, Khabbaz K, Lerner A, Berg KM, et al. Postoperative lactate levels and hospital length of stay after cardiac surgery. *J Cardiothorac Vasc Anesth.* 2015;29:1454–60
6. Donnino MW, Cocchi MN, Smithline H, Carney E, Chou PP, Saliccioli J. Coronary artery bypass graft surgery depletes plasma thiamine levels. *Nutrition.* 2010;26(1):133–6
7. Donnino MW, Carney E, Cocchi MN, et al. Thiamine deficiency in critically ill patients with sepsis. *J Crit Care* 2010; 25:576–581.

8. Lima LF, Leite HP, Taddei JA. Low blood thiamine concentrations in children upon admission to the intensive care unit: risk factors and prognostic significance. *Am J Clin Nutr* 2011; 93:57–61.

9. Wiesen P, Van Overmeire L, Delanaye P, Dubois B, Preiser JC. Nutrition disorders during acute renal failure and renal replacement therapy. *JPEN J Parenter Enteral Nutr.* 2010;35:217-222. doi: <http://dx.doi.org/10.1177/0148607110377205>

10. Hanninen SA, Darling PB, Sole MJ, et al. The prevalence of thiamin deficiency in hospitalized patients with congestive heart failure. *J Am Coll Cardiol.* 2006 Jan 17.47(2):354-61.

11. Seligmann H(1), Halkin H, Rauchfleisch S, Kaufmann N, Motro M, Vered Z, Ezra D. Thiamine deficiency in patients with congestive heart failure receiving long-term furosemide therapy: a pilot study. *Am J Med.* 1991 Aug;91(2):151-5.

12. Moskowitz A, Andersen LW, Cocchi MN, Karlsson M, Patel PV, Donnino MW. Thiamine as a Renal Protective Agent in Septic Shock. A Secondary Analysis of a Randomized, Double-Blind, Placebo-controlled Trial. *Ann Am Thorac Soc.* 2017 May; 14(5):737-741.

13. Andersen L.W., Holmberg M.J, Berg K.M., Chase M., Cocchi M.N., Sulmonte C., Balkema J., MacDonald M., Montissol S., Senthilnathan V., Liu D., Khabbaz K., Lerner A., Novack V., Liu X., Donnino M.W. Thiamine as an adjunctive therapy in cardiac surgery: a randomized, double-blind, placebo-controlled, phase II trial. *Crit Care.* 2016 Mar 14;20:92

## Supplementary

### Appendix A

#### Conversion to norepinephrine equivalents

Drug	Dose	Norepinephrine Equivalent
Epinephrine	0.1 mcg/kg/min	0.1 mcg/kg/min
Norepinephrine	0.1 mcg/kg/min	0.1 mcg/kg/min
Dopamine	15 mcg/kg/min	0.1 mcg/kg/min
Phenylephrine	1.0 mcg/kg/min	0.1 mcg/kg/min
Vasopressin	0.04 U/min	0.1 mcg/kg/min

## Appendix B

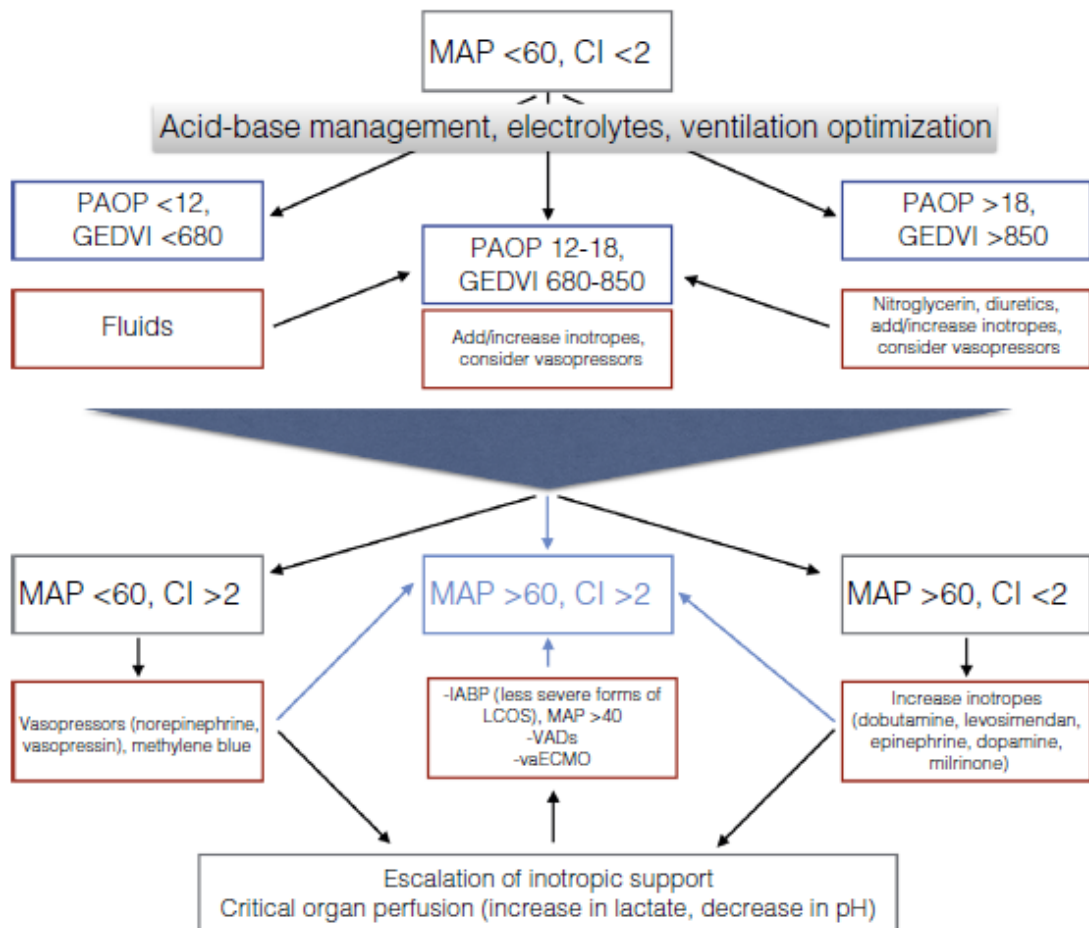
### Sequential Organ Failure Score (SOFA)

Score points	1	2	3	4
<i>Respiration</i>				
PaO <sub>2</sub> /FiO <sub>2</sub>	<400	<300	<200	<100
			with respiratory support	with respiratory support
<i>Cardiovascular</i>				
Hypotension*	MAP <70 mmHg	Dopamine ≤5 or dobutamine in any dose	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
<i>Liver</i>				
Bilirubin mg/dl	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
<i>Renal</i>				
Creatinine mg/dl	1.2–1.9	2.0–3.4	3.5–4.9	5.0
or urine output			or <500ml/24h	or <200ml/24h
<i>Coagulation</i>				
Platelets ×10 <sup>3</sup> /mm <sup>3</sup>	< 150	< 100	< 50	< 25
<i>Central nervous system</i>				
Glasgow Coma Scale	13–14	10–12	6–9	< 6

\* Adrenergic agents administered for at least 1 h (doses are given in µg/kg/min)

## Appendix C

### Low-cardiac-output treatment algorithm.



(Lomivorotov V.V., Efremov S.M., Kirov M.Y., e.a. Low-cardiac-output syndrome after cardiac surgery. J Cardiothorac Vasc Anesth. 2017 Feb;31(1):291-308).