Levosimendan in cardiac surgery : To the editor

Putzu, Alessandro ; Clivio, Sara ; Cassina, Tiziano

DOI: https://doi.org/10.1056/NEJMc1711938

2. Shroyer AL, Grover FL, Hattler B, et al. On-pump versus off-pump coronary-artery bypass surgery. N Engl J Med 2009; 361:1827-37.
3. Hattler B, Messenger JC, Shroyer AL, et al. Off-pump coronary artery bypass surgery is associated with worse arterial and saphenous vein graft patency and less effective revascularization: results from the Veterans Affairs Randomized On/Off Bypass (ROOBY) trial. Circulation 2012;125:2827-35.
4. Hattler B, Grover FL, Shroyer AL. Letter by Hattler et al. regarding article, "Graft patency after off-pump coronary artery bypass surgery." Circulation 2013;127(2):e276.
5. Novitzky D, Baltz JH, Hattler B, et al. Outcomes after conversion in the Veterans Affairs Randomized On versus Off Bypass trial. Ann Thorac Surg 2011;92:2147-54.

DOI: 10.1056/NEJMc1712000

Levosimendan in Cardiac Surgery

TO THE EDITOR: Landoni et al. (May 25 issue)[1] examined levosimendan administration versus placebo for patients requiring hemodynamic support after cardiac surgery. In their trial (Levosimendan to Reduce Mortality in High Risk Cardiac Surgery Patients: A Multicenter Randomized Controlled Trial [CHEETAH]), they found no significant difference in mortality between the two groups. The investigators aimed to include patients with shock after cardiac surgery and cardiopulmonary bypass. However, many of the patients were likely to have distributive shock (i.e., 57.7% received epinephrine, 45.3% norepinephrine, and 15.2% dopamine) rather than cardiogenic shock (28.3% received dobutamine and 12.5% enoximone) (Table S5 in the Supplementary Appendix, available with the full text of the article at NEJM.org). The vasodilator effect of levosimendan[2] may be detrimental in those with vasoplegia after cardiopulmonary bypass. Indeed, hypotension, possibly due to low diastolic and coronary perfusion pressure,[3] is associated with 30-day mortality in multivariate analysis (P=0.005), whereas low cardiac output is not. In addition, the investigators did not target their drug administration to either cardiac output or markers of tissue hypoxia (e.g., lactate level, mixed venous oxygen saturation, or the venoarterial carbon dioxide gradient). Inotropic drugs are likely to exert only detrimental effects on myocardium[4] if an increase in cardiac output, along with oxygen delivery,[5] is not accompanied by evidence of improvement in oxygen consumption.

Antonio M. Dell'Anna, M.D.
Gennaro De Pascale, M.D.
Massimo Antonelli, M.D.

A. Gemelli School of Medicine
Rome, Italy
anthosdel@yahoo.it

No potential conflict of interest relevant to this letter was reported.

1. Landoni G, Lomivorotov VV, Alvaro G, et al. Levosimendan for hemodynamic support after cardiac surgery. N Engl J Med 2017;376:2021-31.
2. Banfor PN, Preusser LC, Campbell TJ, et al. Comparative effects of levosimendan, OR-1896, OR-1855, dobutamine, and milrinone on vascular resistance, indexes of cardiac function, and O2 consumption in dogs. Am J Physiol Heart Circ Physiol 2008; 294:H238-H248.
3. McEvoy JW, Chen Y, Rawlings A, et al. Diastolic blood pressure, subclinical myocardial damage, and cardiac events: implications for blood pressure control. J Am Coll Cardiol 2016;68: 1713-22.
4. DeWitt ES, Black KJ, Thiagarajan RR, et al. Effects of commonly used inotropes on myocardial function and oxygen consumption under constant ventricular loading conditions. J Appl Physiol (1985) 2016;121:7-14.
5. Monnet X, Julien F, Ait-Hamou N, et al. Lactate and venoarterial carbon dioxide difference/arterial-venous oxygen difference ratio, but not central venous oxygen saturation, predict increase in oxygen consumption in fluid responders. Crit Care Med 2013; 41:1412-20.

DOI: 10.1056/NEJMc1711938

TO THE EDITOR: The trial by Landoni et al. randomly assigned cardiac-surgery patients with postoperative cardiovascular dysfunction to receive levosimendan or placebo. The trial showed no significant beneficial effects on postoperative outcome, similar to the findings of the trial by Mehta et al. (May 25 issue).[1] In the latter trial (Levosimendan in Patients with Left Ventricular Systolic Dysfunction Undergoing Cardiac Surgery Requiring Cardiopulmonary Bypass [LEVO-CTS]), levosimendan was administered just after anesthesia induction to patients with preoperative cardiac dysfunction.

Pharmacokinetic and pharmacodynamic studies suggest that the steady-state concentration of levosimendan is reached within 4 to 8 hours after initiation of the infusion and remains constant over a period of 24 hours.[2] Active plasma metabolites can be detected after 12 hours, with a peak in 48 to 78 hours; such metabolites contribute further to the hemodynamic effects of the drug.[2] The hemodynamic effects of levosimendan increase progressively, reaching a plateau after

3 to 6 hours.[3,4] Taking into account these pharmacologic features, there is still room for a study to define the real effect on clinical outcome of levosimendan administered preoperatively — for instance, beginning the day before surgery.

Alessandro Putzu, M.D.
Sara Clivio, M.D.
Tiziano Cassina, M.D.
Cardiocentro Ticino
Lugano, Switzerland
alessandroputzu@ymail.com

No potential conflict of interest relevant to this letter was reported.

1. Mehta RH, Leimberger JD, van Diepen S, et al. Levosimendan in patients with left ventricular dysfunction undergoing cardiac surgery. N Engl J Med 2017;376:2032-42.
2. Antila S, Sundberg S, Lehtonen LA. Clinical pharmacology of levosimendan. Clin Pharmacokinet 2007;46:535-52.
3. Lilleberg J, Laine M, Palkama T, Kivikko M, Pohjanjousi P, Kupari M. Duration of the haemodynamic action of a 24-h infusion of levosimendan in patients with congestive heart failure. Eur J Heart Fail 2007;9:75-82.
4. Kivikko M, Lehtonen L, Colucci WS. Sustained hemodynamic effects of intravenous levosimendan. Circulation 2003;107:81-6.

DOI: 10.1056/NEJMc1711938

DR. LANDONI AND COLLEAGUES REPLY: We disagree with Dell'Anna and colleagues that most patients enrolled in our trial had a primary vasoplegic syndrome rather than predominant myocardial dysfunction as the cause of their hemodynamic instability. In fact, 498 of 506 patients (98.4%) had reasons different from receipt of norepinephrine alone for inclusion in the trial, and a subgroup analysis did not identify any subgroup effect between patients receiving norepinephrine at randomization and those not receiving it (Fig. S4B in the Supplementary Appendix of our article). We acknowledge that it is difficult to separate a degree of inflammatory vasoplegia from cardiogenic shock as the cause of hypotension after cardiac surgery. However, despite the use of epinephrine in nearly 60% of patients, dobutamine in nearly 30%, dopamine in 15%, and enoximone in more than 10% and a mean pulmonary-artery occlusion pressure of 15.5 mm Hg, the mean cardiac index at randomization was only 2.2 liters per minute per square meter of body-surface area. This is not the hemodynamic picture of primary vasodilatory shock, as seen in the recent Angiotensin II for the Treatment of High-Output Shock (ATHOS-3) trial.[1]

We also disagree with the unproven notion that clinicians would not have targeted their therapy to lactate level, mixed venous oxygen saturation, cardiac index, and other clinical, physiological and biochemical markers of perfusion. Although we did not collect the specific information, such a notion assumes, without evidence, that literally hundreds of clinicians dealing with these patients in multiple intensive care units would have failed to adjust treatment according to such principles.

We agree, however, with Dell'Anna and colleagues that levosimendan-induced hypotension could have attenuated its possible beneficial effects. Such a hypotensive effect is a property of this drug and one of its major limitations as an inotropic agent in cardiac surgery.

We appreciate the view of Putzu and colleagues that the administration of levosimendan beginning the day before surgery may optimize its inotropic effects. However, given the lack of effect seen in CHEETAH, the LEVO-CTS trial, and the Levosimendan in Coronary Artery Revascularization (LICORN) trial,[2] it is difficult to imagine that the additional gain from more prolonged administration before surgery would have a clinically important effect.

Giovanni Landoni, M.D.
San Raffaele Scientific Institute
Milan, Italy
Vladimir V. Lomivorotov, M.D., Ph.D.
E. Meshalkin National Medical Research Center
Novosibirsk, Russia
Rinaldo Bellomo, M.D., Ph.D.
University of Melbourne
Melbourne, VIC, Australia
rinaldo.bellomo@austin.org.au

Since publication of their article, the authors report no further potential conflict of interest.

1. Khanna A, English SW, Wang XS, et al. Angiotensin II for the treatment of vasodilatory shock. N Engl J Med 2017;377:419-30.
2. Cholley B, Caruba T, Grosjean S, et al. 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;318:548-56.

DOI: 10.1056/NEJMc1711938

DRS. MEHTA AND ALEXANDER REPLY: We concur with Putzu et al. that a future study to evaluate the efficacy of levosimendan among patients undergoing cardiac surgery with cardiopulmonary bypass may be warranted, particularly given the favorable trend for lower 90-day mortality observed with levosimendan in the LEVO-CTS trial. We agree that one reason levosimendan may not

have worked in the LEVO-CTS trial was that it was started soon before surgery (median, 20 minutes). However, the "pharmacokinetic and pharmacodynamic" information that Putzu et al. provided to support their hypothesis for a new study was reported in patients with heart failure[1-3] rather than those undergoing cardiac surgery with cardiopulmonary bypass, for whom pharmacokinetic data with levosimendan are unavailable and may differ. Until the pharmacokinetic data from the LEVO-CTS trial or other studies in cardiac surgery are available, the assumption that the pharmacokinetic properties of levosimendan are similar in patients with heart failure and those undergoing cardiac surgery with cardiopulmonary bypass should be made with caution.

Rajendra H. Mehta, M.D.,
John H. Alexander, M.D., M.H.S.
Duke Clinical Research Institute
Durham, NC
raj.mehta@duke.edu
for the LEVO-CTS Steering Committee Members and Trial Investigators

Since publication of their article, the authors report no further potential conflict of interest.

1. Antila S, Sundberg S, Lehtonen LA. Clinical pharmacology of levosimendan. Clin Pharmacokinet 2007;46:535-52.
2. Lilleberg J, Laine M, Palkama T, Kivikko M, Pohjanjousi P, Kupari M. Duration of the haemodynamic action of a 24-h infusion of levosimendan in patients with congestive heart failure. Eur J Heart Fail 2007;9:75-82.
3. Kivikko M, Lehtonen L, Colucci WS. Sustained hemodynamic effects of intravenous levosimendan. Circulation 2003;107:81-6.

DOI: 10.1056/NEJMc1711938

Midostaurin in *FLT3*-Mutated Acute Myeloid Leukemia

TO THE EDITOR: Stone et al. (Aug. 3 issue)[1] found that adding midostaurin to a standard chemotherapy regimen containing daunorubicin at a dose of 60 mg per square meter of body-surface area significantly prolonged overall and event-free survival among patients with acute myeloid leukemia (AML) and a *FLT3* mutation (point mutation in the tyrosine kinase domain [TKD] or internal tandem duplication [ITD] mutation) as compared with placebo plus standard chemotherapy.

In a previous study, a nonsignificant trend for benefit beyond 12 months was shown in patients with a *FLT3* mutation of the ITD subtype who received daunorubicin at a dose of 90 mg per square meter as compared with a dose of 60 mg per square meter.[2] It is more appropriate to give the higher dose of daunorubicin to patients with the ITD mutation,[3] and anthracycline intensification may be beneficial in such patients.[4] Recently, high-dose daunorubicin (90 mg per square meter) was found to be more effective than idarubicin (12 mg per square meter) in patients with a *FLT3* mutation of the ITD subtype.[5] These data raise the questions of whether daunorubicin alone at a dose of 90 mg per square meter would induce better responses and outcomes than adding midostaurin to daunorubicin at a dose of 60 mg per square meter and whether the combination of midostaurin and the higher dose of daunorubicin would further improve the outcomes of patients with *FLT3*-mutated AML.

A. Emre Eskazan, M.D.
Istanbul University
Istanbul, Turkey
emreeskazan@hotmail.com

No potential conflict of interest relevant to this letter was reported.

1. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a *FLT3* mutation. N Engl J Med 2017;377:454-64.
2. Burnett AK, Russell NH, Hills RK, et al. A randomized comparison of daunorubicin 90 mg/m2 vs 60 mg/m2 in AML induction: results from the UK NCRI AML17 trial in 1206 patients. Blood 2015;125:3878-85.
3. Burnett AK, Russell NH, Hills RK. Higher daunorubicin exposure benefits FLT3 mutated acute myeloid leukemia. Blood 2016;128:449-52.
4. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129:424-47.
5. Lee JH, Kim H, Joo YD, et al. Prospective randomized comparison of idarubicin and high-dose daunorubicin in induction chemotherapy for newly diagnosed acute myeloid leukemia. J Clin Oncol 2017;35:2754-63.

DOI: 10.1056/NEJMc1711340

TO THE EDITOR: The interaction among mutations in a polyclonal disease such as newly diagnosed AML determines the prognosis. In *FLT3*-mutated AML, co-occurring mutations such as in *NPM1* and *DNMT3* alter the outcome considerably.[1] Again, *FLT3* inhibition by lestaurtinib was greater when *NPM1* was also mutated.[2] Therefore, clarification of the *NPM1* status in the trial by Stone et al. would facilitate data interpretation.