even in a clone that is not part of the malignant process) can have an effect on clinical responses. The serial tracking of *TP53* mutation clearance in our study gave us confidence that the *TP53* mutations that we detected were in fact relevant for pathogenesis and responses.

John S. Welch, M.D., Ph.D.
Allegra A. Petti, Ph.D.
Timothy J. Ley, M.D.
Washington University School of Medicine
St. Louis, MO
timley@wustl.edu

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

1. Duong VH, Komrokji RS, List AF. Update on the pharmacotherapy for myelodysplastic syndromes. Expert Opin Pharmacother 2014;15:1811-25.
2. Diesch J, Zwick A, Garz AK, Palau A, Buschbeck M, Götze KS. A clinical-molecular update on azanucleoside-based therapy for the treatment of hematologic cancers. Clin Epigenetics 2016;8:71-82.
3. Podoltsev NA, Stahl M, Zeidan AM, Gore SD. Selecting initial treatment of acute myeloid leukaemia in older adults. Blood Rev 2016 October 8 (Epub ahead of print).

DOI: 10.1056/NEJMc1616062

Levosimendan in Sepsis

TO THE EDITOR: Like many critical care physicians, we excitedly awaited the results of the Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis (LeoPARDS) trial by Gordon et al. (Oct. 27 issue)[1] to find out whether to use levosimendan in hemodynamically unstable patients with sepsis. The rationale for using levosimendan in sepsis is based on studies that have shown a mortality benefit among patients with septic cardiomyopathy who were treated with levosimendan.[2,3]

Unfortunately, the number of patients with myocardial dysfunction who were included in the LeoPARDS trial was evidently rather low, according to the sparse hemodynamic information (only 30% of the patients underwent baseline cardiac-output assessment), the liberal inclusion criteria, and the negligible use of dobutamine. In addition, neither routine echocardiography nor hemodynamic monitoring was required during the course of the trial. Therefore, this trial does not add more than the information that patients with sepsis who presented with reduced systemic vascular resistance but without clinical signs of myocardial dysfunction did not benefit from treatment with a potent inodilator drug. Thus, rather disappointingly, the trial design was too simple to answer the question of whether "to use or not to use" levosimendan in patients with hemodynamically relevant septic cardiomyopathy.

Heinrich-Volker Groesdonk, M.D.
Saarland University
Homburg/Saar, Germany
Michael Sander, M.D.
Justus Liebig University
Giessen, Germany
Matthias Heringlake, M.D.
University of Lübeck
Lübeck, Germany
heringlake@t-online.de

Dr. Groesdonk reports receiving lecture fees from Orion Pharma; Dr. Sander, receiving consulting and lecture fees from Amomed Pharma and Orion Pharma; and Dr. Heringlake, receiving consulting and lecture fees from Orion Pharma and Amomed Pharma and serving as a steering board member for Tenax Therapeutics. No other potential conflict of interest relevant to this letter was reported.

1. Gordon AC, Perkins GD, Singer M, et al. Levosimendan for the prevention of acute organ dysfunction in sepsis. N Engl J Med 2016;375:1638-48.
2. Morelli A, De Castro S, Teboul JL, et al. Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression. Intensive Care Med 2005;31:638-44.
3. Zangrillo A, Putzu A, Monaco F, et al. Levosimendan reduces mortality in patients with severe sepsis and septic shock: a meta-analysis of randomized trials. J Crit Care 2015;30:908-13.

DOI: 10.1056/NEJMc1616632

TO THE EDITOR: The results of the LeoPARDS trial of levosimendan in patients with sepsis suggest no beneficial effects on clinical outcomes. Early treatment is a cornerstone of sepsis therapy, and a meta-analysis of randomized trials supported a beneficial effect of levosimendan among patients with sepsis who had a rate of death of up to 60%,[1] which suggests that high-risk patients with septic shock may receive the greatest benefit from levosimendan infusion. Gordon et al. enrolled low-risk patients relatively late after the diagnosis of septic shock without confirmed concomitant cardiac dysfunction and administered a high dose of levosimendan (up to 0.2 μg per kilogram of body weight per minute), which induced tachycardia and hypotension. Under these conditions, the authors found no difference in survival with

levosimendan as compared with placebo. Nonetheless, pragmatic, multicenter, randomized, controlled trials represent the best available design to test treatments,[2] and all previous evidence on mortality reduction with levosimendan in patients with sepsis and those undergoing surgery was based on poor-quality single-center, randomized, controlled trials. Results of two large, multicenter, randomized, controlled trials on perioperative use of levosimendan[3,4] are awaited to see whether this drug is only an inotropic agent or can also improve survival.

Alessandro Putzu, M.D.
Cardiocentro Ticino
Lugano, Switzerland
alessandroputzu@ymail.com

Alessandro Belletti, M.D.
Alberto Zangrillo, M.D.
San Raffaele Scientific Institute
Milan, Italy

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

1. Zangrillo A, Putzu A, Monaco F, et al. Levosimendan reduces mortality in patients with severe sepsis and septic shock: a meta-analysis of randomized trials. J Crit Care 2015;30:908-13.
2. Ford I, Norrie J. Pragmatic trials. N Engl J Med 2016;375:454-63.
3. Mehta RH, Van Diepen S, Meza J, et al. Levosimendan in patients with left ventricular systolic dysfunction undergoing cardiac surgery on cardiopulmonary bypass: rationale and study design of the Levosimendan in Patients with Left Ventricular Systolic Dysfunction Undergoing Cardiac Surgery Requiring Cardiopulmonary Bypass (LEVO-CTS) trial. Am Heart J 2016;182:62-71.
4. Zangrillo A, Alvaro G, Pisano A, 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: 10.1056/NEJMc1616632

TO THE EDITOR: In the LeoPARDS trial, no benefit was found with the addition of levosimendan to standard treatment in terms of organ dysfunction and mortality among patients with sepsis. The results of this trial are not surprising, since levosimendan, as a myofilament Ca^{2+}-sensitizing positive inotropic drug, should be reserved for patients with sepsis who have signs of myocardial dysfunction. Otherwise, only deleterious effects can be expected for the drug because of its vasodilating properties. Surprisingly, in the LeoPARDS trial, there was no echocardiographic evaluation to identify patients who could have benefited from the inotropic effect of levosimendan. The authors report that even in the subset of patients with a low cardiac index, the drug provided no benefit. However, during sepsis, a low cardiac output cannot be considered synonymous with altered cardiac contractility without echocardiographic assessment. The fact that even in this subgroup of patients cardiac output did not increase with the drug confirms this lack of correlation.

Olfa Hamzaoui, M.D.
Hôpital Antoine Béclère
Clamart, France
olfa.hamzaoui@aphp.fr

Jean-Louis Teboul, M.D., Ph.D.
Hôpital Bicêtre
Le Kremlin-Bicêtre, France

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

DOI: 10.1056/NEJMc1616632

TO THE EDITOR: In the LeoPARDS trial, levosimendan was added to standard care to reduce the severity of organ dysfunction in sepsis. Previous studies,[1-4] in which more severely ill patients were enrolled, focused on the effects of levosimendan on organ perfusion rather than function, and improved organ perfusion was observed with improved systemic hemodynamics when additional volume was administered. In our view, the patients in the LeoPARDS trial were not receiving sufficient volume loading during levosimendan infusion, which led to relative hypovolemia, causing tachycardia, supraventricular arrhythmia, and eventually decreased organ perfusion. In this trial, the central venous oxygen saturation was significantly higher after 24 hours in the levosimendan group than in the placebo group, despite a significantly lower ratio of partial pressure of arterial oxygen to fractional inspired oxygen and an unchanged cardiac index. In addition, lactate levels tended to be lower. These findings suggest that even under the worst hemodynamic conditions, levosimendan was still effective in improving microcirculation. The results of the LeoPARDS trial strengthen the importance of providing adequate volume before the administration of levosimendan for improving systemic hemodynamics, tissue perfusion, and, potentially, function in patients with sepsis.

Andrea Morelli, M.D.
Luigi Tritapepe, M.D.
Sapienza University of Rome
Rome, Italy
andrea.morelli@uniroma1.it

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

1. Morelli A, De Castro S, Teboul J-L, et al. Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression. Intensive Care Med 2005;31:638-44.
2. Morelli A, Donati A, Ertmer C, et al. Levosimendan for resuscitating the microcirculation in patients with septic shock: a randomized controlled study. Crit Care 2010;14:R232.
3. Memiş D, Inal MT, Sut N. The effects of levosimendan vs dobutamine added to dopamine on liver functions assessed with noninvasive liver function monitoring in patients with septic shock. J Crit Care 2012;27(3):318.e1-318.e6.
4. Morelli A, Teboul J-L, Maggiore SM, et al. Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: a pilot study. Crit Care Med 2006; 34:2287-93.

DOI: 10.1056/NEJMc1616632

THE AUTHORS REPLY: We disagree with Putzu et al. that low-risk patients were enrolled late after the diagnosis of septic shock in our trial. The median dose of norepinephrine (0.28 μg per kilogram per minute) and a rate of death of 31% at 28 days in the placebo group — a rate that is markedly higher than that in recent trials of early goal-directed therapy among patients in early septic shock[1] — suggest that most patients were not at low risk. Patients had to still be in shock at the time of randomization to ensure that those who had already been treated successfully were not included in the trial. Similar results were seen in the highest-risk subgroups (lactate level, >2 mmol per liter; and norepinephrine dose, >0.28 μg per kilogram per minute), among whom 28-day mortality was up to 40%.

Groesdonk et al. question the level of hemodynamic monitoring, and Morelli and Tritapepe discuss the patients' intravascular volume status. Sites were encouraged to use their routine clinical monitoring practices for septic shock to ensure that all patients had received adequate fluid resuscitation before inclusion and that these measures were repeatedly reassessed. Arterial and central venous catheters were standard, but cardiac-output monitoring was not mandated. As pointed out by Hamzaoui and Teboul, simple cardiac-output monitoring may not be sufficient to fully assess myocardial dysfunction. Echocardiography provides the most detailed assessment of altered cardiac contractility, but its use requires expert hands. Measurements are user-dependent, especially when made by less experienced staff members. A strong supportive evidence base for echocardiography is lacking, and the risk of misinterpretation exists.[2] More objective assessments of ventricular dysfunction, such as total isovolemic time and strain-rate imaging using speckle-tracking echocardiography (which characterizes and measures myocardial deformation),[3] are certainly not within the scope of a clinician with basic echocardiographic training and thus are not suitable to use for inclusion in a large, multicenter clinical trial.

Studies have shown that myocardial dysfunction is present in up to 60% of the patients with septic shock and may not be apparent at initial presentation.[3,4] Therefore, the majority of patients with septic shock could still be expected to benefit from the inotropic effects of levosimendan, not to mention its antiinflammatory, antioxidative, antiapoptotic, and cardioprotective effects.[5] Such effects may offer additional systemic benefit, regardless of the presence of myocardial dysfunction. We did not see any benefit from levosimendan in the predefined subgroups of patients with a low cardiac index (≤2.44 liters per minute per square meter of body-surface area) or those with impaired oxygen delivery (central venous oxygen saturation, <70%) nor in the post hoc subgroup of patients being treated with an inotrope at inclusion, findings that are consistent with the results in the whole population.

Anthony C. Gordon, M.D.
Imperial College London
London, United Kingdom
anthony.gordon@imperial.ac.uk

Robert M.L. Orme, M.B., Ch.B.
Gloucestershire Hospitals NHS Foundation Trust
Cheltenham, United Kingdom

Mervyn Singer, M.D.
University College London
London, United Kingdom

Since publication of their article, Dr. Gordon reports receiving lecture fees from Amomed Pharma and consulting fees from GlaxoSmithKline; and Dr. Singer, receiving consulting fees from Amomed Pharma. No further potential conflict of interest relevant to this letter was reported.

1. The ARISE Investigators, the ANZICS Clinical Trials Group. Goal-directed resuscitation for patients with early septic shock. N Engl J Med 2014;371:1496-506.
2. Mayo P, Mekontso Dessap A, Vieillard-Baron A. Myths about critical care echocardiography: the ten false beliefs that intensivists should understand. Intensive Care Med 2015;41:1103-6.
3. Shahul S, Gulati G, Hacker MR, et al. Detection of myocardial dysfunction in septic shock: a speckle-tracking echocardiography study. Anesth Analg 2015;121:1547-54.
4. Vieillard-Baron A, Caille V, Charron C, Belliard G, Page B, Jardin F. Actual incidence of global left ventricular hypokinesia in adult septic shock. Crit Care Med 2008;36:1701-6.
5. Farmakis D, Alvarez J, Gal TB, et al. Levosimendan beyond inotropy and acute heart failure: evidence of pleiotropic effects on the heart and other organs: an expert panel position paper. Int J Cardiol 2016;222:303-12.

DOI: 10.1056/NEJMc1616632