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

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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.

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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.

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