

ORIGINAL ARTICLE

Trial of Early, Goal-Directed Resuscitation for Septic Shock

Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc., David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D., Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D., Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, D.M., and Kathryn M. Rowan, Ph.D., for the ProMISe Trial Investigators*

ABSTRACT

BACKGROUND

Early, goal-directed therapy (EGDT) is recommended in international guidelines for the resuscitation of patients presenting with early septic shock. However, adoption has been limited, and uncertainty about its effectiveness remains.

METHODS

We conducted a pragmatic randomized trial with an integrated cost-effectiveness analysis in 56 hospitals in England. Patients were randomly assigned to receive either EGDT (a 6-hour resuscitation protocol) or usual care. The primary clinical outcome was all-cause mortality at 90 days.

RESULTS

We enrolled 1260 patients, with 630 assigned to EGDT and 630 to usual care. By 90 days, 184 of 623 patients (29.5%) in the EGDT group and 181 of 620 patients (29.2%) in the usual-care group had died (relative risk in the EGDT group, 1.01; 95% confidence interval [CI], 0.85 to 1.20; $P=0.90$), for an absolute risk reduction in the EGDT group of -0.3 percentage points (95% CI, -5.4 to 4.7). Increased treatment intensity in the EGDT group was indicated by increased use of intravenous fluids, vasoactive drugs, and red-cell transfusions and reflected by significantly worse organ-failure scores, more days receiving advanced cardiovascular support, and longer stays in the intensive care unit. There were no significant differences in any other secondary outcomes, including health-related quality of life, or in rates of serious adverse events. On average, EGDT increased costs, and the probability that it was cost-effective was below 20%.

CONCLUSIONS

In patients with septic shock who were identified early and received intravenous antibiotics and adequate fluid resuscitation, hemodynamic management according to a strict EGDT protocol did not lead to an improvement in outcome. (Funded by the United Kingdom National Institute for Health Research Health Technology Assessment Programme; ProMISe Current Controlled Trials number, ISRCTN36307479.)

From the Clinical Trials Unit, Intensive Care National Audit and Research Centre (P.R.M., G.S.P., D.A.H., R.J., S.E.H., K.M.R.), Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine (M.Z.S., R.D.G.), and Faculty of Medicine, Imperial College London (D.B.), Department of Acute Medicine, Chelsea and Westminster Hospital NHS Foundation Trust (D.B.), and Bloomsbury Institute of Intensive Care Medicine, University College London (M.S.), London, the Department of Intensive Care Medicine, University of Birmingham, Birmingham (J.F.B.), Department of Cardiovascular Sciences, University of Leicester, Leicester (T.J.C.), and Nuffield Division of Anaesthetics, University of Oxford, Oxford (J.D.Y.) — all in the United Kingdom; and the Departments of Surgery and Emergency Medicine, Washington University at St. Louis, St. Louis (T.M.O.). Address reprint requests to Dr. Rowan at the Intensive Care National Audit and Research Centre, Napier House, 24 High Holborn, London WC1V 6AZ, United Kingdom, or at kathy.rowan@icnarc.org.

*A complete list of investigators in the Protocolised Management in Sepsis (ProMISe) trial is provided in the Supplementary Appendix, available at NEJM.org.

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THE INCIDENCE OF SEVERE SEPSIS AND septic shock in adults is estimated to range from 56 to 91 per 100,000 population per year.¹ Affected patients have high rates of death, complications, and resource utilization.²⁻⁵

Since 2002, the Surviving Sepsis Campaign (SSC) has promoted best practice, including early recognition, source control, appropriate and timely antibiotic administration, and resuscitation with intravenous fluids and vasoactive drugs.⁶⁻⁸ Resuscitation guidance is largely based on a 2001 single-center, proof-of-concept study by Rivers et al., which indicated that protocolized delivery of 6 hours of early, goal-directed therapy (EGDT) to patients presenting to the emergency department with early septic shock reduced hospital mortality and hospital stay.⁹ Such therapy aims to optimize tissue oxygen transport with the use of continuous monitoring of prespecified physiological targets — central venous pressure, mean arterial pressure, and central venous oxygen saturation (ScvO₂) — to guide delivery of intravenous fluids, vasoactive drugs, and red-cell transfusions.

However, despite the SSC recommendations, the adoption of EGDT has been limited, with concern about the external validity of results from a single center, the complexity of delivery, the potential risks of the components, and resources required for implementation.^{10,11}

To address these concerns, multicenter trials of EGDT were conducted in the United States (Protocolized Care for Early Septic Shock [ProCESS] trial),¹² Australasia (Australasian Resuscitation in Sepsis Evaluation [ARISE] trial),¹³ and England (Protocolised Management in Sepsis [ProMiSe] trial). In all three trials, harmonized methods¹⁴ were used to permit subsequent meta-analysis of data from individual patients.¹⁵ The two published studies^{12,13} reported no benefit for EGDT. However, both reported lower-than-anticipated mortality, with a 60-day in-hospital mortality of 18.9% (as compared with an anticipated rate of 30 to 46%) in the ProCESS trial and 90-day mortality of 18.8% (as compared with an anticipated rate of 38%) in the ARISE trial. Consequently, neither trial could rule out the potential for a 20% relative reduction in 90-day mortality for EGDT, as compared with usual care, with a relative risk of 0.94 (95% confidence interval [CI], 0.77 to 1.15) in the ProCESS trial and a relative risk of 0.98 (95% CI, 0.80 to 1.21) in the ARISE trial. We based sample-size calculations for the ProMiSe study on a relative risk reduction of 20%.

The ProMiSe study, which was conducted in a setting in which the reported mortality for septic shock is high and was designed with an integrated economic evaluation, tested the hypothesis that the 6-hour EGDT resuscitation protocol is superior, in terms of clinical and cost-effectiveness measures, to usual care in patients presenting with early septic shock to National Health Service (NHS) emergency departments in England.

METHODS

STUDY DESIGN AND OVERSIGHT

Our study was a pragmatic, open, multicenter, parallel-group, randomized, controlled trial. The North West London Research Ethics Committee approved the study protocol, which is available with the full text of this article at NEJM.org. The United Kingdom National Institute for Health Research (NIHR) funded the study and convened a trial steering committee and independent data monitoring and ethics committee. The Clinical Trials Unit at the United Kingdom Intensive Care National Audit and Research Centre (ICNARC) managed the study (for details, see the Supplementary Appendix, available at NEJM.org). Edwards Lifesciences loaned monitors and provided training and technical support but had no other role in the study.

SITES AND PATIENTS

The study was conducted in English NHS hospitals that did not routinely use EGDT that included continuous ScvO₂ monitoring. Adults (≥18 years of age) were eligible if within 6 hours after presentation to the emergency department they had a known or presumed infection, two or more criteria of the systemic inflammatory response syndrome,¹⁶ and either refractory hypotension (systolic blood pressure, <90 mm Hg; or mean arterial pressure, <65 mm Hg, despite resuscitation with at least 1 liter of intravenous fluids within 60 minutes) or hyperlactatemia (blood lactate level, ≥4 mmol per liter) and did not meet any exclusion criteria (see the Methods section in the Supplementary Appendix).

Randomization had to be completed within 2 hours after the patient met the inclusion criteria. All patients provided written informed consent, or consent was granted through an agreement with a personal or professional consultee or independent clinician.¹⁷ Patients were assigned in

a 1:1 ratio by means of 24-hour telephone randomization to receive either EGDT or usual care. Study-group assignment was performed by means of randomized permuted blocks, with variable block lengths of 4, 6, and 8, and stratified according to site. In all study patients, antimicrobial drugs were initiated before randomization.

STUDY INTERVENTIONS

After randomization, the usual-care group continued to receive monitoring, investigations, and treatment as determined by the treating clinicians, whereas the EGDT group started the resuscitation protocol (Fig. S1 in the Supplementary Appendix). For the latter, during the first hour, which was defined as the next whole hour (e.g., if randomization was performed at 9:24, then by 11 o'clock), a central venous catheter capable of continuous ScvO₂ monitoring was placed. The resuscitation protocol was followed for 6 hours (intervention period) with personnel involved and treatment location decided according to the site. At least one trained staff member was available throughout the intervention period. Key staff members were trained before the initiation of recruitment at each site. All other treatment, during the intervention period and after, was at the discretion of the treating clinicians. Blinding to study-group assignment was not possible. During the intervention period, data were collected prospectively for the EGDT group and retrospectively for the usual-care group to avoid the influence of data collection on treatment delivery.

OUTCOME MEASURES

The primary clinical outcome was all-cause mortality at 90 days. Secondary outcomes were the score on the Sequential Organ Failure Assessment (SOFA)¹⁸ at 6 hours and 72 hours; receipt of advanced cardiovascular, advanced respiratory, or renal support and the number of days in the first 28 days after randomization that were free from such support¹⁹; length of stay in the emergency department, intensive care unit (ICU), and hospital; duration of survival; all-cause mortality at 28 days, at hospital discharge, and at 1 year; and health-related quality of life (as measured on the European Quality of Life–5 Dimensions [EQ-5D] five-level questionnaire), resource use, and costs at 90 days and 1 year. Adverse events were monitored up to 30 days. All definitions are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

Using the ICNARC Case Mix Program Database,²⁰ we estimated that 90-day mortality would be 40% in the usual-care group. On the basis of this estimation, we calculated that an enrollment of 1260 patients would have a power of 80% to detect a relative reduction of 20% in risk (absolute risk reduction, 8 percentage points) in the EGDT group, allowing for a loss to follow-up or withdrawal of 6%.²¹

All analyses were performed according to the intention-to-treat principle and were prespecified in the statistical analysis plan.²² A P value of less than 0.05 was considered to indicate statistical significance. All tests were two-sided with no adjustment for multiple comparisons. Continuous variables are reported as means and standard deviations or medians and interquartile ranges. Categorical variables are reported as proportions.

We used Fisher's exact test to compare between-group differences in the primary outcome. Relative and absolute reductions in risk are reported with 95% confidence intervals without adjustment. Secondary analyses of the primary outcome included odds ratio with adjustment for Mortality in Emergency Department Sepsis (MEDS) score components, sensitivity analyses for missing data, learning-curve analysis, and adherence-adjusted analysis. We conducted prespecified subgroup analyses by testing interactions between the effect of EGDT and the degree of protocolized care (in the usual-care group), age, MEDS score,²³ SOFA score, and the time from presentation at the emergency department to randomization.

In the cost-effectiveness analysis, we reported quality-adjusted life-years (QALYs) by combining survival data with quality-of-life scores at 90 days and estimated incremental net benefits by valuing incremental QALYs at the recommended threshold for a QALY gain (£20,000 [U.S. \$28,430]) and then subtracting the incremental costs from this value.²⁴ Stata/SE software, version 13.0, was used for all analyses. (Details about methods are provided in the Statistical Analysis section in the Supplementary Appendix.)

RESULTS

STUDY PATIENTS

From February 16, 2011, to July 24, 2014, we screened 6192 patients at 56 sites (including 29% that are teaching hospitals), which resulted in the enrollment of 1260 patients (Tables S1 and

S2 and Fig. S2 and S3 in the Supplementary Appendix). Four patients requested complete withdrawal and five were ineligible, which left 1251 patients in the initial analysis (625 in the EGDT group and 626 in the usual-care group). Eight patients withdrew before 90 days, which left 1243 patients in the analysis of outcomes (623 in the EGDT group and 620 in the usual-care group) (Fig. 1, and Table S3 in the Supplementary Appendix). The two study groups were well matched at baseline (Table 1, and Table S4 in the Supplementary Appendix).

The criterion for refractory hypotension was met in 338 patients (54.1%) in the EGDT group and 348 patients (55.6%) in the usual-care group, and the criterion for hyperlactatemia was met in 409 patients (65.4%) and 399 patients (63.7%), respectively. The intravenous-fluid volume before randomization was similar in the two groups, as were median times from presentation at the emergency department until inclusion criteria were met and until randomization. Only about two thirds of patients in either group were deemed likely to be admitted to the ICU from the emergency department if they were not enrolled in the study; those deemed unlikely to be admitted were less severely ill. The sites of infection (most commonly lung) were well balanced in the two groups. All patients received antimicrobial drugs before randomization.

ADHERENCE TO THE PROTOCOL

Most patients in the EGDT group underwent timely insertion of a central venous catheter capable of continuous ScvO₂ monitoring. Two catheters that were inserted in error in the usual-care group were not used for monitoring ScvO₂ (Table 2, and Table S5 in the Supplementary Appendix). In the EGDT group, reasons for failure of insertion were as follows: patient no longer met inclusion criteria or met exclusion criteria (22 patients), there was a lapse in the process of care (lack of equipment, staff, beds, communication, or error) (20 patients), there were technical difficulties or problems with a patient (18 patients), there was a decision by a clinician (9 patients), or the patient declined to have a catheter inserted but did not withdraw from the trial (5 patients); in 4 patients, no reason was provided, and 2 patients died before catheter insertion. The mean (±SD) first ScvO₂ value recorded (at hour 1) was 70±12%

(Fig. S4 in the Supplementary Appendix). Standard central venous catheters were not mandated but were placed in 50.9% of the patients in the usual-care group, and ScvO₂ was measured from aspirated blood samples in 6 patients. Arterial catheters were also not mandated but were placed in most patients.

EGDT was stopped prematurely in 21 patients (median time to cessation, 3 hours) because active treatment was withdrawn (9 patients), the patient was no longer considered to have sepsis (5 patients), or EGDT was terminated in error (3 patients); in addition, 1 patient was transferred to an operating room, 1 patient declined treatment, and no reason was provided for 2 patients. Among the 35 patients who died within 6 hours (17 in the EGDT group and 18 in the usual-care group), 5 in the EGDT group and 6 in the usual-care group had withdrawal of active treatment. Adherence to EGDT ranged from 86 to 95%, depending on the method of assessment (Fig. S5 in the Supplementary Appendix).

INTERVENTION PERIOD

During the 6-hour intervention period, patients in the EGDT group received more intravenous fluids than did patients in the usual-care group (Table 2). Hourly fluid volume decreased over the 6 hours, but patients in the usual-care group received a larger initial volume (Fig. S6 in the Supplementary Appendix). Crystalloids were administered more frequently than colloids in the two groups. More patients in the EGDT group than in the usual-care group received vasopressors and dobutamine. Although more patients in the EGDT group received red-cell transfusions, larger volumes were transfused in the usual-care group. During the 6-hour intervention period, administration of platelets and fresh-frozen plasma was similar in the two groups, although the volume of each was higher in the EGDT group (Table 2). At 6 hours, values for central venous pressure, mean arterial pressure, systolic blood pressure, and hemoglobin were similar in the two groups among patients in whom they were measured, which happened with greater frequency in the EGDT group (Table S6 in the Supplementary Appendix).

AFTER THE INTERVENTION PERIOD

Between 6 and 72 hours, the numbers of patients in the two groups receiving intravenous fluids

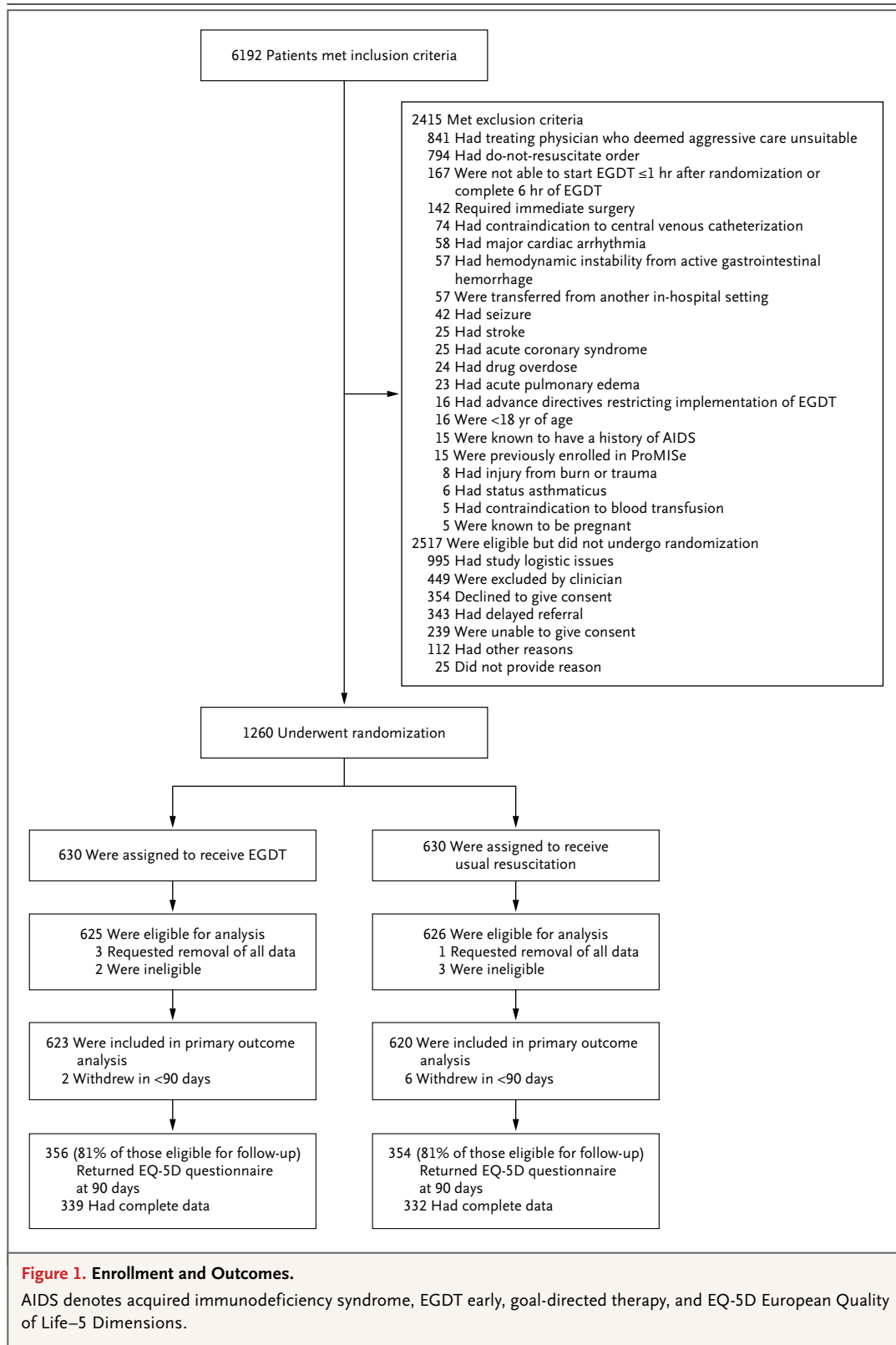


Table 1. Characteristics of the Patients at Baseline.*		
Characteristic	EGDT (N=625)	Usual Care (N=626)
Age — yr	66.4±14.6	64.3±15.5
Male sex — no. (%)	356 (57.0)	367 (58.6)
Refractory hypotension — no. (%)	338 (54.1)	348 (55.6)
Systolic blood pressure — mm Hg	77.7±11.0	78.4±10.2
Mean arterial pressure — mm Hg	58.8±15.8	59.0±10.7
Hyperlactatemia — no. (%)	409 (65.4)	399 (63.7)
Blood lactate level — mmol/liter	7.0±3.5	6.8±3.2
Intravenous fluids administered†		
Before hospitalization until randomization — no./total no. (%)	612/625 (97.9)	606/625 (97.0)
Median total before hospitalization until randomization (IQR) — ml	1950 (1000–2500)	2000 (1000–2500)
Supplemental oxygen — no./total no. (%)‡	397/539 (73.7)	407/542 (75.1)
Median time from presentation in emergency department to randomization (IQR) — hr	2.5 (1.8–3.5)	2.5 (1.8–3.5)
Patient would have been admitted directly from emergency department to ICU if not enrolled in study		
Yes		
Patients — no. (%)	419 (67.0)	427 (68.2)
APACHE II score§	20±6.9	19.0±7.1
No		
Patients — no. (%)	206 (33.0)	199 (31.8)
APACHE II score§	15.0±6.1	15.8±6.5
APACHE II score§	18.7±7.1	18.0±7.1
MEDS score¶	8.0±3.4	7.9±3.3
SOFA score	4.2±2.4	4.3±2.4
Severe condition in medical history — no./total no. (%)**	181/622 (29.1)	161/626 (25.7)
Site of infection — no. (%)		
Lungs	228 (36.5)	207 (33.1)
Abdomen	40 (6.4)	51 (8.1)
Blood	97 (15.5)	86 (13.7)
Central nervous system	12 (1.9)	9 (1.4)
Soft tissue	39 (6.2)	39 (6.2)
Urinary tract	108 (17.3)	117 (18.7)
Other	21 (3.4)	37 (5.9)
No sepsis††	4 (0.6)	3 (0.5)
Unknown	76 (12.2)	77 (12.3)
Change from initial antimicrobial drugs by 72 hr — no./total no. (%)	359/615 (58.4)	342/617 (55.4)

* Plus–minus values are means ±SD. There were no significant differences between the two groups except for age (P=0.01). EGDT denotes early, goal-directed therapy, and IQR interquartile range.

† Intravenous fluids include crystalloids and colloids measuring more than 20 ml in volume and all blood products.

‡ The use of supplemental oxygen was based on the fraction of inspired oxygen.

§ Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating greater severity of illness. The APACHE II score was calculated on the basis of the last recorded data before randomization.

¶ Scores on the Mortality in Emergency Department Sepsis (MEDS) scale range from 0 to 27, with higher scores indicating greater severity of illness. The MEDS score was calculated on the basis of the last recorded data before randomization.

|| Scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating a greater degree of organ failure. The SOFA score was calculated on the basis of the last recorded data before randomization. The SOFA renal score was based on the plasma creatinine level only and did not include urine output.

** Severe conditions in the medical history were defined according to the APACHE II score.

†† The lack of sepsis was confirmed after randomization.

Table 2. Interventions Delivered during and after the 6-Hour Intervention Period.*

Intervention	Hour 0 to 6		Hour >6 to 72	
	EGDT (N=625)	Usual Care (N=626)	EGDT (N=608)	Usual Care (N=607)
Supplemental oxygen — no./total no. (%)	558/623 (89.6)	557/625 (89.1)	520/603 (86.2)	515/603 (85.4)
Insertion of central venous catheter with ScvO ₂ monitoring capability				
Patients — no./total no. (%)	545/624 (87.3)	2/625 (0.3)	NA	NA
Before hour 1 — no./total no. (%)	459/543 (84.5)	NA	NA	NA
Insertion of any central venous catheter				
Patients — no./total no. (%)	575/624 (92.1)	318/625 (50.9)	NA	NA
Median time from randomization to insertion (IQR) — hr	1.1 (0.8–1.5)	1.4 (0.6–2.9)	NA	NA
Insertion of arterial catheter				
Patients — no./total no. (%)	462/623 (74.2)	389/625 (62.2)	NA	NA
Median time from randomization to insertion (IQR) — hr	1.1 (0.4–1.9)	1.0 (0.2–1.9)	NA	NA
Median total intravenous fluids (IQR) — ml†	2000 (1150–3000)	1784 (1075–2775)	3623 (1800–6060)	3981 (1895–6291)
Intravenous colloids				
Patients — no./total no. (%)†	197/623 (31.6)	180/625 (28.8)	171/603 (28.4)	150/603 (24.9)
Median volume (IQR) — ml	1000 (500–1500)	750 (500–1000)	750 (500–1750)	750 (500–1500)
Intravenous crystalloids				
Patients — no./total no. (%)†	584/623 (93.7)	597/625 (95.5)	537/603 (89.1)	543/603 (90.0)
Median volume (IQR) — ml	1750 (999–2750)	1500 (900–2380)	3403 (1576–5647)	3694 (1832–5911)
Vasopressor — no./total no. (%)	332/623 (53.3)	291/625 (46.6)	349/603 (57.9)	317/603 (52.6)
Dobutamine — no./total no. (%)	113/623 (18.1)	24/625 (3.8)	107/603 (17.7)	39/603 (6.5)
Red-cell transfusion				
Patients — no./total no. (%)	55/623 (8.8)	24/625 (3.8)	76/603 (12.6)	51/603 (8.5)
Median volume (IQR) — ml	309 (285–577)	535 (305–607)	351 (291–579)	552 (317–620)
Platelets				
Patients — no./total no. (%)	11/623 (1.8)	10/625 (1.6)	23/603 (3.8)	25/603 (4.1)
Median volume (IQR) — ml	315 (200–340)	180 (163–342)	274 (182–366)	187 (172–357)
Fresh-frozen plasma				
Patients — no./total no. (%)	15/623 (2.4)	14/625 (2.2)	28/603 (4.6)	30/603 (5.0)
Median volume (IQR) — ml	1007 (539–1095)	793 (526–1085)	587 (483–1000)	846 (528–1057)
ICU admission — no./total no. (%)	551/625 (88.2)	467/626 (74.6)	NA	NA
Median time from randomization to ICU admission (IQR) — hr	1.2 (0.4–2.8)	1.2 (0.3–2.8)	NA	NA

* ICU denotes intensive care unit, NA not applicable, and ScvO₂ central venous oxygen saturation.

† Included in this category is the administration of more than 20 ml of an intravenous fluid.

were similar, but patients in the usual-care group received larger volumes. More patients in the EGDT group received intravenous colloids, but overall volumes were similar in the two groups. The number of patients receiving intravenous crystalloids was similar in the two groups, but volumes were larger in the usual-care group. The number of patients receiving red-cell transfusions was higher in the EGDT group, but vol-

umes were larger in the usual-care group. The use of vasopressors and dobutamine remained higher in the EGDT group. Although the numbers of patients receiving platelets and fresh-frozen plasma were similar in the two groups, the volume of platelets was larger in the EGDT group, whereas the volume of fresh-frozen plasma was higher in the usual-care group (Table 2, and Table S7 in the Supplementary Appendix). At 72

hours, physiological, biochemical, and SOFA values were similar in the two groups (Table S8 in the Supplementary Appendix).

PRIMARY OUTCOME

Mortality at 90 days was not significantly different in the two groups, with deaths reported in 184 of 623 patients (29.5%) in the EGDT group versus 181 of 620 patients (29.2%) in the usual-care group, with an unadjusted relative risk in the EGDT group of 1.01 (95% CI, 0.85 to 1.20; $P=0.90$), for an absolute risk reduction of -0.3 percentage points (95% CI, -5.4 to 4.7). After adjustment for baseline characteristics, the odds ratio was 0.95 (95% CI, 0.74 to 1.24; $P=0.73$)

(Table 3). Sensitivity analyses for patients with a missing primary outcome (2 in the EGDT group and 6 in the usual-care group) showed relative risks ranging from 0.99 to 1.03. There was no evidence of a learning-curve effect ($P=0.56$). In the adherence-adjusted analysis, the relative risk was 1.02 (95% CI, 0.78 to 1.32; $P=0.90$) (Table S9 and Fig. S7 in the Supplementary Appendix).

SECONDARY OUTCOMES

The mean SOFA score at 6 hours, the proportion of patients receiving advanced cardiovascular support, and the median length of stay in the ICU were significantly greater in the EGDT group than in the usual-care group. No other secondary

Table 3. Study Outcomes.*

Outcome	EGDT (N=625)	Usual Care (N=626)	Incremental Effect (95% CI)	P Value
Clinical effectiveness				
Primary outcome: death from any cause at 90 days — no./total no. (%)	184/623 (29.5)	181/620 (29.2)		
Relative risk			1.01 (0.85 to 1.20)	0.90†
Absolute risk reduction — percentage points			-0.3 (-5.4 to 4.7)	
Unadjusted odds ratio			1.02 (0.80 to 1.30)	
Adjusted odds ratio			0.95 (0.74 to 1.24)	0.73
Secondary outcomes				
SOFA score‡				
At 6 hr	6.4±3.8	5.6±3.8	0.8 (0.5 to 1.1)§	<0.001
At 72 hr	4.0±3.8	3.7±3.6	0.4 (-0.0 to 0.8)§	0.056
Receipt of advanced cardiovascular support — no./total no. (%)	230/622 (37.0)	190/614 (30.9)	1.19 (1.02 to 1.40)¶	0.026†
Receipt of advanced respiratory support — no./total no. (%)	179/620 (28.9)	175/615 (28.5)	1.01 (0.85 to 1.21)¶	0.90†
Receipt of renal support — no./total no. (%)	88/620 (14.2)	81/614 (13.2)	1.08 (0.81 to 1.42)¶	0.62†
Days free from advanced cardiovascular support up to 28 days	20.3±11.9	20.6±11.8	-0.3 (-1.5 to 1.0)§	0.63
Days free from advanced respiratory support up to 28 days	19.6±12.1	19.8±12.0	-0.2 (-1.5 to 1.1)§	0.78
Days free from renal support up to 28 days	20.6±12.1	20.6±11.9	0.0 (-1.3 to 1.3)§	0.97
Median length of stay in emergency department (IQR) — hr	1.5 (0.4 to 3.1)	1.3 (0.4 to 2.9)		0.34
Median length of stay in ICU (IQR) — days	2.6 (1.0 to 5.8)	2.2 (0.0 to 5.3)		0.005
Median length of stay in hospital (IQR) — days	9 (4 to 21)	9 (4 to 18)		0.46
Death from any cause — no./total no. (%)				
At 28 days	155/625 (24.8)	152/621 (24.5)	1.01 (0.83 to 1.23)¶ 0.95 (0.73 to 1.25)**	0.90† 0.73
At hospital discharge	160/625 (25.6)	154/625 (24.6)	1.04 (0.86 to 1.26)¶ 0.98 (0.75 to 1.29)**	0.74† 0.90

Table 3. (Continued.)

Outcome	EGDT (N=625)	Usual Care (N=626)	Incremental Effect (95% CI)	P Value
Cost-effectiveness				
Health-related quality of life on EQ-5D at 90 days††	0.609±0.319	0.613±0.312	-0.004 (-0.051 to 0.044)§	0.88
Quality-adjusted life-yr up to 90 days	0.054±0.048	0.054±0.048	-0.001 (-0.006 to 0.005)§	0.85
Costs up to 90 days				0.26
Pounds	12,414±14,970	11,424±15,727	989 (-726 to 2,705)§	
Dollars	17,647±21,280	16,239±22,356	1,406 (-1,032 to 3,845)§	
Incremental net benefit up to 90 days‡‡				0.25
Pounds	NA	NA	-1,000 (-2,720 to 720)§	
Dollars	NA	NA	-1,422 (-3,866 to 1,023)§	
Serious adverse events — no. (%)	30 (4.8)	26 (4.2)	1.16 (0.69 to 1.93)¶	0.58†

* All values for the incremental effect are for the EGDT group as compared with the usual-care group. Plus-minus values are means ±SD.
 † The P value was calculated with the use of Fisher's exact test.
 ‡ Renal scores on the Sequential Organ Failure Assessment (SOFA) were based on the plasma creatinine level only. Patients in whom the variables for SOFA renal and SOFA coagulation scores were not recorded between randomization and 6 hours had these values carried forward from baseline, if recorded. Scores for 181 patients who died or were discharged before 48 hours (84 in the EGDT group and 97 in the usual-care group) were not included in SOFA score at 72 hours.
 § This value is the difference between the means.
 ¶ This value is the relative risk.
 || The P value was calculated by means of the Wilcoxon rank-sum test.
 ** This value is the adjusted odds ratio.
 †† Scores on the European Quality of Life-5 Dimensions (EQ-5D) questionnaire range from 0 (death) to 1 (perfect health), with higher scores indicating a better quality of life.
 ‡‡ The incremental net benefit was calculated according to methods of the National Institute for Health and Care Excellence (NICE) by multiplying the mean gain or loss in quality-adjusted life-years by £20,000 (\$28,430) and subtracting from this value the incremental cost. The currency conversion factor that was used was £1 equals \$1.4215.

outcomes were significantly different (Table 3, and Table S10 in the Supplementary Appendix). There was no significant difference in the duration of survival between the two groups (P=0.63 by the log-rank test; adjusted hazard ratio, 0.94, 95% CI, 0.79 to 1.11; P=0.46) (Fig. 2). Mean EQ-5D scores and QALYs were similar in the two groups. The average cost was higher in the EGDT group (£12,414 [U.S. \$17,647]) than in the usual-care group (£11,424 [U.S. \$16,239]), but the difference was not significant (P=0.26) (Table 3, and Tables S11 through S16 and Fig. S8 in the Supplementary Appendix). The incremental net benefit for EGDT as compared with usual care was negative and similar across prespecified subgroups and alternative scenarios that were considered in sensitivity analyses (Tables S17 and S18 and Fig. S9 in the Supplementary Appendix). The probability that EGDT was cost-effective was below 20% (Fig. S10 in the Supplementary Appendix).

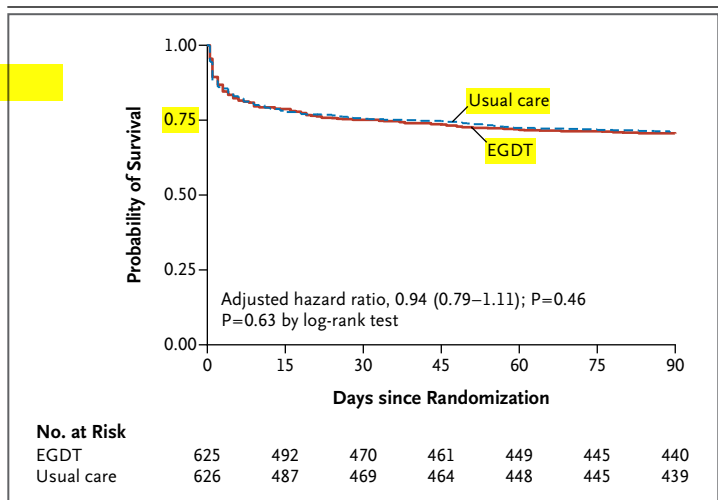


Figure 2. Kaplan-Meier Survival Estimates. Shown is the probability of survival for patients with severe sepsis receiving early, goal-directed therapy (EGDT) and those receiving usual care at 90 days.

SUBGROUP ANALYSES

There was no significant difference regarding the effect of EGDT according to prespecified subgroups as defined by the degree of protocolized care used in the usual-care group, age, MEDS score, SOFA score, or time from presentation at the emergency department to randomization ($P=0.39$ to 0.72 for interaction) (Table S9 and Fig. S11 in the Supplementary Appendix).

SERIOUS ADVERSE EVENTS

At least one serious adverse event was reported in 30 patients (4.8%) in the EGDT group and 26 patients (4.2%) in the usual-care group ($P=0.58$) (Table 3, and Table S19 in the Supplementary Appendix). Four serious adverse events were reported as being related to EGDT (two cases of pulmonary edema and one of arrhythmia, which were deemed to be probably related, and one case of myocardial ischemia, which was deemed to be definitely related), as compared with four events (in three patients) related to usual care (two cases of pneumothorax and one case of pulmonary edema, which were deemed to be probably related, and one case of ventricular fibrillation, which was deemed to be definitely related).

DISCUSSION

In our study involving adults with early signs of septic shock who presented to emergency departments in England, there was no significant difference in mortality at 90 days among those receiving 6 hours of EGDT and those receiving usual resuscitation. Although the overall rate of death in the usual-care group was lower than anticipated (29% rather than 40%), it is unlikely that patients in the EGDT group would have a relative reduction of more than 15% in risk. The effect of EGDT was not significantly different in prespecified subgroups. More patients receiving EGDT were admitted to and spent more days in the ICU. Treatment intensity was greater in the EGDT group, driven by adherence to the protocol and indicated by the increased use of central venous catheters, intravenous fluids, vasoactive drugs, and red-cell transfusions. Increased intensity was reflected by significantly higher SOFA scores and more days of receiving advanced cardiovascular support. There were no significant differences in any other secondary outcomes, including health-related quality of life, which was substantially poorer in this severely ill group of

patients (0.60) than in the general population matched for age and sex (0.80).²⁵ On average, the use of EGDT increased costs, and given similar QALYs in the two groups, the probability that EGDT was cost-effective was below 20%.

Our study was set in a real-world context and in a large, representative, mixed sample of approximately one quarter of NHS hospitals in England. Site setup was rapid, and the study recruited the full 1260 patients over a shorter time period than those of the two similar studies in the United States¹² and Australasia.¹³ This factor minimized the potential for other changes in clinical practice to affect outcomes. Unlike previous studies, our study reports on quality of life and cost-effectiveness at 90 days. Loss to follow-up was low, and all analyses were conducted according to a prespecified statistical analysis plan and included adjusted analyses to address the degree of adherence to EGDT and the possibility of the existence of a learning curve for its delivery.

Our study has several limitations. As in all studies that enroll patients presenting to emergency departments, recruitment was more challenging on weekends and during out-of-office hours; overall, only one third of eligible patients were recruited, although exclusion from the study by a clinician was rare. The intervention could not be blinded, but the risk of bias was minimized through central randomization to ensure the concealment of study-group assignments and the use of a primary outcome that was not subject to observer bias. Since the rate of death was lower than anticipated, our study data may not apply to settings with higher mortality.

Unlike Rivers et al., in their 2001 study, we did not observe a significant reduction in hospital mortality with the use of EGDT. Many aspects of initial sepsis management have changed during the past 15 years, as can be seen in comparing the usual-care groups. In our study, as compared with the study by Rivers et al., mortality was substantially reduced, randomization occurred later, patients appeared to be less sick at baseline (with lower blood lactate levels and Acute Physiology and Chronic Health Evaluation [APACHE] II scores), and all patients received antibiotics before randomization. In addition, our patients received much lower volumes of intravenous fluids and more vasoactive drugs (Table S20 in the Supplementary Appendix).

The level of adherence to EGDT was good and was equivalent to adherence levels in the ProCESS¹²

and ARISE¹³ trials and higher than reported rates of compliance with the SSC guidelines.²⁶ Most outcomes were similar to those reported in the ProCESS and ARISE trials, although the rate of death at 90 days that was reported in our study was lower than that in the ProCESS trial but higher than that in the ARISE trial. Of note, a higher proportion of patients in our study than in the ProCESS and ARISE trials met both of the two inclusion criteria — refractory hypotension and hyperlactatemia (Table S21 in the Supplementary Appendix) — a factor that is associated in our national ICU database with a doubling of hospital mortality (Table S22 in the Supplementary Appendix).

In conclusion, our results suggest that techniques used in usual resuscitation have evolved over the 15 years since the landmark study by Rivers et al.⁹ In our study, NHS hospitals achieved

levels of in-hospital survival in patients receiving usual care that were similar to those achieved with EGDT in the earlier study for patients with septic shock who were identified early and received intravenous antibiotics and adequate fluid resuscitation. The addition of continuous ScvO₂ monitoring and strict protocolization did not improve outcomes in the EGDT group. Our results complete the planned trio of studies of EGDT, all of which showed that EGDT was not superior to usual care.

The views expressed in this article are those of the authors and do not necessarily reflect those of the National Institute for Health Research, the Health Technology Assessment Programme, the National Health Service, or the Department of Health.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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CORRESPONDENCE



Early, Goal-Directed Resuscitation for Septic Shock

TO THE EDITOR: The Protocolised Management in Sepsis (ProMISe) trial (April 2 issue)¹ completes a trio of studies¹⁻³ that question the further application of early, goal-directed therapy (EGDT) as suggested by Rivers et al.⁴ In particular, these trials consistently show no survival benefit with regard to the mandated use of central venous oxygen saturation (ScvO₂) monitoring. However, it remains questionable whether the results of the three trials support this claim. According to the EGDT protocol, an ScvO₂ value of less than 70% is a trigger for hemodynamic intervention. Unlike in the study by Rivers et al., the reported mean values at baseline in all three trials do not require any intervention. Whether the reported survival benefit in the study by Rivers et al. is based on the treatment of patients with initially extremely low ScvO₂ values and determines the targeted patient population that benefits from EGDT remains, therefore, unanswered. Pope et al.⁵ reported increased mortality when ScvO₂ values were initially low (<70%) or high (>80%). Unless subgroup analyses and further studies that focus on these high-risk patients do not rule out a sur-

vival benefit, the final conclusion of the three trials cannot be supported.

Katja Auinger, M.D.

Marco Maggiorini, M.D.

University Hospital Zurich

Zurich, Switzerland

katja.auinger@usz.ch

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

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TO THE EDITOR: The ProMISe trial investigators report that EGDT did not reduce 90-day mortality among patients with early septic shock. Fluid therapy is crucial in EGDT. By 72 hours, approximately 40% of the study patients had received a median of 1.0 liter of intravenous colloids, and 98% of the patients had received a median of 4.9 liters of intravenous crystalloids (Table S7 in the Supplementary Appendix of the article, available with the full text of the article at NEJM.org). The values for the interquartile range indicate that individual patients had received considerably larger amounts. Similar amounts of fluids in the treatment of early septic shock have been shown to increase mean serum chloride concentrations from 100 mmol per liter initially to 106 to 108

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mmol per liter during the first 72 hours,¹ probably related to the use of hyperchloremic solutions. Such solutions are well known to be associated with numerous adverse outcomes.^{2,3} Red-cell transfusion is also associated with worse outcomes, including those in critically ill patients.⁴ Because the use of hyperchloremic solutions and blood transfusions might have obscured potential treatment effects, information regarding types of fluids, serum chloride concentrations, and the reason for the significantly higher frequency of red-cell transfusions in the EGDT group than in the usual-care group is required.

Hans-Joachim Priebe, M.D.

University Hospital Freiburg
Freiburg, Germany
hans-joachim.priebe@uniklinik-freiburg.de

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

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TO THE EDITOR: The ProMISE trial, the Australasian Resuscitation in Sepsis Evaluation (ARISE) trial, and the Protocolized Care for Early Septic Shock (ProCESS) trial suggest no additional benefit from hemodynamic management with strict EGDT, characterizing EGDT only as a hemodynamic study. In addition to hemodynamic monitoring from the EGDT component, the Surviving Sepsis Campaign (SSC) guidelines¹ include early detection of high-risk patients with the use of the criteria of the systemic inflammatory response syndrome, the shock index (ratio of heart rate to systolic blood pressure), and measurement of serum lactate levels. EGDT has played a central role in the development of current tenets of shock management. In the triad of randomized, controlled trials, each component of EGDT was applied in all groups except monitoring of central venous pressure and ScvO₂, and they were pro-

vided in more than 50% of the participants in the usual-care groups. Mortality decreased in both control and intervention groups by more than 50% — a greater degree than in previous trials. These results strongly support the pivotal role of the SSC guidelines that include EGDT.¹⁻³ Although these trials reveal that monitoring of central venous pressure is not mandatory, they show no harm in EGDT and certainly do not suggest that other aspects of the guidelines be called into question. We are concerned that the conclusions promulgated by the triad of trials will be misinterpreted and will cast doubt on the importance of SSC protocols for sepsis detection and treatment.

Sharad Manaktala, M.D., Ph.D.

Stephen R. Claypool, M.D.

Wolters Kluwer Health
Minneapolis, MN
steve.claypool@wolterskluwer.com

Drs. Claypool and Manaktala report being paid employees of Wolters Kluwer Health, which provides decision support for sepsis. No other potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Auinger and Maggiorini suggest that the ProCESS,¹ ARISE,² and ProMISE trials reported mean ScvO₂ values at baseline that are considerably higher than those in both the EGDT group and the usual-care group in the study by Rivers et al.³ The values to which they refer for the EGDT groups in the three trials, however, are not baseline values and are typically from at least 1 hour postrandomization (after insertion of the catheter with ScvO₂ monitoring capability). The values in the study by Rivers et al. are prerandomization (all patients received catheters with ScvO₂ monitoring capability before randomization in this study), and, therefore, the comparison is not valid. Subgroup analyses of high-risk patients in the three multicenter trials, using illness-severity scores, serum lactate concentrations, or both as proxies for baseline

ScvO₂ (because ScvO₂ data were not available for the usual-care groups), showed no evidence of benefit.

We agree with Priebe that administration of intravenous isotonic saline solutions can cause hyperchloremia and acidosis. In the ProMISE trial, although we did not record the type of crystalloid administered or the serum chloride level, the volume of crystalloid administered by 72 hours after randomization was similar in the EGDT and usual-care groups, and it is likely that, on average, the fluids used were the same in the two groups. With respect to red-cell transfusions, the evidence base is conflicting, with more recent data^{4,5} indicating no evidence of harm caused by transfusions.

Manaktala and Claypool are concerned about misinterpretation of the results of the ProCESS, ARISE, and ProMISE trials. With interpretation in mind, we stated in the Conclusions section of the abstract of our article that “in patients with septic shock who were identified early and received intravenous antibiotics and adequate fluid

resuscitation, hemodynamic management according to a strict EGDT protocol did not lead to an improvement in outcome.”

Paul R. Mouncey, M.Sc.

G. Sarah Power, M.Sc.

Intensive Care National Audit and Research Centre
London, United Kingdom

Timothy J. Coats, M.D.

University of Leicester
Leicester, United Kingdom

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

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DOI: 10.1056/NEJMc1506514

Rociletinib in EGFR-Mutated Non–Small-Cell Lung Cancer

TO THE EDITOR: Sequist et al. (April 30 issue)¹ report that rociletinib can overcome the resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in patients with non–small-cell lung cancer (NSCLC) harboring the EGFR T790M resistance mutation. Rociletinib treatment was associated with significantly longer progression-free survival among such patients than among patients not harboring these mutations. We noted that of the 92 study patients who received therapeutic doses of rociletinib, 35 (38%) also received glucose-lowering therapy (typically metformin) to treat hyperglycemia.

Metformin, an antidiabetic drug, has been shown to exert anticancer activity. Lin et al. reported that metformin administration is associated with improved survival among patients with stage IV NSCLC with diabetes.² Our study showed that metformin sensitizes NSCLC cells that are resistant to EGFR tyrosine kinase inhibitors.³ Furthermore, metformin suppresses the expression of the main detoxification enzyme, cytochrome P-450 3A4.⁴ Therefore, it could theoretically elevate plasma concentrations of rociletinib. These effects raise the possibility that metfor-

min may have affected the results of the study by Sequist et al. I would like to know whether the patients who received rociletinib and metformin had better outcomes than those who received rociletinib only.

Yong He, Ph.D., M.D.

Daping Hospital of the Third Military Medical University
Chongqing, China
heyong8998@126.com

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

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THE AUTHORS REPLY: We agree that some evidence suggests that metformin has intrinsic anticancer