blockers is reserved for "patients with heart failure or a left ventricular ejection fraction <40% unless contraindicated,"[1] and therefore it does not apply to the patients in the SECURE trial. Finally, only 1014 of 1237 patients (82.0%) in the polypill group and 1037 of 1229 patients (84.4%) in the usual-care group in our trial received beta-blockers, so we lacked power to investigate whether the effect of treatment with the polypill differed according to beta-blocker use. This was not a prespecified secondary analysis, so any results would be speculative.

We agree with the incisive observation of Carney and Freedland. In a study of the factors that contribute to inadequate adherence in secondary prevention, we found that nonadherence was significantly higher among patients with a higher score for depression (measured with the use of the Patient Health Questionnaire-9) than among those with a lower score.[2] In the SECURE trial, we did not measure whether treatment simplification had an effect on stress and depression as it did on adherence, but if this were the case, it would be an added benefit of the polypill over usual care.

Zhang et al. raise the question about bias in reporting of patient adherence. Adherence was a secondary outcome in our trial, and we consciously sought to avoid overexposing participants to questionnaires during follow-up given that adherence is a behavior, and people tend to modify their behavior simply because they are being observed (in what is classically known as the Hawthorne effect). Because this effect will probably be more marked the more frequently participants are asked about the target behavior, a randomized clinical trial is probably not the most suitable setting in which to measure detected patterns of adherence. With additional questionnaires, the usual-care group would probably have had better adherence than they would had they not been enrolled in the SECURE trial.

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

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DOI: 10.1056/NEJMc2213446

## Aggressive or Moderate Fluids in Acute Pancreatitis

**TO THE EDITOR:** With respect to the trial conducted by de-Madaria et al. (Sept. 15 issue),[1] WATERFALL (the Early Weight-Based Aggressive vs. Nonaggressive Goal-Directed Fluid Resuscitation in the Early Phase of Acute Pancreatitis: an Open-Label Multicenter Randomized Controlled Trial), I concur with the authors that overly aggressive resuscitation in pancreatitis is harmful. However, the results lead me to a different conclusion. In the aggressive-resuscitation group, the initial fluid bolus was 20 ml per kilogram of body weight, followed by a fluid bolus of approximately 1.5 to 2 liters in all patients without determination of volume status, whereas in the moderate-resuscitation group, the initial smaller bolus (10 ml per kilogram) was administered only if the patient was deemed to have hypovolemia. Approximately 50% of the patients in each group were judged to have baseline hypovolemia. The difference in fluid administration was almost entirely achieved in the first 12 hours, and on the basis of the data provided in the article, I estimate that approximately 75% of the difference was attributable to the initial bolus. It would seem that an important part of the fluid overload is the result of fluid administration in patients who did not have a lack of fluid. Therefore, this trial shows that before the administration of fluids, the appropriateness of fluid administration should be assessed.

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

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DOI: 10.1056/NEJMc2213440

**TO THE EDITOR:** The eligibility criteria in WATERFALL resulted in a trial population at low risk for severe complications of acute pancreatitis. Patients in the moderate-resuscitation (control) group of this trial had a lower risk of necrotizing pancreatitis (approximately 7%), organ failure (approximately 4%), and death (<1%) than patients in the control groups of trials that included patients with predicted severe acute pancreatitis (necrotizing pancreatitis in 16 to 62%, organ failure in 15 to 42%, and death in 6 to 9%).[1-3]

Because of the small absolute number of patients in WATERFALL in whom severe complications developed (13 patients with persistent organ failure, infected necrotizing pancreatitis, or death), caution must be taken in extrapolating the results of this trial, which involved mostly low-risk patients, to patients with predicted severe acute pancreatitis or to those who have persistent signs of clinically significant intravascular volume contraction within the first 48 hours after presentation, in whom the benefit of aggressive hydration could be substantial but remains understudied. However, the findings of this trial will undoubtedly affect care in the majority of patients with uncomplicated acute pancreatitis, for which aggressive hydration appears to be unsalutary.

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

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DOI: 10.1056/NEJMc2213440

**TO THE EDITOR:** In WATERFALL, the risk of fluid overload was almost 4 times as high among patients with pancreatitis treated with aggressive fluid resuscitation as among those treated with a more restrictive strategy. However, minimal separation between the groups was achieved in the total volume of fluid received in 72 hours, with a difference of only 1.7 liters. This observation calls into question whether it is truly the fluid that is driving the observed effect.

Notably, there was no concealment of the trial-group assignments for physicians making assessments of volume status. Therefore, the physicians who were adjudicating this outcome were aware of which patients had been assigned to receive larger volumes of fluid, which could have biased their assessments. This is especially worrying given that the assessment of volume status was based in large part on subjective assessment of symptoms and on signs of volume overload on physical examination, which have been shown to have limited diagnostic usefulness.[1] The findings of this trial would have been far more robust if the evaluation of volume status had been done by assessors who were unaware of the trial-group assignments and if more objective measures (e.g., ultrasonographic measurements of venous congestion) had been used.[2]

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

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DOI: 10.1056/NEJMc2213440

**THE AUTHORS REPLY:** WATERFALL compared early goal-directed aggressive fluid resuscitation with moderate fluid resuscitation with the aim to inform the frequently encountered decision of what fluid volume to use in patients who are hospitalized with acute pancreatitis. Many clinicians have used an intensive hydration strategy for all such patients, as is done in patients with burns or trauma. The goal of this approach is to improve systematic and pancreatic blood flow under the working hypothesis that this would

mitigate systematic complications and local pancreatic injury.[1]

Zijlstra, Elmunzer and Tarnasky, and McIver express concerns about the extrapolation of the trial findings to patients with predicted severe pancreatitis. Addressing this question requires a reliable definition of patients at greatest risk for severe disease. We used the criteria for the systemic inflammatory response syndrome (SIRS) as a metric for disease severity, because it is widely espoused in our field.[2] The results of prespecified subgroup analyses involving patients with baseline SIRS and those without and involving patients with hypovolemia and those without mirrored our overall findings. Given that the proportion of patients with baseline SIRS was consistent with those in large, prospective cohort studies,[3] we are confident that our sample represents unselected patients with pancreatitis. Although the trial was not powered to detect efficacy, the development of considerably more fluid overload in the patients with SIRS or hypovolemia receiving aggressive fluid hydration than in those receiving moderate hydration, without even a signal of clinical improvement, underscores our belief that the blunt sword of aggressive hydration for all patients with acute pancreatitis should be sheathed.

Nevertheless, more work is needed to accurately define which patients are at high risk for severe pancreatitis. In addition to the reliable identification of patients in this important subgroup, we agree with our colleagues that double blinding and more objective measurements of fluid status are needed to address the question of fluid strategy in patients with predicted severe pancreatitis. Use of passive leg raises and mini-fluid challenges (the measurement of heart stroke volume before and after the intravenous infusion of crystalloids; e.g., 250 ml of normal saline in 10 minutes to detect patients with a response to fluid resuscitation) are interesting proposals in this area.[4] Finally, a fluid strategy for the specific subset of the early phase, as measured from the inceptions of symptoms, is needed. With these developments, we will be able to craft evidence-based resuscitation strategies that are tailored to the volume needs of individual patients with acute pancreatitis.

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

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DOI: 10.1056/NEJMc2213440


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