We also confirm that the DES inserted in the three cases we reported \(^1\) were in compliance with the Victoria DHS Guidelines for DES, which fall within the FDA guidelines, and therefore do not constitute ‘off-label’ use. With respect to the protocol developed in the Geelong Hospital, we assumed that the DES was a ‘high-risk lesion’ in the coronary circulation and devised a treatment regimen to reduce the risk of coronary occlusion while at the same time minimizing the risk of bleeding at the time of surgery.

We are not sure what the view of ‘most surgeons’ with respect to antiplatelet agents is, but would add some data from our unpublished survey of 24 patients with DES presenting for a total of 43 non-cardiac surgery procedures at this institution. On 15 occasions clopidogrel was stopped, although aspirin was continued. Three patients suffered myocardial infarction due to in-stent thrombosis and two of the myocardial infarcts occurred before surgery. Of the 18 patients undergoing surgery while still on clopidogrel, the only patient to suffer excessive bleeding was transferred from a rural hospital and required two emergency laparotomies, after an episode of severe rectal bleeding.

Our institutional guidelines now advise that patients undergoing superficial, ophthalmic, or minor surgery (including endoscopy without biopsy) should continue clopidogrel throughout the perioperative period. More complex surgery should be planned in consultation with a perioperative physician or cardiologist experienced in the management of these patients at the time of surgery.

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Effects of hydroxyethyl starch in critically ill patients

Editor—The Sepsis Occurrence in Acutely ill Patients (SOAP) trial group have published another analysis from their database \(^1\) on hydroxyethyl starch (HES) and its effects on renal function. \(^2\) However, we are concerned that the methods used were not adequate, and the conclusion drawn ‘that HES had no influence on renal function or the need for renal replacement therapy (RRT)’ must therefore be viewed with caution. Our main concerns are as follows.

(1) Cohort studies must be planned in such a way that available data about potential confounding factors are of good quality. To ensure this, outcome events must be clearly pre-specified in the protocol and the data which will be collected must specifically address the question. \(^3\) \(^4\) Unfortunately, this is not the case with the SOAP protocol. Its short case report form is quite condensed and was primarily designed to study the epidemiology of sepsis and related therapeutic measures, not to answer nearly every open question in critical care medicine.

(2) The “subsequent need for RRT” was defined in the SOAP protocol as the initiation of RRT in the ICU at least 24 h after HES administration or 24 h after admission in patients who did not receive HES’. Thus, the multivariate analyses compared groups with differing definitions for RRT, which is not acceptable.

(3) Median stay in ICU for the cohort of 3147 patients was only 3 days. Multivariate analysis was done on the 1970/3147 patients who stayed more than 24 h in the ICU. Since the multivariate analysis was undertaken in this subgroup, these patients would need to be characterized in more detail.

(4) ‘A total of 1287 received only crystalloids’—this means that 41% of patients either did not receive colloids or did not need volume expansion. This does not mean that 41% of the patients received fluid resuscitation with only crystalloids. As crystalloids are often infused as maintenance fluids, this heterogeneous patient group cannot serve as a comparator to the HES group.

(5) ‘The degree of organ failure assessed by the SOFA score, procedures, and the presence of sepsis syndromes on admission in patients who did not receive HES and at onset of HES administration in those who did were also included as independent variables’. Again, adjustment of confounding factors was performed for different time periods in HES and non-HES groups.

(6) The median amount of HES administered was 555 (IQR, 500–1000) ml per day and the total amount was only 1000 (500–2250) ml per patient. This is an unusually low HES dosage compared with other studies.
in which patients with sepsis received median cumulative HES dosages of 4550 ml or 31 ml kg\(^{-1}\) (IQR 19–51), respectively.\(^5\)\(^6\)

(7) Finally, ‘subsequent need for RRT’ is an inadequate end-point because it is highly dependent on ICU practices, especially in a study with 198 participating ICUs from 24 European countries.

What does this study\(^2\) add to our knowledge? The results from this observational study should be taken with extreme caution. No conclusions for clinical practice can be drawn in view of the limitations of the study methods. For answers to outcome-related questions, we still need to await results of large prospective randomized trials or well-designed independent prospective cohort studies.\(^4\)

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Editor—The SOAP study\(^7\) was a collaborative effort involving more than 200 European investigators. The use of HES and its effects on renal function is one of the post hoc analyses of this database.\(^2\) We agree with Drs Brunkhorst and Schortgen that cohort studies must be planned in such a way that available data about potential confounding factors are of good quality, and these elements were carefully considered in the SOAP study. Definitions and guidelines were provided to the investigators before data collection. Data management was done centrally with daily plausibility analyses to assure good quality of data. Data to be collected were pre-specified by the steering committee.

If the aim of the SOAP study was solely to investigate the epidemiology of sepsis, we would not have collected data on many therapeutic measures, including fluid therapy. Indeed, the intention was to use the SOAP database to address a number of questions in critical care medicine. Useful data have been reported previously from similar databases and have contributed to our understanding of several aspects in the management of critically ill patients. To give only one example, the SUPPORT study,\(^8\) whose aim was to improve end-of-life decision making and care, served as a basis for challenging the use of the pulmonary artery catheter.\(^9\)

Drs Brunkhorst and Schortgen claim that the multivariate analyses we have presented in our paper\(^2\) compared groups with different definitions for RRT, but this is not true. Events should follow predisposition. It was logical to define the ‘subsequent need for RRT’ as the initiation of RRT at least 24 h after HES administration or 24 h after ICU admission in patients who did not receive HES because pre-admission events could have led to renal failure already being present on ICU admission. It is also logical to adjust for the degree of organ failure, procedures, and sepsis syndromes at the onset of HES administration in patients who received HES and at admission in patients who did not receive HES because the latter group has no equivalent time point. The evolution of renal variables in patients with length of stay (LOS) >24 h can be extrapolated from Figures 2 and 3 (patients with LOS <24 h contribute logically only to the first box or column); there was no evidence for an adverse effect of HES on renal function.

Drs Brunkhorst and Schortgen seemed also to have overlooked the data presented in our paper, when they claim that we used patients who received only crystalloids as a comparator to the HES group. Data on the use of other colloids were provided and adjusted for in the multivariate analysis. In addition, the no-HES group included patients who received other colloid solutions. Drs Brunkhorst and Schortgen describe the amount of HES administered in the SOAP study as unusual, but again these are the data. Our study is the first large observational study, to date, to report the type and amount of i.v. fluids in European countries. One cannot compare the amounts of fluids used in an observational study with those used in interventional studies.

Finally, we feel that ‘subsequent need for RRT’ is an adequate end-point in our observational study, especially in view of the large number of centres. We included a large number of factors in our analysis, including the most relevant confounding factors known to influence renal function and outcome of critical illness.

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8 The SUPPORT Principal Investigators. A controlled trial to improve care for seriously ill hospitalized patients. The study to
Pain relief after thoracotomy

Editor—We read with interest the editorial regarding alternatives to epidural analgesia after thoracotomy and congratulate the authors on their account of the pathophysiology of pain after thoracotomy. However, we are concerned that their advocacy of intrathecal morphine as an adjunct to paravertebral analgesia in place of thoracic epidural analgesia may be over-enthusiastic.

It is widely believed that intrathecal morphine will provide analgesia for up to 24 h before additional administration of opioid is required. After a single intrathecal dose of opioid, the subsequent means of delivering opioid would be via an i.v. patient-controlled analgesia (PCA) system. Even when combined with a paravertebral infusion of local anaesthetic solution, supplementary systemic opioids will be required after 24 h. There is potential for significant respiratory depression during the overlapping of the residual intrathecal opioid and the subsequent i.v. opioid. On a more practical note, the presence of a concurrent paravertebral local anaesthetic infusion necessitates the use of a second infusion device with cost and risk management implications. An epidural catheter with a single infusion of a combination of local anaesthetic and opioid can safely be left in situ for up to 72 h and avoids the need for a second infusion device.

We recognize that in a large case series of patients undergoing mainly non-thoracic surgical interventions, the serious adverse effects of intrathecal opioid administration, with a dose range of 0.2–0.8 mg, are relatively low (3%). Our experience would suggest that in the rather elderly and often respiratory-impaired thoracic surgical patient population the incidence is somewhat greater. In our randomized-controlled study looking at the role of intrathecal morphine as an adjunct to i.v. PCA after thorascopic talc pleurodesis surgery, we found that a single lumbar intrathecal injection of preservative-free morphine (5 μg kg⁻¹, range 0.25–0.5 mg) resulted in a 10% incidence of respiratory depression requiring treatment with naloxone.

In discussing the side-effects of thoracic epidural analgesia when compared with paravertebral administration of local anaesthesia, we would suggest that the hypotension often associated with thoracic epidural analgesia and, perhaps to a lesser extent, paravertebral blockade is largely due to an unmasking of underlying hypovolaemia and can usually be alleviated with appropriate and judicious fluid replacement. We note that the studies that demonstrated a greater hypotensive effect with epidural block used a bupivacaine 0.25% infusion regime. Our practice is to combine levo-bupivacaine 0.125% with fentanyl 4 μg ml⁻¹ in our thoracic epidural infusions. Hypotension requiring vasoconstrictor therapy is rarely a problem.

We have been unable to find a randomized controlled trial comparing thoracic epidural analgesia with the combination of intrathecal opioids and paravertebral analgesia in thoracotomy patients. The review of Davies and colleagues conceded that ‘negative studies are less likely to be submitted or accepted for publication and considerable variation can exist between studies in terms of different interventions and different clinical circumstances’. This potential for publication bias should not be ignored when authors commend a potentially useful but untested analgesic technique without the support of randomized-controlled trials.

We applaud the debate Drs Ng and Swanevelder will no doubt stimulate, but feel that any technique for providing pain relief after thoracotomy will have to be compared with the gold standard of a thoracic epidural infusion delivering a combination of local anaesthetic solution and opioid, and must be effective for at least 24 h after operation.

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Editor—Thank you for the opportunity to respond to this letter. We appreciate the comments as acute and chronic pain after thoracotomy is a problem and thus requires healthy debate.

The first point to which McGovern and colleagues refer is the postoperative administration of i.v. morphine by PCA. We would like to stress that morphine by PCA was neither mentioned nor implied in our Editorial. We suggested that a bimodal technique comprising low-dose intrathecal morphine and a paravertebral infusion of local anaesthetic would be effective for analgesia after thoracotomy. In this situation, morphine by PCA would not be required.

In the study in which intrathecal morphine 0.25–0.50 mg and i.v. morphine by PCA were given to patients who had thorascopic talc pleurodesis, we were unable to obtain further details of the study. However, naloxone appeared to be necessary in 10% of patients. This problem can occur after administration of opioids by any route, and epidural opioids are also associated with concentration-dependent respiratory depression. In addition, we find it surprising that intrathecal morphine was used for management of pain after talc pleurodesis. We suggest that...