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Choosing Inclusion Criteria and Publishing Mortality Data: A Critique

To the Editor:

We would like to make some remarks about the article by Dr. Görlinger and his colleagues.[1] Their study demonstrates vividly the primary end point: Hemostatic therapy based on point-of-care testing reduced the number of packed erythrocytes after cardiac surgery.

The study has a very straightforward and precise design. We appreciate the structure of the algorithm even though the progression of the therapeutic options, analyzed step by step, is quite different from the one chosen by our group.

However we disagree with one of the two inclusion criteria outlined. We consider the second criterion reported—"intraoperative or postoperative blood loss exceeding 250 ml/h or 50 ml/10 min"—is very precise because it leads to a reproducible choice of the sample from the population. On the contrary, the first criterion is absolutely dependent on the personal assessment by the singular physician looking after the patient: "diffuse bleeding from capillary beds at wound surfaces requiring haemostatic therapy." Moreover, it seems to be in conflict with the following algorithm of management that aims to investigate if the patients need treatment for bleeding issues and to assess which therapeutic option to choose.

Our second point of criticism is on the description of the results regarding numerous different secondary outcomes. We agree that many of them may be considered very interesting and probably close to statistically significant results, such as the decreased number of fresh frozen plasma and platelet concentrate units transfused in the point-of-care group. We always have to consider that the sample size analysis and the interim analysis reveal the sample size required to statistically demonstrate the primary outcome, and not other outcomes.

Regarding this, we think that publishing the Kaplan-Meier curve is misleading. In this article, this curve demonstrates a survival rate completely different from the one reported in a lot of other articles on the mortality in cardiac surgical patients.[2,3]

According to this Kaplan-Meier curve, the mortality rate after six months in complex cardiac surgery reaches the value of 20%.[1] On the other hand, we noticed that the authors have chosen another important study as a main reference published in 2007 in Circulation.[2] In this article, the Kaplan-Meier curve shows a mortality rate around 6%.[2]

We think that proving a statistically significant reduction in exposure to allogenic blood products in patients treated with hemostatic therapy based on point-of-care testing is interesting, as some previous studies demonstrate an increased mortality in patients transfused in the same surgical context.

Nevertheless, we think that publishing a misleading graph may not help the reader or give value to the notion demonstrated.

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In Reply:

We appreciate Dr. Ziemann-Gimmel's commendation of our randomized clinical trial (RCT) on efficacy of point-of-care (POC) testing in coagulopathic cardiac surgery patients and are happy to comment on his two important considerations.[1]

We agree that increased intraoperative blood loss and subsequent retransfusion of salvaged washed erythrocytes can result in dilutional coagulopathy and, therefore, may further increase transfusion requirements. In addition, transfusion of fresh frozen plasma in order to treat or avoid dilutional coagulopathy results in dilution of erythrocytes and platelets and may increase transfusion requirements for erythrocytes and platelets, too. The only way to avoid this vicious circle is to stop bleeding as quickly as

possible. We thank Dr. Ziemann-Gimmel for pointing out that POC testing-guided hemostatic therapy in our RCT not only reduced postoperative chest tube blood loss by 33%, but also reduced intraoperative retransfused salvaged washed erythrocytes by about 50%, reflecting a significant reduction in intraoperative blood loss. As in our study cell salvage was not used before weaning from cardiopulmonary bypass and heparin-reversal by protamine, this demonstrates again that our POC-guided hemostatic therapy was superior to the conventional algorithm. These results are in line with our retrospective cohort study in 3,865 cardiac surgical patients showing a significant reduction in intraoperative erythrocyte and fresh frozen plasma transfusion requirements after implementation of a coagulation management algorithm based on POC testing and first-line therapy with specific coagulation factor concentrates.[2] Accordingly, both studies demonstrated a significant reduction in the incidence of massive transfusion by 88% and 50%, respectively.[1,2]

In regard to the second comment of Dr. Ziemann-Gimmel, we have to point out that in our prospective RCT the patients were randomly assigned to the conventional or POC group after heparin reversal following cardiopulmonary bypass, as clearly described in the methods section on page 532. Therefore, the first part of the POC algorithm presented in figure 1C (Multiplate [Roche Diagnostics GmbH, Mannheim, Germany]® testing in patients on clopidogrel at the beginning of surgery and ROTEM [Tem International GmbH, Munich, Germany]® analysis after declamping of the aorta) has not been used in this RCT. We agree that presenting the whole POC algorithm primarily used in our retrospective cohort study[2] is capable of being misunderstood by the reader even if the entrance point into the POC algorithm was clearly defined in the methods section. Therefore, we straighten again that neither POC testing nor hemostatic interventions have been performed before detection of diffuse bleeding after heparin reversal by protamine and randomization of the patients. Therefore, costs of unnecessary testing or hemostatic therapy have not been considered in this RCT. However, the comment of Dr. Ziemann-Gimmel that POC testing was applied to all cardiac patients in our retrospective cohort study[2] is not correct. As clearly pointed out in the methods (page 1183) and results sections (page 1184) of this study, POC testing and hemostatic therapy were done solely in patients at high risk of bleeding or with clinically relevant diffuse bleeding after heparin reversal with protamine. In this cohort study, thromboelastometry was performed in approximately 17.5% and impedance aggregometry in 10.6% of the study population after implementation of the POC algorithm.[2] This was done because we wanted to restrict POC testing and hemostatic therapy to bleeding patients, solely, and to avoid treating numbers. Therefore, we completely agree with Dr. Ziemann-Gimmel's comment that reduction in transfusion requirements and cost savings can be assumed to be substantially less in an institution with a low rate of high-risk complex cardiac surgery or low baseline transfusion requirements. This has already been shown by Avidan *et al.*,[3] and accordingly, we performed our RCT in a highly selected patient population undergoing complex cardiac surgery with diffuse bleeding after heparin reversal.

We thank Drs. Colombo and Ghori for their kind comment on our straight and precise study design and the clear results in regard to the primary endpoint (number of transfused units of packed erythrocytes) of our RCT.[1]

We agree that the intraoperative inclusion criterion "diffuse bleeding from capillary beds at wound surface requiring hemostatic therapy" after heparin reversal with protamine is highly dependent on the personal assessment. However, this inclusion criterion has just been used in order to exclude nonbleeding patients from our RCT before randomization. Therefore, it is unlikely that this inclusion criterion may have resulted in any differences between both study groups. As it was not possible to use the same inclusion criterion after closing the chest and transferring the patient to the intensive care unit, we chose the second criterion "blood loss exceeding 250 ml/h or 50 ml/10 min" for postoperative inclusion of patients. By the way, the aim of our RCT was not to predict bleeding but to stop bleeding as quickly and effectively as possible.

We also agree that reporting on the primary endpoint of a study is most important. However, it seems not reasonable for us to waive on reporting on predefined secondary endpoints. Furthermore, the secondary endpoints number of transfused units of fresh frozen plasma, intraoperative retransfused salvaged washed erythrocytes, postoperative chest tube blood loss, time of mechanical ventilation, and incidence of composite adverse events were not only close to statistical significance (as stated by Dr. Colombo and Ghori), but also showed highly significant difference between both study groups ($P < 0.001$).[1] Furthermore, we disagree that publishing the Kaplan–Meier curve is misleading. We are aware of the fact that the reported survival rate in the conventional group of our RCT is different from that in other studies cited by Colombo and Ghori.[2,4] However, this can be explained by the highly selective patient population in our RCT, including patients undergoing complex cardiac surgery and suffering from diffuse bleeding after heparin reversal, solely. Obviously, this group of highly selected patients suffering from microvascular bleeding after complex cardiac surgery present a higher mortality compared to observational studies including all kind of cardiovascular surgery.[2,4] Notably, the 6-month mortality in the conventional group of our RCT (20%) is very close to the 30-day mortality in cardiac surgical patients with postoperative hemorrhage reported by Christensen and von Heymann (22.4%), whereas the mortality in our POC group (4%) corresponds well to the mortality in the nonhemorrhage group (5.5%) of the study published by Christensen and von Heymann.[5] This supports the hypothesis that early POC-guided hemostatic therapy improves patient outcome by avoiding massive transfusion and

subsequent transfusion-associated adverse events. However, we pointed out in our publication several times that this RCT was not powered for mortality and a multicenter study with a larger study population is needed to confirm the results of our single-center RCT.

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Case Scenario Consistent with Lack of Knowledge and Psychological Bias

To the Editor:

Scemama and Hull present a "Case Scenario" followed by a fascinating discussion of leadership principles.[1] However, several of the scenario's observations can be explained based on operational (physical) and behavioral (psychological) principles rather than organization (leadership).

> (1) "The anesthesiology department of a large academic medical center has recently implemented a series of operating room (OR) and anesthesia efficiency measures designed to improve on-time starts, reduce turnover times, and manage patient preoperative times." (2) "These measures will be used to set targets and to measure the performance of providers … She is very focused on being as efficient as possible when running her cases …" (3) "Some of the residents she oversees … do not seem to take the newly implemented efficiency initiatives seriously."

1) Improved on-time starts and reduced turnover times can increase OR and anesthesia group efficiency, but neither is a measure of (allocative or technical) efficiency.[2,3] Suppose every Monday a service has mean ± SD of 7.2 ± 0.5 h of cases. The staffing (allocated time) should be 8 h. If reducing turnovers were to reduce the mean from 7.2 to 6.8 h, there would be no change in staffed hours, overutilized time, or efficiency.[3] If the workload were 8.4 ± 0.5 h, 8-h staffing would be more efficient than 10 h.[3] An equal reduction in turnovers would reduce the mean from 8.4 to 8.0 h, reduce overutilized time, and increase efficiency.[2,3]

2) Comparing on-time starts and turnovers among anesthesiologists is not evidence based.[4–6] Furthermore, unless organizations provide cues (recommendations), decisions made by anesthesiologists supervising (medically directing, *etc.*) multiple ORs to improve on-time starts and reduce turnover times can worsen efficiency.[7] The reason is that anesthesiologists apply rules-of-thumb ("heuristics") rational for decisions involving single ORs, but suboptimal when applied to multiple ORs.[8] Individuals' and organizations' perceptions that on-time starts are important for efficiency are due to both lack of scientific knowledge and psychological bias (*e.g.*, known that most cases take less time than scheduled yet [incorrectly] think starting a few minutes late results in the list of cases finishing a few minutes late).[9–11]

3) Perhaps "some of the residents" not taking the "efficiency initiatives seriously" received systems-based practice training (*i.e.*, knew better).[12] I appreciate this is unlikely and that the authors' goal for the case scenario may have been one of presentation to motivate their excellent review. Yet, it seems to me ideal for leadership to rely on the evidence-based management science, especially when developed in part by and for anesthesiologists.

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