BLEEDING COMPLICATIONS AFTER OFF-PUMP CORONARY ARTERY BYPASS SURGERY: INTERPRETING THE CONTRIBUTION OF HETASTARCH

To the Editor:

I read with interest the article by Hecht-Dolnik and colleagues¹ examining the association between intraoperative administration of hetastarch and bleeding complications after off-pump coronary artery bypass graft surgery. The authors conclude that administration of 1 L of hetastarch in addition to albumin and crystalloid versus albumin and crystalloid alone resulted in increased risk of postoperative transfusion requirement and chest tube drainage. Given the existing body of evidence showing an association between greater quantitative blood loss with the use of high molecular weight (HMW) hetastarch compared with both lower molecular weight hetastarch and albumin, in both cardiac^{2,3} and noncardiac surgery,^{4,5} it is not clear what further information this study provides. Also, features of the study design and ambiguity within the manuscript itself both create difficulty for a reader hoping to interpret the validity or clinical significance of these findings.

First, the composition of hetastarch solution used in the study was never specified. Choice of commercially available hetastarch solutions in the United States at the time this study took place was limited to HMW, highly

substituted starches composed in either saline or balanced salt solution. The differing behavior of hetastarch solutions related to their molecular weight, degree of substitution, and electrolyte composition has been a topic of frequent investigation and commentary.⁶⁻¹¹ Unfortunately, failure of Hecht-Dolnik and colleagues to better identify the hetastarch used does not allow us to fully interpret their results.

Second, the reason for greater blood loss and transfusion requirement is not entirely clear. Standardized (protocol or goal-directed) fluid administration was not described in the methods and presumably was not used during the conduct of the study, nor does it appear that the anesthesiologists administering fluids during the case were blinded to subject randomization. Not surprisingly, the overall volume of colloid was significantly greater in patients in the hetastarch versus albumin group. This greater overall colloid administration may have expanded plasma volume sufficiently to cause subsequently greater clotting factor dilution, decreased blood viscosity, and increased venous return and cardiac output. In turn, these circulatory effects alone may explain the increased chest tube drainage and transfusion requirement seen in the hetastarch group, irrespective of any specific influence hetastarch may or may not have had on platelet aggregation or coagulation.¹²

Although transfusion requirement certainly constitutes one clinically important end point, some equally compelling secondary outcomes, including length of ventilation, intensive care unit stay and hospitalization, rate of return to the operating room, and survival to hospital discharge, did not differ significantly. It would have been interesting to know whether thromboelastogram measurements showed correlation with subsequent transfusion requirement. Beyond that, the opportunity was not taken to explore other physiologic consequences reasonably attributable to fluid management. For example, effective

plasma volume expansion with any colloid, particularly hetastarch, may improve microvascular perfusion and tissue oxygenation, even at the cost of greater quantitative blood loss.¹²⁻¹⁵

Therefore, a tradeoff between approaches may exist. Although the chosen sample size may not have been sufficient to find a difference between measures indicative of tissue oxygenation, their omission is nevertheless unfortunate. The clinical importance of plausibly relevant end points such as infection, wound healing, organ function, cognition, overall cost of care, and longer-term mortality would have justified their inclusion as secondary outcome variables.

Ultimately, clinical interventions must be made with a balanced understanding and consideration of their possible benefit and harm. The recent availability of lower molecular weight hetastarch solutions in the United States, which exhibit lesser dose-dependent coagulation impairment and platelet inhibition, may eventually lead to shift in practice away from HMW hetastarch solutions altogether. There will undoubtedly be more post-marketing studies comparing these newer hetastarch solutions to HMW hetastarch and albumin. Unfortunately, Hecht-Dolnik and colleagues¹ studied only those end points that are easily predicted and measured. I sincerely hope that future investigative efforts will encompass a more comprehensive set of clinically meaningful end points, so that dollars and effort spent on research will yield novel, informative data that will be helpful in guiding clinical decision-making.

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1. Hecht-Dolnik M, Barkan H, Taharka A, Loftus J. Hetastarch increases the risk of bleeding complications in patients after off-pump coronary bypass

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Reply to the Editor:

We thank Dr McKay for her comments regarding our article. We examined the relative safety in off-pump coronary artery bypass grafting (CABG) of two volume replacement fluids in widespread use at the time we conducted our study.¹ Dr McKay argues that the questions we investigated are moot, that the fluids whose safety we investigated are not in widespread contemporary use, and that there were methodologic flaws in our study conduct. We will now address each of Dr McKay's arguments, showing that the choice between the volume replacement fluids we studied remains clinically relevant, that her methodologic concerns are overstated, and that our findings raise a series of further questions.

Dr McKay states that there is existing evidence demonstrating that use of high molecular weight (HMW) hetastarch, one of the fluids we studied, is associated in both cardiac and noncardiac surgery with greater blood loss than is either low molecular weight (LMW) hetastarch or albumin. Dr McKay offers two examples of prior studies of bleeding risk in cardiac surgery. Unfortunately, whereas we examined bleeding risk in off-pump CABG, the first of the cardiac papers Dr. McKay cites² investigated the impact of hetastarch and albumin as pump prime in on-pump cardiac procedures, and the second³ examined the impact of hydroxyethyl starch (Voluven), an LMW hetastarch, in orthopedic procedures. Generalization of findings from either of these studies to the risk posed by HMW hetastarch in off-pump procedures is at best problematic. The differences between the hemodynamic properties of on-pump versus off-pump cardiac procedures are well documented.⁴⁻⁷ McKay also cites two prior reviews of the risks associated with volume replacement fluids in noncardiac surgery. The first⁸ cites 10 studies of volume replacement that actually examined the effects of its use in cardiac surgery. All of these

studies of cardiac surgery examined on-pump procedures and/or other use of fluids and/or postoperative fluid administration. None of these studies examined perioperative administration of hetastarch versus albumin in off-pump procedures. The second cited article⁹ again examined only on-pump cardiac procedures. Perhaps Dr McKay inadvertently switched the citations to Gandhi³ and Wilkes⁹ and their associates. That second article⁹ was actually one of the sparks for our decision to investigate risks associated with volume replacement fluid use in off-pump procedures. Parenthetically, that second article is considered by many to have established that the particular formulation of hetastarch carries too high a bleeding risk for it to be used routinely for volume replacement in CABG procedures performed on-pump. We instead examined the bleeding risk carried by HMW hetastarch in off-pump procedures. Approximately 20% of the CABG procedures in 2007 were performed off-pump.¹⁰ We note that the recently published results of a large-scale randomized clinical trial that favor on-pump over off-pump procedures may impact this practice pattern, contributing to an increase in the relative frequency of on-pump procedures.¹¹

Second, Dr McKay was not clear regarding the hetastarch formulation used in our study. Our study examined Hextend, a formulation of HMW hydroxyethyl starch 6% in a buffered electrolyte dextrose solution. This composition of the test solution infused is identified on our article's first page, and its administration is discussed in the section describing randomization and sample size. We inadvertently omitted mentioning this fluid a second time in the Clinical Protocol section of our article. We apologize for any confusion this may have caused for Dr McKay or other readers. Participants were randomly assigned to receive an initial infusion of 1000 mL of Hextend or 1000 mL of albumin. Any subsequent infusions of