well-documented excess long-term mortality associated with uncorrected severe aortic stenosis. In contrast, recently published follow-up data from the PARTNER trial³ showed that among 1-year survivors, mortality during year 2 of follow-up was significantly lower among TAVR patients than among SM patients (18% vs 35%; hazard ratio, 0.58; $P = .02$). Doble and colleagues' approach¹ is therefore very likely to have underestimated the survival benefit that TAVR provides for inoperable patients.

Finally, in their model for high-risk surgical candidates, Doble and colleagues¹ assumed that the increased risk of stroke with TAVR relative to SAVR observed in the first year of follow-up in the PARTNER trial would continue at a constant rate through the 20-year time horizon of the model. Detailed analyses of neurologic events in the PARTNER trial,⁴ as well as recently published longer-term follow-up data,⁵ suggest that after the first 30 days of follow-up, stroke rates for TAVR and SAVR were similar.

We believe that Doble and colleagues' cost-effectiveness model¹ should be updated in light of these important new data. If this were to be done, the articles conclusions could be significantly altered.

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DOES ALBUMIN INTERFERE WITH COAGULATION-RELATED OUTCOMES WHEN COMPARING COLLOIDS IN CARDIAC SURGERY?

To the Editor:

The publication by Navickis and colleagues¹ highlights a subject with conflicting results in the literature, the effect of hydroxyethyl starch (HES) on bleeding after cardiac surgery. Their study included 18 trials with 970 patients reported between 1982 and 2008. The primary end point was postoperative blood loss during the first 24 postoperative hours, and secondary end points were reoperation for bleeding and blood product transfusion within the same period. Navickis and colleagues¹ concluded that HES 450/0.7 and 200/0.5 increased postoperative blood loss, reoperation rates and blood product transfusion relative to albumin, with the statement that despite the lack of sufficient direct data for HES 130/0.4, its effects could be assumed equivalent to those of HES 200/0.5 on the basis of head-to-head comparisons.

In this valuable meta-analysis, we think that there is yet another topic to be discussed. The deleterious effects of HES solutions on bleeding have been emphasized, but the possible positive effects of albumin on

coagulation were not discussed. The older meta-analysis by the same group published in 2001 discussed this topic in detail.² In that article, they stated that albumin, with its antioxidant and free-radical scavenging activity, may serve to avert bleeding after cardiopulmonary bypass (CPB).² They also declared that albumin was shown to block erythrocyte crenation caused by CPB and to preserve functional and morphologic integrity of platelets, which are heavily affected during CPB. They speculated that the difference in bleeding tendency could be attributable to the deleterious effect of HES solutions alone or in combination with protective effects of albumin. Lange and associates³ in their recent and very detailed review on use of colloids in cardiac surgery, defined the anticoagulant action of albumin while summarizing the characteristics of colloids.³ Many controversial results are being published regarding effects of colloids on coagulation, so the effects of albumin on coagulation could be detailed in this valuable meta-analysis.

We believe that the discussion on HES products and their effects on coagulation will continue. In particular, since the retraction of the publications of Boldt, who made substantial contributions to the colloid-colloid and colloid-crystalloid debates in favor of HES, the subject has shifted to a more complicated pattern, leading readers to a more skeptical approach. Physicians can benefit greatly from meta-analyses such as that of Navickis and colleagues.¹ We as readers thank the authors for sharing their knowledge and the experience of their detailed research.

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Reply to the Editor:

Our thanks to Durukan and colleagues for their positive comments about our meta-analysis on bleeding after cardiopulmonary bypass (CPB).¹ We agree that it is important to consider the role of albumin in preserving coagulation system function among patients undergoing CPB. In particular, CPB places these patients at risk for acquired transient platelet dysfunction attended by diffuse nonsurgical postoperative bleeding.

A protective effect against hemorrhage is suggested by observations in cardiac surgical patients with albumin deficiency. In a prospective study of 5168 consecutive patients undergoing coronary artery bypass grafting, preoperative hypoalbuminemia (serum albumin <25 g · L⁻¹) was an independent risk factor of reexploration for bleeding, with an odds ratio (OR) of 1.4 (95% confidence interval [CI], 1.0-2.1; *P* = .04) after adjustment for 17 other variables.² Preoperative hypoalbuminemia was also an independent risk factor for mortality in that study (OR, 2.0; 95% CI, 1.3-3.0; *P* = .002).

In a meta-analysis of 21 controlled clinical trials with 1346 total patients, extracorporeal circuit priming with albumin maintained on-bypass platelet

counts at a significantly higher level than that seen with crystalloid alone.³ Furthermore, albumin priming was significantly associated with postoperative reductions in thrombocytopenia, blood loss, and reoperations for bleeding relative to crystalloid-alone priming in a retrospective study of 377 patients undergoing CPB. In a randomized trial, addition of albumin to a priming solution containing artificial colloid (dextran 70) also resulted in significantly higher platelet counts as long as 48 h after CPB, with significantly less blood loss from the mediastinal drains.

Albumin is capable of modulating platelet activity through biologically specific mechanisms. Platelet aggregability can be modulated both by complexes of fatty acids bound to albumin and by nitric oxide-albumin adduct. Albumin also binds with high affinity to platelet-activating factor, thereby reducing its activity, and this binding occurs exclusively in domain II of the albumin molecule extending from polypeptide chain amino acid position 240 to 386.

As Lange and coauthors⁴ acknowledge, it is accepted that albumin does not interfere with coagulation, other than possibly by hemodilution. Those authors nevertheless cite two pieces of contrary evidence, neither concerned with cardiac surgery. First, after in vitro dilution of blood samples from patients scheduled for elective general surgery, albumin impaired thromboelastographically assessed coagulation to a greater extent than normal saline solution or hydroxyethyl starch 450/0.7. However, in 3 randomized trials of colloid use in vivo among patients undergoing CPB, 1 involving pump priming and the other 2 involving postoperative volume expansion, albumin significantly improved clotting as measured by thromboelastography compared with hydroxyethyl starch 120/0.7, 130/0.4, 200/0.5, or 450/0.7.¹

Second, in a subgroup analysis of data from the SAFE (Saline versus

Albumin Fluid Evaluation) study, activated partial thromboplastin time on day 2 increased by 7% in patients receiving albumin while decreasing 2% in recipients of normal saline solution.⁵ The SAFE study investigators conceded that this difference was “small and thus of questionable clinical importance.”⁵ Furthermore, the difference can be readily explained by greater hemodilution in the albumin group. Thus the ratio of saline solution to albumin infused during the first 2 days of the SAFE study was only 1.4, whereas in a randomized trial of patients undergoing CPB, the ratio needed for equivalent plasma volume expansion was 5.8.

From a physiologic perspective, it appears highly unlikely that albumin, the most abundant protein in plasma, would specifically interfere with coagulation. The components of the coagulation system have evolved to function under constant exposure to serum albumin concentrations of approximately 35 to 50 g · L⁻¹ during normal conditions.

Albumin remains the criterion standard for fluid management in cardiac surgery. A chief advantage, either for extracorporeal circuit priming or perioperative volume expansion, is maintenance of a competent coagulation system.

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