Reply to the Editor:

My colleagues and I appreciate the comments by Lin and colleagues regarding potential issues that may influence outcomes in pexelizumab-treated patients. Their hypothesis that pexelizumab may cause platelet aggregation, however, is not supported by the literature. We note that their reference 3 (Røger and colleagues) actually suggested that inhibiting the terminal complement cascade with a molecule such as pexelizumab might inhibit platelet aggregation. The suggestion of Lin and colleagues that this compound's cardioprotective effect may depend on the presence of adequate antithrombotic therapy is an interesting but unproven hypothesis. Unfortunately, Lin and colleagues' suggestion that large amounts of heparin may achieve longer activated clotting times to suppress thrombin activity is also not supported by the literature.¹

We also disagree that as time passes, heparin-bonded circuits may replace the traditional bypass circuits, because the literature is equivocal that reducing perioperative heparin improves safety in cardiac surgical patients. In fact, there is literature suggesting that providing even more systemic heparin might be important in producing less bleeding in cardiac surgical patients.^{2,3}

Lin and colleagues is suggested that we reanalyze the Pexelizumab for Reduction of Infarction and Mortality in Coronary Artery Bypass Graft Surgery data with regard to the use of heparin-bonded perfusion circuits, presumably as a surrogate for total heparin dose, to test their hypothesis. We have reviewed the data from the Pexelizumab for Reduction of Infarction and Mortality in Coronary Artery Bypass Graft Surgery II trial, in which 27% of the patients were operated on with heparin-bonded circuits. The primary end point did not differ between pexelizumab and placebo groups (relative risk, 1.02; $P = .9319$). Heparin

dosing was not captured in the case report forms.

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COMMENT ON "EFFECT OF STORAGE TIME OF TRANSFUSED PLASMA ON EARLY AND LATE MORTALITY AFTER CORONARY ARTERY BYPASS GRAFTING"

To the Editor:

Plasma from blood donors is frozen and stored at -30°C for a maximum of 2 years. van Straten and colleagues¹ recently reported a 3 times increased 30-day mortality after coronary artery bypass grafting if patients received fresh-frozen plasma (FFP) that had been stored for more than 323 days (old) compared with FFP that had

been stored for a shorter time (young). If longer storage of FFP is truly independently associated with a higher mortality, we would need to consider changing the regulations on storage times of FFP. However, before jumping to this conclusion, one needs to carefully consider alternative explanations for the observed association, such as potential biases and confounding.

The design of the study, a cohort among consecutive patients undergoing coronary artery bypass grafting in a period of 10 years, was well chosen, because the choice to transfuse old or young FFP is random. Patients who have received old FFP and patients who have received young FFP can therefore be compared as if from a randomized trial. Table 1 in the report can be used to check whether the randomization was successful. Unfortunately, there are several remarkable differences between the intervention groups, such as the number of patients who underwent reexploration (young FFP 36% vs old FFP 25%) and platelet transfusion (young FFP 0.29 units vs old FFP 0.42 units). Therefore, we conclude that proper randomization was not achieved.

There are several possible explanations for unequal distribution of prognostic factors across the intervention groups. Changes in techniques to produce and store FFP, such as leucodepletion since 2001 and the male-only plasma measure since 2007, have all affected the storage times of FFP during the 10-year period of the study. Therefore, although the choice to

TABLE 1. Time trends in number of patients receiving only young or old fresh-frozen plasma

Year	Only young FFP*	Mixed FFP	Only old FFP*	Total
2004	2 (2.7%)	1 (1.4%)	71 (96%)	74
2005	0 (0%)	4 (1.1%)	365 (99%)	369
2006	5 (1.2%)	20 (4.8%)	390 (94%)	415
2007	120 (27%)	88 (20%)	243 (54%)	451
2008	283 (57%)	121 (25%)	89 (18%)	493
2009	28 (18%)	25 (16%)	103 (66%)	156

FFP, Fresh-frozen plasma. *Only young and only old defined according to van Straten and colleagues¹ at a cutoff of 323 days. Figures represent number of patients and percentages (in parentheses) of the total number of FFP recipients in that year.

transfuse old or young FFP is random at any given time, the probability of receiving old or young FFP varied over the study period. In addition, during the 10-year period, operation techniques, transfusion strategies, and supportive care have also changed. As a result, the increased survival of patients receiving young FFP might not be related to the properties of the transfused plasma but rather to the improvements in operative, supportive, or nursing strategies, which happen to temporally coincide with the probability of receiving young FFP.

We examined time trends in FFP storage time in The Netherlands by documenting the storage time of FFP between 2004 (a new transfusion information system was introduced in our hospital in 2004) and 2009 in the Leiden University Medical Center. Table 1 shows that the number of patients who have received only old FFP and only young FFP has changed significantly during these years. Similar differences may form an alternative explanation for the association between old FFP and mortality as reported by van Straten and colleagues. We agree with the authors that additional studies are necessary to resolve this issue.

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HUMAN SAPHENOUS VEIN “NO-TOUCH” HARVESTING AND VASA VASORUM

To the Editor:

Dreifaltdt and colleagues¹ carried out an elegant image study to evaluate the impact of vein graft harvesting technique on the structure and function of vasa vasorum. The total area of vasa vasorum in vein grafts harvested with the conventional technique was significantly reduced in both the media and the adventitia compared with vein grafts harvested with the “no-touch” technique that preserved an intact vasa vasorum, whereas the conventional technique did not.¹ These findings corroborate Dashwood and colleagues² hypothesis that vasa vasorum preservation could represent one of the mechanisms underlying the possible improved patency of saphenous vein grafts harvested with this technique.² We would like to share with the authors some thoughts and speculations based on evidence from the literature.

Three processes are responsible for vein graft failure: thrombosis, intimal hyperplasia, and accelerated atherosclerosis, which contribute to graft failure. Studies have shown that perioperative antiplatelet therapy can reduce early thrombosis and graft failure. The “no-touch” technique for harvesting grafts may be effective in preventing disruption to the endothelial layer and subsequent intimal hyperplasia and graft loss,³ but at least one apparent paradox has to be clarified about human saphenous vein vasa vasorum. This apparent paradox is based on the well-known fact that absence of vasa vasorum is a probable protection against intramyocardial arteries and left thoracic artery atherosclerosis.

Recent evidence has shown no clinical disadvantages, and even advantages, of not replacing angiographically pristine grafts at long-term follow-up. Measurements of nitric oxide release of old saphenous vein grafts, when angiographically pristine, are equal to that

of native saphenous veins. These findings support the recent clinical observations that long-term angiographically disease-free vein grafts are biologically privileged.⁴

The vasa vasorum form a network of microvasculature to supply oxygen and nutrients to the outer layers of the arterial wall. The expansion of the vasa vasorum to the second order is associated with neovascularization related to progression of atherosclerosis. It was shown that, when arterial grafts are used in coronary bypass surgery (eg, internal thoracic artery and right gastroepiploic artery), the poorly developed vasa vasorum is related to better patency.⁵ However, in saphenous vein graft, the preservation of vasa vasorum can be associated with reduction of graft failure.^{1,2} As already mentioned, is this fact a paradox or are there functional differences between arteries and veins? In other words, the presence of vasa vasorum in arteries “facilitates” atherosclerosis and, on the other hand, its presence “protects” against the same process of atherosclerosis? That would be an important point to be investigated.

There are histologic and image studies showing the human saphenous structures preservation by using the “no-touch” harvesting. In dealing with studies on the patency of saphenous vein, Dashwood and colleagues² provided interesting information about increasing the human saphenous vein graft patency in the long-term. However, the number of patients studied is small and large trials are still needed to prove the superiority of grafts harvested by the no-touch technique.

The discussion on human saphenous vein harvesting can repeat the internal thoracic artery skeletonization saga. In the end, the results of coronary artery bypass grafting with saphenous veins would be similar. It is necessary to emphasize an important salutary bias toward the “no-touch” technique, which in principle implies obsessive care in harvesting the veins.