Efforts during the past 5 to 10 years to increase the proportion of patients in the United States who receive maintenance hemodialysis via a fistula have been successful. In 2008, 55% of prevalent patients in the United State were undergoing dialysis via a fistula compared with only 35% in 2003 (1,2). Despite this substantial progress, challenges remain, among the most important of which is the high rate of fistula maturation failure. Recent studies report that up to 40 to 60% of newly created fistulas fail to mature adequately to be used for dialysis (3,4). Maturation failure often necessitates multiple surgical procedures for patients and prolongs use of central venous catheters, the vascular access type with greatest risk for complications and costs. Reducing maturation failure is essential for improving vascular outcomes among patients who receive long-term hemodialysis.

The presence of angiographically demonstrable stenoses in a large proportion of fistulas with maturation failure has led to assumptions that (1) these stenoses contribute to maturation failure and (2) reducing or eliminating the lesions could facilitate maturation. This reasoning is consistent with the well-accepted view that stenoses underlie failure of synthetic AV grafts, although, in contrast to fistulas, failure of synthetic grafts typically occurs after initial function of the access. In a histologic study of a small number of fistulas with maturation failure, Roy-Chaudhury et al. (5) found stenotic lesions that looked similar to those in synthetic grafts: neointimal hyperplasia with myofibroblasts as the predominant cell type. Surgical revision of the AV anastomosis for peri-anastomotic stenoses and percutaneous angioplasty for lesions that are either peri-anastomotic or downstream in the draining vein are increasingly being used to facilitate maturation of newly created fistulas (6,7).

The findings of the study by Lee et al. (8) in this issue of CJASN provide important information about the long-term outcomes of fistulas that have undergone maturation-enhancing interventions. In their retrospective analysis of 173 fistulas that were ultimately usable for dialysis, these investigators found that the cumulative survival was shorter and the number of postmaturation procedures was greater for the 77 fistulas (45%) that had one or more surgical or endovascular interventions before use for dialysis compared with the 96 fistulas that had no procedures before use. Cumulative survival, defined as the time from initial fistula cannulation until abandonment, was 92% at 1 year for fistulas that were usable without intervention. In contrast, fistulas that required one procedure or two or more procedures to enhance maturation had 1-year cumulative survivals of 78 and 68%, respectively. After initial use of the fistula, the average number of procedures performed per year to maintain function were 0.76, 1.37, and 3.51 for fistulas that had zero, one, and two or more procedures before use, respectively.

How should we interpret these findings, and why are they important? As the authors acknowledge, maturation-enhancing interventions provide benefit. They enable use of fistulas that would otherwise be abandoned. However, for many patients, the benefit seems to be short-lived and not as great as may have been previously assumed, especially when more than one maturation-enhancing procedure is performed. Lee et al. emphasize the possibility that the interventions themselves, particularly angioplasty, are harmful to the vasculature and may actually hasten fistula failure. This is a reasonable concern based on what we know about the response of the endothelium to injury and given the results of several trials evaluating endovascular repair of stenoses in synthetic grafts (9). However, the data from the study by Lee et al. cannot be used to evaluate this issue. Surgical revision, a procedure that is probably less damaging to the endothelium than angioplasty, was used too infrequently in their cohort to allow assessment of the contribution of the angioplasty intervention to the poor long-term outcome of the fistulas. An alternative interpretation of the study findings is that fistulas that do not mature on their own are of poor quality and are “doomed from the start.” Maturation-enhancing procedures can help temporarily, but the benefit is not sustained, especially when multiple procedures are needed. There are similarities between the findings of the study by Lee et al. and those of the Dialysis Access Consortium (DAC) trial that tested the ability of clopidogrel to prevent early failure of new fistulas (4). The DAC trial found that clopidogrel prevented early thrombosis but did not increase the proportion of fistulas that were usable for dialysis. The DAC trial intervention targeted thrombosis, whereas the procedures used in the study by Lee et al. targeted stenosis. Both interventions had benefit with respect to the targeted lesion; however, neither the DAC intervention nor the interventions used in the study by Lee et
al. satisfactorily altered the outcome of fistulas that perhaps were “doomed from the start.”

The findings of this study also have implications for selecting outcome measures for clinical trials. Given the generally satisfactory outcomes of fistulas that have successfully matured, most interventions for fistulas aim to reduce maturation failure. However, the finding that fistulas that have undergone endovascular or surgical maturation-facilitating procedures have good short-term but disappointing long-term outcomes suggests that fistulas that require endovascular or surgical procedures to become usable for dialysis should probably be classified as treatment failures in clinical trials. Given that such procedures are being increasingly incorporated into clinical practice, a reduction in the need for these procedures might become a goal for novel maturation-enhancing interventions.

Importantly, the study by Lee et al. reminds us that defining fistula maturation is complicated. Although usability for dialysis is often considered an indicator of successful maturation, how the fistula got there (i.e., how it became usable) seems to be important. The “Fistula First” approach was adopted because fistulas last. In moving forward, we need to ensure that this continues to be true.

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References