a stasis thrombosis model, and extrapolation of a dosing regimen derived from a different patient population with a different indication. The Food and Drug Administration and the European Medicines Agency have recommended against the use of dabigatran in patients with mechanical heart valves. Off-label use will place patients at undue risk and is rightfully prohibited. The results of RE-ALIGN are disappointing, but there is a palpable downside as well to potential premature abandonment of research into the use of such drugs in patients with mechanical heart valves.

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C1q-Binding Antibodies in Kidney Transplantation
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Antibody-mediated injury is now recognized as a major cause of renal-allograft injury and loss. Antibodies can cause vascular injury that is acute or chronic as well as abrupt or progressive loss of function. The diagnosis of antibody-mediated injury is based most critically on the detection of donor-specific antibodies, along with evidence of complement activation in the graft and signs of tissue injury and inflammation. Methods of detecting antibodies have become increasingly sensitive and precise, and the repertoire of potentially pathogenic antibodies includes a broad range of anti–class I HLA antibodies and anti–class II HLA antibodies, as well as non-HLA antibodies. Antibodies develop in many allograft recipients, with associated graft loss that may occur years later.

A critical issue for patient care is discerning which of the detected antibodies are pathogenic. Antibody class, specificity, and strength can be correlated with the occurrence of antibody-mediated rejection, graft outcome, or both, but such correlation is imprecise. Since complement activation by antibodies is an important initiator of graft injury, assessment of the ability of antibodies to fix complement has become of increasing interest. C4d binding by antibodies was shown to correlate with graft survival in small cohorts of recipients of solid-organ allografts. Since the “signal” for C4d binding by antibodies is relatively low, the ability of antibodies to bind C1q is a current focus. Recent small series have shown that the presence of C1q-binding antibodies correlates with worse graft survival of kidney and heart transplants.

The study by Loupy et al. in this issue of the Journal is an important contribution to this growing literature. It is a large study designed to determine whether detection of C1q binding by donor-specific antibodies that develop after transplantation improves prediction of allograft loss and risk stratification. C1q binding by antibodies was strongly correlated with antibody-mediated rejection in the first year after transplanta-
tion, with more microvascular inflammation and injury, more C4d deposition in the peritubular capillaries of the graft, and a lower estimated glomerular filtration rate (GFR) at 1 year. C1q-binding antibodies also correlated with worse 5-year graft survival, whether they were detected at the time of rejection during the first year or at 1 year, and with a higher risk of graft loss in each of three categories of estimated GFR at 1 year.

C1q binding also correlated with the strength of donor-specific antibodies as measured according to the mean fluorescence intensity. Two thirds of the cohort with C1q-binding antibodies had a mean fluorescence intensity of 6000 arbitrary units or higher, whereas only 10% of those with non–C1q-binding donor-specific antibodies had similarly high levels of mean fluorescence intensity. Clearly, the likelihood of detecting C1q-binding antibodies will increase with higher antibody levels, as previously reported.\(^8\,9\) Thus, it is likely that the strength (titer) of donor-specific antibodies would be a strong predictor of outcome, though this was not directly analyzed in the study. However, C1q binding by antibodies did refine risk assessment within both the lower-titer and higher-titer antibody groups.

The study by Loupy et al. does not provide data on the relationship between class and the specificity of donor-specific antibodies, C1q binding, and outcome. Anti–class I antibodies are more likely to be associated with early overt antibody-mediated rejection, whereas anti–class II antibodies are more likely to be associated with more indolent microvascular injury, with slower progression to graft loss. In the study by Loupy et al., the C1q-binding antibodies were associated with an increased risk of early antibody-mediated rejection. Since the follow-up time in this study was relatively short, the slower kinetics of injury and graft loss that are typical of anti–class II antibodies may not be as well captured. It would be of interest to see a comparison of C1q binding by anti–class I versus anti–class II donor-specific antibodies in this large cohort. Of note, the C1q assay does not detect non-HLA antibodies, which may be pathogenic through non–complement-fixing mechanisms,\(^2\,11\) nor does it detect the presence of multiple low-titer donor-specific antibodies that individually do not fix complement.

This large cohort study confirms that detection of C1q binding by donor-specific antibodies identifies patients who are at risk for graft loss, even in grafts that are functioning well at 1 year after transplantation. Critical pieces of the puzzle such as the response of these C1q-binding antibodies to therapy and the effect of therapy on outcomes require prospective clinical trials. The results of the present study suggest that detection of C1q binding by donor-specific antibodies should be considered as part of the protocol in clinical trials of treatment and outcomes in antibody-mediated allograft injury.

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