Kidney transplant recipients have a markedly increased risk of premature cardiovascular disease (CVD) and death. Hypertension is an established risk factor for CVD in this population and is associated with reduced graft survival in registry analyses. Most renal transplant recipients routinely receive antihypertensive agents. Against this background, it is remarkable to those outside the transplant community that we lack robust information on selection of antihypertensive agents or BP targets. The only trial of antihypertensive therapy in kidney transplant recipients (Study on Evaluation of Candesartan Cilexetil after Renal Transplantation), which examined the benefits of the angiotensin-receptor blocker candesartan, was closed early because of a low endpoint rate; there seems to be little appetite or funding for the necessary trials of antihypertensive therapy in transplant recipients.

The paper by Carpenter and colleagues in this issue of JASN reinforces the power of post hoc analyses of large-scale clinical trials to inform on issues outside the primary aim of the study. The Folic Acid for Vascular Outcomes Reduction in Transplantation trial failed to show a benefit of folic acid therapy on CV events in 4110 kidney transplant recipients. However, it generated a large dataset of carefully phenotyped transplant recipients, with follow-up and validated endpoints, which the investigators have used to study the role of BP on CVD. The results are clear but challenging with respect to the underlying mechanism and implications for treatment. First, higher systolic BP is associated with increased cardiovascular risk; the risk for CVD is increased 43% with each 20-mmHg increase in systolic BP. This is intuitive and confirms both registry and prior post hoc trial analyses in kidney transplant recipients. Second, lower diastolic BP (at least <70 mmHg) is also associated with increased CV risk; the hazard ratio is 31% higher for each 10 mmHg below 70 mmHg. This latter observation is more difficult to reconcile, although it confirms previous findings from the Assessment of LEscol in Renal Transplantation study on the divergent relationships between systolic and diastolic BP and CV outcomes. In fact, the data from these two large-scale trials in transplantation come to near-identical conclusions—in different populations, including whites and nonwhites, patients with diabetes and those without diabetes—suggesting that these relationships are likely to have universal relevance in transplant populations.

We should not be surprised by these findings. Similar relationships between systolic BP and a J-shaped relationship for diastolic BP have been demonstrated in patients receiving maintenance hemodialysis, as well as in patients with less advanced CKD who do not require dialysis. In the absence of aortic valve insufficiency, the pattern of high systolic BP, low diastolic BP, and increased pulse pressure are a marker of vascular stiffness. This has been extensively studied in CKD and ESRD, and it reflects accelerated arteriosclerosis and vascular calcification in progressive renal disease. Such extensive, established peripheral vascular disease is the norm in incident transplant recipients, and although it does not progress as rapidly after transplantation, it does not regress. Moreover, it is strongly associated with the development of left ventricular hypertrophy, which, in turn, is linked to cardiovascular morbidity and mortality in kidney transplant recipients—specifically to sudden cardiac death. The increase in sudden death is believed to be due to increased myocardial mass, cardiac fibrosis, increased arrhythmogenicity, and reduced diastolic filling of the coronary circulation. Prevention of vascular calcification, uremic cardiomyopathy, and sudden cardiac death are the leading challenges in the management of patients with CKD.

Carpenter and colleagues identify BP as a risk factor; however, given that we cannot undo the underlying vascular disease, the question is how to treat it and which targets or agents to use. In practice, only systolic BP offers a manageable target; agents that decrease systolic BP will also reduce pulse pressure and, to a lesser extent, diastolic BP. For patients with a diastolic BP >70 mmHg, it is reasonable to use established targets for systolic BP until diastolic BP falls to <70 mmHg; for patients with a high systolic BP and diastolic BP <70 mmHg, one would need to balance the benefits of lowering systolic BP with the additional hazard of reduced diastolic BP and its consequences. The 2012 Kidney Disease Improving Global Outcomes clinical practice guideline for management of BP in CKD recommend a target BP of 130/80 mmHg in kidney transplant recipients, regardless of other risk factors. These guidelines are based on research in other
high-risk renal populations but appear reasonable as an optimal target in kidney transplant recipients with diastolic BP in the normal range, based on the findings of the current analysis.

A second issue is the choice of medication. Many short-term observational and retrospective analyses have assessed different classes of antihypertensive medication in kidney transplant recipients. Although the circulating renin angiotensin system is not overtly active in transplant recipients, registry data and some small controlled trials have indicated a possible favorable role of these agents in this population, whereas others have shown no benefit. Efforts to recruit large numbers of transplant recipients into a randomized, controlled hypertension trial with “hard” endpoints seem to be difficult or even futile. Remarkably, despite the absence of appropriate trial data, the good news is that the CV mortality rate is decreasing in kidney transplant recipients and that the use of antihypertensive agents—and other agents that may protect against CVD—is increasing.

There is a tendency for commentaries or editorials in transplant medicine to end with the plea that “a large, randomized, controlled trial with CV endpoints is needed.” In the current funding and regulatory environment, and with the challenges facing the development of novel pharmaceutical agents, the transplantation community is unlikely to see a conventional BP-lowering trial. Thus, Carpenter and colleagues’ careful analyses provide the highest-quality support we will get for what is established clinical practice: keep BP low, but not too low.

DISCLOSURES
None.

REFERENCES
those at high versus low risk for developing late kidney allograft failure. While donor-reactive effector T cells (Teff) are recognized as crucial mediators of allograft injury and regulatory T cells (Treg) suppress Teff and protect against transplant injury, increasing evidence supports a multifaceted role for B cells in driving and regulating allograft injury as well.

One traditionally recognized function of B cells and their plasma cell progeny is that they produce donor-specific anti-HLA antibodies, which can contribute to graft injury.2,3 B cells can also process and present donor antigens to alloreactive T cells, thereby amplifying T cell–mediated damage to the transplanted organ.4 B cells are commonly present in transplant biopsy specimens with acute rejection,5 and molecular analyses have shown strong correlations between rejection and B cell–specific gene products, indirectly supporting a pathogenic role for B cells in human allograft injury.6,7

On the other hand, multiple studies in mouse models of autoimmune disease and transplant rejection have shown that subsets of B cells can exhibit immunoregulatory properties and that these regulatory B cells (Breg) function by directly inhibiting pathogenic Teff and by facilitating induction of Treg, in part by producing the immune-suppressive cytokine IL-10.8,9

In humans, molecular analyses of cellular RNA from blood and urine in two distinct populations of operationally tolerant kidney transplant patients who voluntarily withdrew from immunosuppression implicated B cell–derived gene products as involved in the tolerant state.10,11 Furthermore, B-cell production of IL-10, as well as plasma cell propensity for apoptosis, differs in operationally tolerant patients versus those with stable graft function on immunosuppression, supporting the concept that IL-10–secreting B cells may be protective in transplant recipients.12 Nonetheless, no studies have directly documented that Breg are present in the periphery of kidney transplant recipients receiving immunosuppression, and there is essentially no published evidence that Breg are relevant to transplant outcomes in this setting.

In this issue of JASN, Cherukuri and colleagues begin to fill this gap in knowledge by providing evidence that a subset of CD27negCD24hiCD38bi TrB, so-called transitional B cells (TrB) exhibit suppressive function, and that cytokine profiles produced by these TrB cells may be informative biomarkers for long-term transplant outcome in kidney transplant recipients receiving immunosuppression.13 Adding to the literature, the authors showed that subsets of B cells from healthy volunteers, including CD27negCD24hiCD38bi TrB, can produce the anti-inflammatory cytokine IL-10, as well as the proinflammatory cytokine TNF-α. They further showed that IL-10–secreting TrB can suppress T helper cell 1–cytokine producing Teff responses in vitro. Interestingly, concomitant production of TNF-α by the B cells overcomes this inhibitory function, indicative of counter-regulatory mechanisms that could result in pro- versus anti-inflammatory outcomes dependent on the relative production of the two cytokines. The factors that guide B-cell production of IL-10 versus TNF-α, and whether

**B Cells and Kidney Transplantation: Beyond Antibodies**

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Despite advances in immunosuppression over the last three decades, long-term kidney transplant survival is suboptimal,1 and mechanisms of late graft injury are incompletely understood. There remains a need for identifying and validating biomarkers capable of accurately stratifying patients into

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See related article, “BP, Cardiovascular Disease, and Death in the Folic Acid for Vascular Outcome Reduction in Transplantation Trial,” on pages 1554–1562.