Vascular Institute (Nashville, Tennessee) describe gains made in heart transplantation over the last 3 decades (1,2). These analyses underline success in lowering smoking rates in cardiac graft recipients, also recently echoed by liver and lung transplantation groups, but not yet duplicated in modern renal transplantation populations, as smoking cessation is not yet mandated by guideline. Notable also are reductions in use of steroid and increases in platelet inhibition associated with newer immunosuppressive protocols. These newer therapies have had an impact on allograft vasculopathy more likely due to smoking cessation, ubiquitous statin use, and avoidance of transplantation in populations with moderate or severe renal insufficiency than to the newer immunosuppressive regimens. Although focus on avoidance of patients at high risk for adverse prognosis, graft failure and allograft vasculopathy are important, it should be recognized that after solid organ transplantation and its initial rejection phenomena, the greatest hazard to recipient survival relates to the immunocompromised state. Current protocol-driven immunosuppression does not take into account additional comorbidities such as diabetes (either as a primary concern or secondary to immunosuppression) (3) or smoking history (current, prior, or never) (4), which are linked to adverse noncardiovascular outcomes in solid organ transplant patients.

The demonstration of decreased all-cause mortality (and composite, retrospectively defined major adverse cardiac events) over the past decades should now highlight the main issues in improving long-term survival for solid allograft recipients. All-cause mortality will only be reduced when we address the predominant and potentially avoidable causes for nonsurvival: infection and malignancy (5). In this regard, there may be some interest in lowering immunosuppressive doses and in using calcium-channel blockers to assist in treatment of antibiotic-resistant infections including gram negative organisms, tuberculosis, malaria, schistosomiasis, and immunosuppressed transplant recipients (6). Do the authors have any infection-related outcomes with respect to use of calcium-channel blockers?

Additional control of comorbidities such as diabetes (either as a primary problem or secondary to immunosuppression); modified courses of immunosuppression ("personalized immunosuppression") (2,3,5); advanced vaccination protocols; calcium-channel (6) or beta-blockade (7); or smoking cessation efforts to improve the excess risk of infectious death is worth exploring. Our aim to increase the longevity of solid organ transplant recipients requires a concerted effort to combine the skills of cardiologists with those of other specialties currently treating solid organ recipients. An international, easily searchable dataset combining all solid organ transplantations and identifying predefined and centrally adjudicated noncardiovascular and cardiovascular endpoints would be a good start.

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## REPLY: Solid Organ Transplantation

We thank Drs. Weinrauch and D'Elia for their interest in our paper (1) and are pleased that they support the concept of personalizing immunosuppression (IS) regimens to account for comorbidities in aging transplant recipients and agree that complications of IS threaten survival.

Regarding calcium-channel blockers, we do not have any evidence that these agents are associated with improved infectious outcomes in the post-transplantation population. With respect to

malignancy, however, calcium-channel blockers have been purported in published research to either be associated with an increased risk for cancer (most commonly) (2) or to confer protection from malignancy (3). Much of this debate, unfortunately, has stemmed from nonrandomized, observational, and even small randomized trials that are quite limited by selection and ascertainment biases. None of these associations have ultimately been confirmed in large-scale clinical trials (4).

Better understanding of IS and its specific effects on cancer, infection, graft dysfunction, and rejection will certainly allow reduction of risk due to excess death from complications of IS and result in improved outcomes. Development of a broad, searchable dataset of solid organ transplantations accessible to all investigators, as described in the letter, would be an excellent start.

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# Heart Rate in Heart Failure With Preserved Ejection Fraction

## Another Example of the Heterogeneity of This Syndrome

Vazir et al. (1) report the prognostic role of temporal changes in resting heart rate (HR) on cardiovascular (CV) death, hospitalization for heart failure (HF), or aborted cardiac arrest in a post hoc analysis of 1,767 patients enrolled in the TOPCAT trial. Studies evaluating the prognostic meaning of serial measurements of clinical variables in patients with HF and preserved ejection fraction (HFpEF) are greatly appreciated, and the authors should be congratulated for this initiative. In this study, the authors concluded that higher baseline resting HR and change in HR over time predict worse outcomes in patients with HFpEF in a nonlinear shape.

HFpEF is a heterogeneous syndrome with different phenotypic subtypes that is especially common in elderly people, women, and highly co-morbid patients (2). Interestingly, some patients with HFpEF display blunted HR response during exercise despite normal resting values, and chronotropic incompetence has been proposed as a pathophysiologic mechanism associated with poorer outcomes in a non-negligible subgroup of patients with HFpEF (3,4). Despite present findings that seem to contradict this concept, we next highlight some issues that support a key role of chronotropic incompetence in the pathophysiology of some patients with HFpEF.

First, hemodynamic effect of HR lowering in HFpEF may be harmful. It is known that HR lowering prolongs the filling of the cardiac chambers, which increases filling pressures, left ventricular diastolic wall stress, and arterial central pressures (4). In addition, in HFpEF with important diastolic dysfunction, higher HR may be considered a compensatory mechanism for maintaining cardiac output and lowering HR may not be beneficial.

Second, in this study, the positive association between HR at any time and adverse events was especially found for HR >70 to 75 beats/min. Below these values, a plateau effect was observed and below 55 beats/min, the confidence intervals were too wide. Expanding the sample size and including more patients with lower HR may unravel a risk U-shaped pattern.

Third, there is no evidence endorsing the beneficial effect of HR lowering in HFpEF (4,5). In fact, in this work, a decline in HR was not significantly associated with lower risk for the primary endpoint irrespective of cardiac rhythm and beta-blocker therapy (1). Along this line, because most patients were treated with beta-blockers, it would be interesting to explore the differential prognostic effect of HR across low or high doses of beta-blockers and other HR-lowering drugs.

Last, intriguingly, the prognostic impact of higher HR was greater in patients enrolled in Russia and Georgia (those at lower risk of adverse events). These findings may lead us to speculate chronotropic incompetence may play a more important role at more advanced stages of the disease.