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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https://doi.org/10.1016/j.jchf.2018.01.002

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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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.

In conclusion, we acknowledge the relevance of these findings for clinical practice, yet in-depth analysis of the pathophysiological role of chronotropic incompetence in HFpEF is warranted for properly tailored and personalized management of HFpEF phenotypes. Indeed, we advocate for the use of cardiopulmonary exercise testing for identifying 2 phenotypes: patients with blunted HR response in which additional HR lowering may have detrimental effects, and those with an excessive HR response in which a pharmacological HR lowering strategy could be beneficial.

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https://doi.org/10.1016/j.jchf.2017.12.003

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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