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EDITORIAL COMMENT

Statin Therapy in Heart Failure With Preserved Ejection Fraction

The Need for Randomized Evidence*

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Randomized evidence investigating the role of statin therapy in chronic heart failure has been restricted to heart failure with reduced ejection fraction (HFrEF). The 2 major randomized clinical trials, namely CORONA (Rosuvastatin in Older Patients with Systolic Heart Failure)[1] and GISSI HF (Effect of rosuvastatin in patients with chronic heart failure),[2] conducted in patients with HFrEF with and without ischemic heart disease failed to demonstrate efficacy of statin therapy in reducing both atherothrombotic and heart failure related events. While trials in HFrEF have been largely neutral, the role of statins in heart failure with preserved ejection fraction (HFpEF) has not been systematically investigated. Most previous studies evaluating the relationship between statin use and outcomes in HFpEF have been observational in nature and are limited either by small sample size, inability to reliably differentiate the 2 main heart failure phenotypes (ie, HFrEF and HFpEF) and methodological limitations such as confounding by indication.[3]

It is in this context that the study performed by Orkaby et al[4] gains importance as the investigators have performed comparative effectiveness research evaluating the role of statins in HFpEF using nationwide data from the Veterans Health Administration. After excluding patients with prevalent atherosclerotic cardiovascular disease (ASCVD) and baseline statin use, the authors identified 7,970 veterans with HFpEF, of which 47% were started on statin during the follow-up period. Over a median follow-up of 6 years, statin use was associated with a 22% relative risk reduction in all-cause mortality. Additionally, statin use was associated with a lower hazard for major adverse cardiovascular events (MACE) (HR: 0.79; 95% CI: 0.74-0.84), all-cause hospitalizations (HR: 0.69; 95% CI: 0.60-0.80), and heart failure related hospitalizations (HR: 0.72; 95% CI: 0.59-0.88).

This hypothesis-generating study overcomes several limitations of prior observational studies. Firstly, the nationwide Veteran Affairs electronic health care records provide a unique opportunity to reliably study HFpEF at the population level due to the availability of serial left ventricular ejection fraction measurements and a validated algorithm with high specificity for identification of HFpEF.[5] Most population-based studies have merely used ICD codes for HFpEF case ascertainment which lacks specificity. Secondly, the investigators had employed the 'new-user design' to help align patients at a unified time to begin follow-up and to maintain the temporality between exposure and covariates.[6] Furthermore, in order to minimize information bias, the authors merged Veteran Affairs data with Medicare and Medicaid data. The authors had also rightly chosen a prolonged follow-up period to allow for long-term effects of statin exposure on outcomes. Finally, the 2 comparison groups of statin and non-statin users had significant differences in baseline characteristics. The investigators appropriately used the overlap propensity score weighting method to achieve a good balance on the mean of important covariates between 2 groups without modifying the target population. This is critical for reducing

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indication bias and increasing the precision of results; however, statistical inference should take into account the fact that balance on the mean may not result in a complete adjustment for confounding.[7]

While the study answers important questions related to statin exposure on outcomes in HFpEF, it also generates important observations on the plausible mechanisms of statin efficacy. Despite the exclusion of patients with prevalent ASCVD, the event rates for MACE during the median follow-up of 6 years were 60.1% for the entire cohort. This is strikingly high and translates to an annual event rate of c.10% in contrast to 2% per year in primary prevention trials.[8] Greater than 75% of the studied cohort were either current or former smokers (<20% in statin trials for primary prevention) and only 25% of the patients had a ASCVD risk score of <5%, signifying that this is plausibly a population at very high risk for MACE than the general population or those recruited in primary prevention trials. This could also explain the reason for the clinical benefits and the magnitude of treatment effects realized with statin exposure in this patient population. These findings coupled with interaction effect of statin with ASCVD risk category, with point estimates favoring lower hazard for MACE in the group with high ASCVD risk category suggest an effect mediated by reduction in atherothrombotic events as opposed to statin pleiotropy.

Some of the limitations of the study include the issues faced by all observational studies despite the robust study design. Individuals initiated on statin will differ in several ways from those who did not get one. Individuals in the nonuser group might have contraindications, including frailty and while overlap weighting methods adjust for the known differences between the 2 groups, there may still be residual confounding from unmeasured variables.

This well-conducted study has yielded important hypothesis-generating observations on the clinical efficacy of statin for primary prevention in a well-defined real-world HFpEF cohort with reliable long-term follow-up. We agree with the authors on the need for randomized evidence to confirm these important findings. However, such an randomized controlled trial would be extremely challenging to conduct as it would necessitate recruitment of patients with no indication for statin, that is, non-ischemic HFpEF with low risk for ASCVD (69% of the participants in EMPEROR-PRESERVED (Empagliflozin in Heart Failure with a Preserved Ejection Fraction) trial were already on statin therapy prior to randomization).[9] Such a trial would also reliably answer the question of statin pleiotropy in HFpEF. Finally, the study findings also emphasize the importance of aggressive primary prevention in patients with HFpEF with intermediate and high risk for ASCVD in clinical practice, where the uptake of statins is still far from optimal!

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