

EDITORIAL

# Old Drug, New Trick? Oral Milrinone for Heart Failure With Preserved Ejection Fraction

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*“Sooner or later, everything old is new again.”  
— Stephen King*

**N**early 30 years after a major outcomes trial in heart failure with reduced ejection fraction provided it a failing grade, oral milrinone returns for a chance at redemption. This time, however, it has been retooled for the “other half”: heart failure with preserved ejection fraction (HFpEF). In the study by Nanayakkara et al in this issue of the *Journal of the American Heart Association (JAHA)*, the authors report on a prospective, single-center, randomized, double-blinded trial assessing the safety and response to oral milrinone in HFpEF.<sup>1</sup>

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**See Article by Nanayakkara et al.**

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Following a 2-week single-blinded placebo run-in period to assess for compliance and nondrug adverse events, the investigators randomized participants to receive oral, extended-release milrinone or placebo for 4 weeks. Baseline characteristics were similar between groups with prevalent elderly age (mean age 77), female sex (74%), and obesity (65%). All participants underwent a transthoracic echocardiogram with Doppler, 6-minute walk test, Kansas City Cardiomyopathy Questionnaire quality-of-life assessment, and natriuretic

peptide testing at screening and again at study completion. Thigh-mounted activity monitors were worn during the 2-week placebo run-in as well as for the final 2 weeks of the study. Although safety was the primary outcome, echocardiographic measures of left ventricular diastolic function including E/e' ratio, right ventricular (RV) systolic pressure, and left atrial volume index as well as quality-of-life measures, RV systolic function, and 6-minute walk test data were evaluated as secondary efficacy outcomes.

Among 12 patients assigned to twice-daily oral milrinone, the medication was well-tolerated with no serious adverse events and, notably, no atrial or ventricular arrhythmias reported in either arm. Subjects randomized to milrinone had a significantly greater improvement in Kansas City Cardiomyopathy Questionnaire score compared with placebo and a trend towards improvement in the 6-minute walk test and glomerular filtration rate. However, there was no difference in level of measured activity, N-terminal pro-B-type natriuretic peptide levels, or echo measures of systolic or diastolic function between the 2 groups.

In a syndrome for which so many therapeutic efforts have been unsuccessful, the authors should be applauded for this novel investigation of a drug with a somewhat notorious track record despite its alluring biological plausibility. After all, oral milrinone did not just show lack of efficacy; the PROMISE (Prospective Randomized Milrinone Survival Evaluation) study had

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to be stopped early because of excess morbidity and mortality associated with drug, likely because of its arrhythmogenicity and potent vasodilatory effects.<sup>2</sup> How is the current drug different? The authors have previously published on their uniquely formulated extended-release milrinone formulation and have tested its safety in a small cohort of Stage D heart failure with reduced ejection fraction patients, identifying no hypotension or increased arrhythmic burden in this at-risk population.<sup>3</sup> The improved safety of the extended-release formulation when compared with the immediate-release version tested decades ago has been attributed to more stable pharmacokinetics, with the extended-release formulation free of (presumably dangerous) serum peak and trough levels. They have wisely tested the safety of this new formulation once more, and the resulting pair of this month-long safety studies are promising. However, longer-term testing will be needed to prove that this novel extended-release formulation has overcome the proapoptotic and prohypertrophic effects that have been previously attributed to chronic milrinone (and indeed nearly all inotrope) administration and to which the drug's negative outcomes have been ascribed.<sup>4</sup> Consideration for the use of ambulatory rhythm monitoring with future testing may be reasonable given the potential for asymptomatic, nonsustained arrhythmias as an early warning sign.

One may also question the reasoning behind the utilization of a known inotrope in HFpEF, where the above-noted precedent would warn of more potential for harm than good. The work described here is, of course, not just a last-ditch effort because of the HFpEF syndrome's growing burden on the healthcare system and status as one of cardiology's lasting enigmas.<sup>5</sup> In fact, there is reasonable rationale for use of a phosphodiesterase inhibitor such as milrinone for this phenotypically diverse syndrome. The search for common pathophysiologic underpinnings that could serve as therapeutic targets received a blueprint with the paradigm set forth by Paulus et al in 2013. In this model, the prominent form of HFpEF was attributed to vascular endothelial inflammation and dysfunction secondary to comorbidities, manifest in the multiorgan dysfunction seen in the HFpEF syndrome.<sup>6</sup> The proposed culprit in this model was a loss of the key effector molecule nitric oxide, where in the setting of widespread inflammation and reactive oxygen species, a reduction in nitric oxide bioavailability could lead to several detriments. Among these detriments is cardiomyocyte hypertrophy and deposition of interstitial collagen that resulted in diastolic dysfunction, as well as vascular dysfunction characterized by resting vasoconstriction and impaired sensitivity to nitric-oxide-mediated vasodilation. Amelioration of such a

pathway provided hope for a potential silver bullet, or at least a first effective therapy.

As is well known, the series of trials targeting this pathway in HFpEF—in particular the phosphodiesterase-5 inhibitor sildenafil and sodium nitrite in nebulized form—have yielded disappointing results despite promising preliminary studies offering proof of concept.<sup>7,8</sup> While mechanistic explanations for the lack of benefit seen with phosphodiesterase-5 inhibition in HFpEF have been presented previously, including the potential for upregulated phosphodiesterase-5A (rendering the phosphodiesterase-5 inhibitor sildenafil ineffective) and only mildly increased levels of cGMP (suggesting the study drug's inability to achieve its intended effect at studied doses), the larger lesson may be in matching the therapy of interest to its target physiologic derangement. Such matching requires careful consideration of a drug's mechanism of action as well as careful characterization of the tested cohort through laboratory, echocardiographic, and invasive hemodynamic testing. So, is the cohort of HFpEF subjects tested here the ideal phenotype to derive benefit from the actions of an extended-release milrinone?

The proposed cardiac benefits afforded by the phosphodiesterase-3 inhibitor milrinone previously hypothesized by the authors included an increase in ventricular compliance or a reduction in preload (or possibly a combination of both).<sup>9</sup> Either action could be valuable in reducing dyspnea in HFpEF patients with elevated filling pressures and vascular congestion. Likewise, phosphodiesterase-3 inhibitors, like phosphodiesterase-5 inhibitors, could reduce RV afterload in the setting of pulmonary hypertension as they regulate vascular and airway smooth muscle remodeling. Thus, a HFpEF phenotype with high resting filling pressure and perhaps combined pre- and postcapillary pulmonary hypertension with RV dysfunction might offer a reasonable target population, or at least one that can show efficacy of such a drug during resting evaluation.

The subjects described in this study, however, exhibited only mildly elevated E/e' values and relatively normal RV function (mean tricuspid annular plane systolic excursion of 2.4 cm). A reported average RV systolic pressure of 28 to 30 mm Hg corresponds to a mean pulmonary arterial pressure of  $\approx$ 20 mm Hg. This would suggest not only lack of significant pulmonary hypertension (likely in part because of the authors' exclusion of patients with moderate or worse tricuspid regurgitation), but also that resting left heart filling pressures on average were 15 mm Hg or less. Thus, the potential for symptomatic benefit from improved unloading may have been attenuated based simply on the

characteristics of the analyzed subjects who may have been already unloaded, well-managed from a volume perspective, less-advanced in their myocardial stiffening, and/or primarily susceptible to an exercise-induced increase in filling pressures. In fact, a prior study of another inotrope aimed at increasing cyclic-AMP signaling (dobutamine) in HFpEF patients found that it enhanced RV to pulmonary artery coupling through afterload reduction alone, rather than through enhanced contractility.<sup>10</sup> Thus, the stage may have been set for an inability to show improvement in resting echocardiographic measures of function and submaximal efforts such as step count and 6-minute walk test distance by selecting patients specifically without elevated RV afterload. In prior work by this group, oral milrinone led to a significant reduction in increase of right atrial pressure, mean pulmonary arterial pressure, and pulmonary artery wedge pressure during exercise when compared with placebo with much less impact on resting hemodynamics. Therefore, measures of RV or left ventricular reserve may offer valuable information and a more sensitive surrogate end point for this HFpEF phenotype.<sup>11–13</sup> Indeed, a recently completed phase 2 study of another phosphodiesterase-3 inhibitor, levosimendan (NCT03541603), included exercise pulmonary artery wedge pressure as its primary end point.<sup>14</sup>

Such discussion of drug efficacy is unavoidable but should be tempered by the reminder that this study was quite small and primarily designed to look at safety. In this regard, it clearly succeeded. Evaluation of the effectiveness is most helpful in considering how future studies might be designed including continued evaluation of its safety profile. This work functions as a reminder that there may be old tools long since retired for the treatment of heart failure with reduced ejection fraction that may hold mechanistic and even therapeutic relevance when applied to HFpEF, where help is so urgently needed. We could only be so luckily if “the old is new again.”

## ARTICLE INFORMATION

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