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Editor's Note

Impediments to Implementing Guideline-Directed Medical Therapies

Despite clinical trial evidence demonstrating improvements in clinical outcomes with new therapies in patients with cardiovascular disease, uptake of these therapies has been stubbornly slow, variable, and incomplete. The angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan has been shown to improve health status, decrease hospitalizations, and reduce mortality in patients with heart failure with reduced ejection fraction (HFrEF) beyond the levels that can be achieved with angiotensin-converting enzyme inhibitor therapy. Despite these considerable benefits and a class I guideline recommendation to replace angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist therapy with ARNI therapy in patients who remain symptomatic, adoption of ARNI therapy in clinical practice has been sluggish.[1] Nonuniform inclusion on formularies, prior authorization requirements, and out-of-pocket costs borne by patients have been reported to be important barriers to greater use of novel cardiovascular therapies, including ARNI therapy.

The Medicare Part D prescription drug benefit plan was intended to assist Medicare beneficiaries in accessibility and affordability of prescription medications. In this issue of *JAMA Cardiology*, DeJong et al[2] analyzed coverage and cost-sharing requirements for Medicare beneficiaries with Part D coverage who have HFrEF and are receiving guideline-directed medical therapy, including sacubitral/valsartan therapy. The findings are sobering. In 2018, all Part D plans covered sacubitril/valsartan, yet monthly patient out-of-pocket costs were substantial, particularly when patients reached the coverage gap (also known as the *donut hole*). This has the potential to deter many patients from filling their prescriptions, potentially exacerbating economic disparities in access to evidence-based therapies.

Medicare patients often face higher copayments than those with commercial insurance for 2 reasons. First, unlike commercial prescription plans, drug manufacturer–provided copayment reduction assistance is prohibited with Medicare Part D plans. Second, once they are in the donut hole, Medicare Part D beneficiaries pay 25% of the list price of the medication, a figure often inflated by a complicated system of rebates. Even with changes being made in 2019 in the Medicare Part D share of costs in the coverage gap, out-of-pocket costs for patients with HFrEF who are receiving sacubitril/valsartan will remain high.

Optimal use of ARNI in HFrEF improves health status, increases survival, and has been projected to prevent 28 484 deaths per year, which would represent a 10% reduction in total annual heart failure deaths in the United States.[3] This underrecognized and substantial out-of-pocket patient expense burden among those with Medicare Part D coverage represents a significant impediment to wider use and improved population health. These circumstances also affect Medicare beneficiaries receiving many other evidence-based prescription medications. Thus, it is important that we continue to seek novel solutions to improve access to life-enhancing therapies. Failing to more effectively address these issues of out-of-pocket expenses will contribute to further widening disparities in care quality and outcomes for patients with and at risk for cardiovascular disease.

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COMMENT & RESPONSE

The Incompleteness of the Social Security Death Master File

To the Editor The excellent work of Navar et al[1] demonstrates the unreliability of using the US Social Security Death Master File (SSDMF) for clinical research. It is important for readers to understand why this is the case. The SSDMF has been incomplete since November 1, 2011, when 4.2 million records were removed from the historical file of 89 million.[2] Since that time, the file has lost approximately 40% of deaths per year. In 2011, the US Social Security Administration concluded that it could not release state-owned data (ie, information from the death certificate) to the SSDMF.[3] The consequences of this decision for researchers were profound, as there is no alternative to the SSDMF, which contained the only up-to-date, publicly available death records for the United States. The National Death Index is now the only reliable source of nationally available, identifiable death information for researchers. However, as the authors state,[1] the National Death Index can be expensive, and there is a 2-year lag. Researchers should heed the study's conclusion that the SSDMF is not reliable and should not be used alone to estimate mortality rates.

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Hypertrophic Cardiomyopathy—Need for Gene-Specific Treatment?

To the Editor We congratulate Coats et al[1] for their report on the randomized clinical trial of trimetazidine, a direct β-oxidation inhibitor, in patients with nonobstructive hypertrophic cardiomyopathy (HCM). Current therapies for HCM are insufficient, and the search for disease-modifying treatments must be continued. The trimetazidine trial is one of few clinical trials in HCM thus far, to our knowledge. We would like to highlight aspects that may have contributed to the negative outcome of the reported trial.

In this study, 51 patients with HCM were included, but no information is provided on the genetic status of these patients.[1] As indicated by the authors, many of the gene variants that cause HCM increase the energetic cost of cardiac contraction and relaxation. In vitro and in vivo studies showed decreased efficiency of cardiac contractility in patients with sarcomere variant-positive HCM compared with those with sarcomere variant-negative HCM and healthy controls.[2] Moreover, the decrease in in vivo myocardial energy efficiency (MEE) was already observed in asymptomatic HCM variant carriers and showed the largest decrease in *MYH7* variant carriers. The study by Witjas-Paalberends et al[2] indicates that effectiveness of therapies may depend on the affected gene. Such a gene-specific treatment effect was reported in a trial of diltiazem showing a positive treatment effect in *MYBPC3* variant carriers.[3] We would like to ask the authors if the genotype of included patients is known.

Effectiveness of therapy may also depend on clinical history of patients. We noted that 16 of 51 patients (31%) show a medical history of septal reduction via myectomy or alcohol ablation. These patients underwent an intervention that considerably affects the myocardium, and the resulting scar tissue may limit effectiveness of trimetazidine. In a 2017 study,[4] surgical removal of obstruction did not improve MEE in patients with obstructive HCM, whereas a significant improvement of MEE was observed in patients with aortic stenosis. We would like to ask the authors whether they have considered prior interventions as exclusion criteria for this study.

The current study did not show an effect of trimetazidine on the end point of peak oxygen consumption during exercise of 80%. There is an ongoing debate on which end point is accurate to assess treatment effectiveness in a rather slow-developing disease, such as HCM. Based on the reduced MEE in asymptomatic HCM variant carriers, we initiated a placebo-controlled randomized clinical trial of trimetazidine in asymptomatic *MYH7* variant carriers (ENERGY trial).[5]

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