Repurposing the \( \beta_3 \)-Adrenergic Receptor Agonist Mirabegron in Patients With Structural Cardiac Disease
The Beta3-LVH Phase 2b Randomized Clinical Trial

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**IMPORTANCE** Left ventricular (LV) hypertrophy contributes to the onset and progression of heart failure (HF), particularly for patients with pre-HF (stage B) for whom no treatment has yet proven effective to prevent transition to overt HF (stage C). The \( \beta_3 \)-adrenergic receptors (\( \beta_3 \)ARs) may represent a new target, as their activation attenuates LV remodeling.

**OBJECTIVE** To determine whether activation of \( \beta_3 \)ARs by repurposing a \( \beta_3 \)AR agonist, mirabegron, is safe and effective in preventing progression of LV hypertrophy and diastolic dysfunction among patients with pre- or mild HF.

**DESIGN, SETTING, AND PARTICIPANTS** The Beta3-LVH prospective, triple-blind, placebo-controlled phase 2b randomized clinical trial enrolled patients between September 12, 2016, and February 26, 2021, with a follow-up of 12 months. The trial was conducted at 10 academic hospitals in 8 countries across Europe (Germany, Poland, France, Belgium, Italy, Portugal, Greece, and the UK). Patients aged 18 years or older with or without HF symptoms (maximum New York Heart Association class II) were screened for the presence of LV hypertrophy (increased LV mass index [LVMI] of \( \geq 95 \) g/m\(^2\) for women or \( \geq 115 \) g/m\(^2\) for men) or maximum wall thickness of 13 mm or greater using echocardiography. Data analysis was performed in August 2022.

**INTERVENTION** Participants were randomly assigned (1:1) to mirabegron (50 mg/d) or placebo, stratified by the presence of atrial fibrillation and/or type 2 diabetes, for 12 months.

**MAIN OUTCOMES AND MEASURES** The primary end points were LVMI determined using cardiac magnetic resonance imaging and LV diastolic function (early diastolic tissue Doppler velocity [E/e’] ratio assessed using Doppler echocardiography) at 12 months. Patients with at least 1 valid measurement of either primary end point were included in the primary analysis. Safety was assessed for all patients who received at least 1 dose of study medication.

**RESULTS** Of the 380 patients screened, 296 were enrolled in the trial. There were 147 patients randomized to mirabegron (116 men [79%]; mean [SD] age, 64.0 [10.2] years) and 149 to placebo (112 men [75%]; mean [SD] age, 62.2 [10.9] years). All patients were included in the primary intention-to-treat analysis. At 12 months, the baseline and covariate-adjusted differences between groups included a 1.3-g/m\(^2\) increase in LVMI (95% CI, –0.15 to 2.74; \( P = .08 \)) and a –0.15 decrease in E/e’ (95% CI, –0.69 to 0.4; \( P = .60 \)). A total of 213 adverse events (AEs) occurred in 82 mirabegron-treated patients (including 31 serious AEs in 19 patients) and 215 AEs occurred in 88 placebo-treated patients (including 30 serious AEs in 22 patients). No deaths occurred during the trial.

**CONCLUSIONS** In this study, mirabegron therapy had a neutral effect on LV mass or diastolic function over 12 months among patients who had structural heart disease with no or mild HF symptoms.

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Heart failure (HF) is a major public health burden that affects 2% to 3% of adults in high-income countries. For up to half of patients, HF evolves with a mildly reduced or preserved ejection fraction (HFpEF); this proportion is expected to grow as the aging population increases. Older individuals and patients with hypertension, diabetes, and obesity are at particularly high risk of HF, including HFpEF. The universal HF classification and the 2022 American College of Cardiology/American Heart Association staging models emphasize the identification of such patients at risk of HF (stage A) or pre-HF (stage B) without and with evidence of cardiac remodeling, respectively, to promote preventive action before progression to symptomatic HF (stage C). Thus, interventions for patients with asymptomatic pre-HF may be important in reducing the incidence of clinically overt HF.

Despite the growing incidence of HFpEF over the last 20 years, the few therapies proven to be effective thus far were mainly tested a posteriori (ie, in patients with symptomatic HF). Given known effects of cyclic guanosine monophosphate (cGMP) on vasodilation, anti-remodeling, and lusitropic properties on the myocardium, previous efforts aimed to increase cGMP–protein kinase G (PKG) signaling, among other possible targets. Although the results of previous trials with soluble guanylyl cyclase stimulators or phosphodiesterase 5 inhibitors have been disappointing for patients with established HFpEF, the efficacy of these approaches may have been hampered by low bioavailability of the nitric oxide (NO) produced and its associated cGMP pool, due to the prevailing oxidative stress in advanced disease. Whether any of these drugs prevent the development of HFpEF at earlier stages has not been confirmed.

In this context, activation of the cardiac β3-adrenergic receptor (β3AR) may offer alternative, more efficient pharmacodynamic activation of the cGMP/PKG pathway. Indeed, β3AR stimulation produces antioxidant effects that are expected to preserve NO/cGMP bioavailability and possibly protect other molecular targets that regulate excitation-contraction coupling and myocardial remodeling. In preclinical studies, β3AR stimulation coupled to the NO/cGMP pathway, resulting in coronary vasodilatation and increased cGMP content in human myocardium, with a subsequent effect on cardiac myocytes that was opposite of classical β1-2AR effects. Activation of β3AR/NO decreases myocardial hypertrophy and fibrosis in response to neurohormonal or hemodynamic stresses without compromising left ventricular (LV) function, and cGMP/PKG-Ia promotes cardiac relaxation through phosphorylation of titin, troponin I, and sarcoendoplasmic reticulum calcium ATPase. Because ample evidence points to the inverse effects of sustained β1-2AR activation, we reasoned that activation of the functionally opposed β3AR/NO pathway would protect against such deleterious effects of chronic adrenergic stimulation, as typically observed in patients with hypertension or obesity who have structural heart disease and are at risk of developing HF.

Medications that specifically activate the human β3AR, such as mirabegron, have recently been developed and marketed for clinical use in overactive bladder disease. Mirabegron had few cardiovascular effects in previous urologic studies. However, patients with high cardiovascular risk were excluded per protocol in those trials, so questions remain regarding the innocuity of mirabegron in this specific population. Therefore, the Beta3-LVH trial tested the hypothesis that repurposing mirabegron for patients at risk of or with mild HF is safe and protects against worsening LV hypertrophy (LVH) and/or diastolic dysfunction.

### Methods

#### Study Design

The Beta3-LVH is a prospective, parallel, placebo-controlled, triple-blind phase 2b randomized clinical trial that was performed in 10 academic hospitals in Germany (3 centers), Poland, France, Belgium, Italy, Portugal, Greece, and the UK. Complete details on the trial protocol were reported previously and are presented in Supplement 1 and in the eMethods in Supplement 2. The study was approved by the ethics committees in all participating countries. Written informed consent was obtained from all participants. An independent data safety monitoring board reviewed unblinded trial data prepared by an independent statistician on a regular basis and issued recommendations on trial continuation. The study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

#### Participants

Men and women aged older than 18 years were invited to participate if they had an increased LV mass index (LVMi) (>115 g/m² for men and >95 g/m² for women) or end-diastolic wall thickness of 13 mm or greater in at least 1 wall segment, in the absence of inherited hypertrophic cardiomyopathy or substantial valvular disease at screening echocardiography. Participants were screened for additional inclusion and exclusion criteria between September 12, 2016, and February 26, 2021 (eTable 1 in Supplement 2). Patients with hypertension were required to receive stable therapy for at least 4 weeks before inclusion and to have well-controlled blood pressure. Patients with documented ischemic cardiac disease (eg, history of acute myocardial infarction, current angina pectoris, or...
known coronary disease) or atrial fibrillation with an uncontrolled heart rate (>100 beats/min) were excluded. All patients with an ejection fraction (EF) of less than 50% or with New York Heart Association (NYHA) functional class symptoms greater than class II were also excluded.

Randomization
Patients were randomized (1:1) to mirabegron (50 mg/d) or placebo, stratified by the presence or absence of type 2 diabetes and atrial fibrillation at randomization. This dosage was chosen on the basis of safety data from previous clinical trials, as allowed by ethics committees in all participating countries. Allocation concealment and randomization were ensured centrally through a secure web-based tool held by Universität Leipzig using a modified minimization procedure with a stochastic component, according to Pocock and Simon.17

Procedures
A trial flow diagram is presented in eFigure 1 in Supplement 2. Eligible patients underwent a baseline evaluation consisting of the following: medical history, clinical examination (including blood pressure measurement), 24-hour ambulatory blood pressure monitoring, determination of NYHA functional class, body mass index (BMI calculated as weight in kilograms divided by height in meters squared), electrocardiography, transthoracic echocardiography, and cardiac magnetic resonance imaging (MRI) (LV volume, left atrial [LA] volume, LV mass, LV function, LV wall thickness, late gadolinium enhancement, and T1 mapping). All imaging procedures were performed according to a standardized operational protocol designed by the echocardiography and cardiac MRI core laboratories at Charité Universität Berlin and the University of Oxford, respectively, and parameters were measured centrally in the respective core laboratories. Patients also performed a cardiopulmonary exercise test on a cycloergometer and underwent urine and blood sampling for measurements of fasting glucose, insulin (homeostatic model assessment [HOMA] of sensitivity), hemoglobin A1c, serum lipids, galectin-3, growth differentiation factor 15, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and high-sensitivity troponin I. Additional procedures, including substudies on brown fat activity by fluorodeoxyglucose positron emission tomography and endothelial function by digital microtomometry, are described in the eMethods in Supplement 2.

Outcomes: Primary and Secondary End Points
To assess both structural and functional aspects of LV remodeling, 2 equally ranked primary end points were chosen: (1) a change in LVMi (in grams per meters squared) measured with cardiac MRI at baseline, 6 months, and 12 months after randomization; and (2) a change in diastolic function, assessed as the ratio of peak early transmitral ventricular filling velocity to early diastolic tissue Doppler velocity (E/e′) measured with echocardiography at baseline, 6 months, and 12 months after randomization.

The following key secondary end points were evaluated: interstitial cardiac fibrosis (extracellular volume fraction), LA volume index, LV stroke volume index, right ventricular (RV) EF (all by cardiac MRI), maximal exercise capacity (peak oxygen consumption), insulin sensitivity (HOMA), and NT-proBNP at 12 months. Additional secondary end points are listed in the eMethods in Supplement 2.

Investigators duly documented and reported all adverse events (AEs), including serious AEs, to the Universität Leipzig Clinical Trial Centre, which passed them immediately to the trial coordinator for medical assessment and a second opinion with respect to the causal relationship with the trial medication. All study procedures followed good clinical practice rules.

Statistical Analysis
The Beta3-LVH trial tested the hypothesis that, compared with placebo, mirabegron as an add-on to standard treatment improves at least 1 of the 2 primary end points over 12 months. The Hochberg method was used to adjust for end-point multiplicity; that is, efficacy was claimed for both primary end points if both P values were below .05 or for the respective primary end point if the smallest P value was below .025. This procedure controlled the familywise error rate at a 2-sided significance level of 5%.18

Sample size calculation was based on the E/e′ ratio, with the aim to detect a difference of 1.2 between the 2 treatment groups. This roughly corresponds to 5 points on the Short Form-36 physical functional scale, a patient-relevant difference.19 With an SD of 3, a total of 272 patients analyzed would result in 85% power at a significance level of 2.5% using a 2-sided t test using nQuery Advisor, version 7.0 (Dottmatics).

Analyses of both primary and secondary end points were identical. Mean changes from baseline were analyzed using a repeated-measures linear mixed model without the intercept containing the fixed, categorical effects of visit (baseline, 6 months, or 12 months), treatment (active or placebo), treatment-by-visit interaction, atrial fibrillation (yes or no), type 2 diabetes (yes or no), and a patient-specific visit random effect (3-dimensional normal with a general unstructured covariance matrix). The model implicitly used the estimated covariance matrix to deal with missed visits. Assuming that missing end points are missing at random, the model can deal with patients with incomplete end-point data provided that at least 1 valid measurement is documented. Given randomization at baseline, the treatment by baseline interaction was not included in the model. This indirectly adjusted for possible random chance fluctuation at baseline and generally increased the power.20 The model was fitted using the nlme package in R, version 4.2.0 (R Foundation for Statistical Computing) (complete formula in the eMethods in Supplement 2).

The per-protocol set included all patients from the full analysis set without major violations of the study protocol. The population in the safety analysis set was defined by all randomized patients belonging to the full analysis set who received at least 1 dose of study medication.

Exploratory subgroup analyses for the 2 primary end points were performed with baseline characteristics, including sex, age, BMI, hypertension, diabetes, atrial fibrillation, and a history of coronary disease.
β-blocker use in standard treatment, type 2 diabetes, atrial fibrillation at registration, age older than 65 years, BMI greater than 30 at baseline, and region (Poland, Germany, or other countries).

We used χ² tests to compare AEs and serious AEs, with special attention to the occurrence of high blood pressure, hepatic impairment, kidney impairment, atrial fibrillation or flutter, and death. Data analysis was performed in August 2022.

Results

Of the 380 patients screened, 60 did not meet the inclusion criteria, 18 declined to take part, and 6 were not recruited for other reasons (Figure 1). Therefore, 296 patients were considered eligible and randomized to either mirabegron or placebo. The mirabegron-treated group included 147 patients (116 men [79%] and 31 women [21%]), with a mean (SD) age of 64.0 (10.2) years. The placebo-treated group included 149 patients (112 men [75%] and 37 women [25%]), with a mean (SD) age of 62.2 (10.9) years. A total of 35 patients (19 in the mirabegron group and 16 in the placebo group) dropped out of the trial (detailed in Figure 1). All randomized patients with at least 1 valid measurement of either LVMI or E/e’ were included in the full analysis set. Of these, 1 patient in the placebo group had no LVMI measurement because of contraindication for MRI but had a valid echocardiographic E/e’ recording. Two more patients in the placebo group and 4 patients in the mirabegron group had no valid E/e’ recording but had valid LVMI measurements. Further description of the per-protocol set is included in the eResults in Supplement 2.

Demographic and clinical characteristics were well balanced between the treatment groups at baseline (Table 1). Overall, the mean (SD) BMI was 30 (4.3); more than 90% of mirabegron- and placebo-treated patients had hypertension (137 [93%] and 137 [92%], respectively) and approximately 20% had type 2 diabetes (26 [18%] and 31 [21%], respectively). According to the study protocol, patients were receiving background cardiovascular therapies that did not differ between groups, including angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, diuretics, and calcium antagonists. Approximately 50% of the mirabegron- and placebo-treated groups (80 [54.4%] and 75 [50.7%]) were treated with β blockers. Most participants had no HF symptoms; only 20 mirabegron-treated patients (13.6%) and 18 placebo-treated patients (12.1%) had NYHA class II symptoms. Adherence to trial medication was excellent in both treatment groups, with a relative dose of greater than 80% for 119 mirabegron-treated patients (81.0%) and 118 placebo-treated patients (79.2%) (eTable 2 in Supplement 2).

Neither primary outcome reached the predefined statistical significance level. At 12 months, baseline and covariate-
**Table 1. Baseline Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient group</th>
<th>Mirabegron (n = 147)</th>
<th>Placebo (n = 149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td></td>
<td>64.0 (10.2)</td>
<td>62.2 (10.9)</td>
</tr>
<tr>
<td>Sex, No. of patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>116 (79)</td>
<td>112 (75)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>31 (21)</td>
<td>37 (25)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td></td>
<td>29.8 (4.3)</td>
<td>30.1 (4.3)</td>
</tr>
<tr>
<td>NYHA functional class, No. of patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td></td>
<td>20 (13.6)</td>
<td>18 (12.1)</td>
</tr>
<tr>
<td>I</td>
<td></td>
<td>7 (4.8)</td>
<td>7 (4.7)</td>
</tr>
<tr>
<td>No symptoms</td>
<td></td>
<td>120 (81.6)</td>
<td>124 (83.2)</td>
</tr>
<tr>
<td>LVEF by echocardiography, %, mean (SD)</td>
<td></td>
<td>61.5 (5.6)</td>
<td>62.5 (6.6)</td>
</tr>
<tr>
<td>E/e′, mean (SD)</td>
<td></td>
<td>9.4 (3.2)</td>
<td>9.7 (3.0)</td>
</tr>
<tr>
<td>LVMI, g/m², mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessed with echocardiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td>124 (28)</td>
<td>126 (33)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td>115 (24)</td>
<td>114 (23)</td>
</tr>
<tr>
<td>LAVI assessed with MRI, mL/m², mean (SD)</td>
<td></td>
<td>43.0 (14.1)</td>
<td>41.8 (14.7)</td>
</tr>
<tr>
<td>Peak oxygen consumption, mL/min/kg, mean (SD)</td>
<td></td>
<td>19.6 (5.4)</td>
<td>19.1 (5.3)</td>
</tr>
<tr>
<td>eGFR, mL/min, mean (SD)</td>
<td></td>
<td>85.1 (21.2)</td>
<td>83.6 (21.3)</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL, median (IQR)</td>
<td></td>
<td>69.0 (32.7-137.9)</td>
<td>65.0 (37.0-119.0)</td>
</tr>
<tr>
<td>Cholesterol, mg/dL, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>170 (37)</td>
<td>177 (43)</td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td></td>
<td>95 (31)</td>
<td>100 (39)</td>
</tr>
<tr>
<td>High-density lipoprotein</td>
<td></td>
<td>48 (13)</td>
<td>46 (13)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL, mean (SD)</td>
<td></td>
<td>128 (65)</td>
<td>153 (129)</td>
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<tr>
<td>HOMA of insulin sensitivity, %, median (IQR)</td>
<td></td>
<td>63.5 (45.3-96.0)</td>
<td>61.5 (42.5-94.6)</td>
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<tr>
<td>Cardiovascular risk factors and medical history, No. of patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>137 (93)</td>
<td>137 (92)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td></td>
<td>26 (18)</td>
<td>31 (21)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td>13 (8.8)</td>
<td>13 (8.7)</td>
</tr>
<tr>
<td>Medication, No. of patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td></td>
<td>66 (44.9)</td>
<td>76 (51.4)</td>
</tr>
<tr>
<td>ARB</td>
<td></td>
<td>54 (36.7)</td>
<td>49 (33.3)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td></td>
<td>80 (54.4)</td>
<td>75 (50.7)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td></td>
<td>57 (38.8)</td>
<td>64 (43.2)</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td></td>
<td>30 (6.8)</td>
<td>13 (8.8)</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td></td>
<td>11 (7.5)</td>
<td>14 (9.5)</td>
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<tr>
<td>Thiazide</td>
<td></td>
<td>33 (22.4)</td>
<td>20 (13.5)</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); E/e′, ratio of peak early transmitral ventricular filling velocity to early diastolic tissue Doppler velocity; eGFR, estimated glomerular filtration rate (using the Modification of Diet in Renal Disease formula); HOMA, homeostatic model assessment; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MRI, magnetic resonance imaging; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association. Si conversion factors: To convert cholesterol and triglycerides to mmol/L, multiply values by 0.0259 and 0.0113, respectively.

Discussion

Changes in the primary end points of LVMI or E/e′ over 1 year of treatment did not differ between the 2 Beta3-LVH groups treated with mirabegron or placebo. The current therapeutic mirabegron dosage (50 mg/d) did not cause harm in a selected patient population at risk of developing or worsening HF.

Thus far, very few clinical trials have tested the effect of mirabegron on cardiovascular outcomes. Two pilot studies (Beta 3 Agonist Treatment in Heart Failure I and II [BEAT-HF I and BEAT-HF II]) evaluated the effect of high dosages of mirabegron (300 mg/d) on LV function in patients with heart failure with reduced ejection fraction (HFrEF). In the BEAT-HF I trial, the effect of 6 months of mirabegron treatment (300 mg/d; under β1-2AR blockade to minimize off-target effects) was neutral. A non-prespecified subgroup analysis suggested a positive effect of the medication on LVEF in patients with more severe HF. The BEAT-HF II trial specifically tested the effect of short-term (1-week) treatment with the same dosage of mirabegron on hemodynamic parameters in hospitalized patients with severe HF (NYHA class III-IV). The results showed a substantial improvement in LVEF function in this acute setting, but long-term data are not available.
available. The results of the SPHERE trial were published recently, in which the effect of mirabegron (titrated up to 250 mg/d, with a majority of patients tolerating 150 mg/d) was tested against placebo on the primary end point of pulmonary vascular resistance in patients with (pre-and postcapillary) pulmonary hypertension originating from HFrEF or HFpEF.23 The study did not meet its primary end point but showed a positive effect of mirabegron on the presupposed secondary outcome of RVEF. The underlying hypotheses tested in these trials were based on rigorous preclinical studies, including large animal models of HF or pulmonary hypertension. Notably, all of these studies identified antioxidant or vasodilatory effects of β3AR activation as a putative mechanism of improvement in hemodynamic parameters. None tested the long-term influence on cardiovascular remodeling.

To our knowledge, Beta3-LVH is the first trial to test the longer-term effects of mirabegron (over 12 months) in a patient population with pre-HF structural heart disease (stage B) at risk of developing (or worsening) HF, particularly HF with preserved or minimally reduced EF. Based on preclinical evidence of antihypertrophic and antifibrotic effects of myocardial β3ARs, the trial tested the hypothesis that mirabegron would prevent the progression of adverse remodeling toward HFpEF. As such, it entailed thorough characterization of morphologic, functional, and biologic parameters in a selected patient population, undertaking cardiac MRI and Doppler echocardiography that followed a standardized protocol and analyzed the data centrally, with a focus on LVMI and E/e′ as primary end points. The original sample size calculation was based on published data on E/e′ as a parameter of diastolic function.24-25 Despite the COVID-19 pandemic, we enrolled our target of 296 patients, randomized them to treatment, and analyzed the data in the intention-to-treat analysis.

Compared with previous literature on similar patients, our study population had lower LVMI and E/e′ at baseline, which left limited room for treatment-specific improvement. Despite our selection of primarily patients with hypertension (>90%), LVMI (determined with cardiac MRI analysis in the core laboratory) was relatively low and did not progress substantially in the placebo group. This finding is consistent with more recent literature on hypertension26,27 and is likely explained by the intensification of antihypertensive treatments according to recent guidelines. Indeed, approximately half of the patients in each treatment group were taking an angiotensin-converting enzyme inhibitor, and approximately a third were taking an angiotensin receptor blocker; both medication classes have known antihypertrophic effects. The follow-up duration may also have been too short to reveal an effect of mirabegron in addition to standard treatment. Notably, cardiac β3ARs were shown to be most abundant in advanced cardiac disease,10,28 which reciprocally would leave fewer targets for mirabegron in our relatively healthy patient population, particularly with the standard therapeutic dosage of 50 mg/d.

The mirabegron dosage used here (50 mg/d) was shown previously to produce white adipocyte “beiging” and improvements in metabolic parameters, including insulin sensitivity in a patient population with obesity that was comparable to that of Beta3-LVH.29,30 Such metabolic effects would be expected to be protective against myocardial remodeling,10 albeit in a time frame possibly longer than the present trial. Contrary to previous smaller pilot studies that were not placebo controlled,30,31 our results do not confirm any statistically significant effect of mirabegron vs placebo on lipids, glycemic control, or insulin sensitivity (assessed with HOMA). Although the number of participants was smaller, the results of the substudy testing the effect of mirabegron on the abundance or activity of beige or brown fat (by fluorodeoxyglucose–positron emission tomography) at 12 months were also neutral. Likewise, digital microtonometry did not identify any difference from placebo in endothelial function. Nevertheless, such effects may be more apparent with recently developed, more potent β3AR agonists.12 Likewise, higher doses of mirabegron associated with β1AR blockers to prevent off-target effects may be useful for patients with more advanced heart failure to
stabilize their hemodynamic state before more intensive interventions are implemented, as suggested from the BEAT-HF trials.\(^{21,22}\) Longer-term benefits could be expected from combined effects on LV function and remodeling through activation of the upregulated β3AR in these patients, without prohibitive hypotension (unlike direct activators of guanylyl cyclase or other vasodilators). This approach as an add-on to contemporary standard therapy remains to be tested in larger trials.

To our knowledge, Beta3-LVH is the first placebo-controlled randomized clinical trial to assess AE incidence in a patient population with a more severe cardiovascular risk...
profile (ie, with hypertension, obesity, and structural heart disease and type 2 diabetes or atrial fibrillation) than in previous phase 3 or 4 trials of mirabegron for overactive bladder disease.33 In this study, particular attention was given to cardiovascular effects, such as arrhythmias and mild or severe hypertensive episodes. Indeed, preclinical evidence pointed to potential adverse effects through kidney sodium retention,34 although the effect of β3-adrenergic stimulation on heart rhythm or conduction is still unclear.35 Our results showed that at the standard mirabegron dosage (50 mg/d) in addition to multidrug treatment for cardiovascular disease, the incidence of AEs (including mild or severe hypertension by 24-hour ambulatory blood pressure monitoring) did not differ between mirabegron- and placebo-treated patients over 1 year of treatment. Because mirabegron is metabolized through CYP3A4 (and to a lesser extent by CYP2D6), drugs known to interfere with this metabolism were excluded per protocol, leaving a caveat for their concomitant use.

**Limitations**

Our inclusion of patients with mild HF and the use of a single standard mirabegron dosage (50 mg/d) may have precluded detection of a treatment effect. Techniques more advanced than measurements of E/e′, such as cardiac strain,36 could have been more powerful in assessing early changes in diastolic function. Although they were relatively infrequent and compensated for by appropriate statistical treatment, missing data and dropouts remain limitations.

**Conclusions**

In the Beta3-LVH randomized clinical trial, the standard therapeutic mirabegron dosage (50 mg/d) did not result in a difference in LV mass or diastolic function over 12-month follow-up in patients who had structural heart disease but no or mild HF symptoms and were receiving standard therapy. Unlike smaller trials using higher dosages for patients with severe illness,21,22 mirabegron had no effect on LV function, RV function, or exercise capacity. In contrast with open pilot studies29,30 with the same lower dose, there were also no beneficial effects of mirabegron on lipid or glycemic control. Longer-term effects of β3-adrenergic stimulation on myocardial remodeling and function need to be tested in patients with established HFpEF, including with recent, more potent agonists.32
Repurposing Mirabegron in Patients With Structural Cardiac Disease

Original Investigation Research

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