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RESEARCH LETTER

Paroxetine-Mediated G-Protein Receptor Kinase 2 Inhibition in Patients With Acute Anterior Myocardial Infarction: Final 1-Year Outcomes of the Randomized CARE-AMI Trial

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Left ventricular (LV) remodeling after ischemic injury is catalyzed by dysregulation of G-protein–coupled receptor kinases (GRKs).[1] Preclinical studies suggest that competitive inhibition of GRK2 mitigates the extent of myocardial fibrosis and improves LV function.[2] Paroxetine, a selective serotonin reuptake inhibitor, selectively inhibits GRK2 and has been shown to attenuate maladaptive remodeling in a mouse model.[3] The CARE-AMI (Paroxetine-Mediated GRK2 Inhibition to Reduce Cardiac Remodeling After Acute Myocardial Infarction) trial was an investigator-initiated, double-blind, randomized controlled trial investigating the potential of paroxetine-mediated GRK2 inhibition compared with placebo to reduce adverse LV remodeling in patients with acute anterior ST-segment–elevation myocardial infarction (STEMI) with a LV ejection fraction (LVEF) ≤45% (ClinicalTrials.gov identifier: NCT03274752). The study protocol was approved by the local ethics committee, and all participants provided written informed consent before randomization. Anonymized data and materials have been made publicly available at the Bern Open Repository and Information System and can be accessed at https://boris.unibe.ch. Eligibility criteria, end point definitions, and details of randomization, masking, and study conduct have been described elsewhere.[4] The primary end point results were assessed by means of cardiac magnetic resonance imaging at 12 weeks after STEMI and have been reported previously.[4] Herein, we report the final clinical and echocardiographic outcomes at 1 year. LV volume and ejection fraction were measured with the use of the biplane Simpson method. LV global longitudinal strain was assessed by speckle-tracking echocardiography. Outcome assessors were blinded to treatment allocation. *P* values for differences in categorical variables were computed using χ^2 or Fisher exact test. We used the Wilcoxon rank sum tests to compare patient-level changes from baseline to follow-up within each treatment group and between the experimental and the control group. Only patients with available serial echocardiographic data were considered for the primary analysis. A total of 50 patients

Key Words: GTP-binding proteins ■ humans ■ myocardial infarction ■ paroxetine

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Table 1. LV Dimension and LV Function Between Baseline and 12 Months, as Assessed by Transthoracic Echocardiography

Variable	Paroxetine				Placebo				Paroxetine vs placebo
	Baseline	12 mo	Change	*P* value	Baseline	12 mo	Change	*P* value	*P* value
LV function									
EF (Simpson, biplane), %	41.0 (37.0 to 44.3)	50.0 (43.5 to 56.5)	8.0 (3.0 to 15.0)	0.005	43.0 (36.0 to 50.0)	54.0 (41.9 to 63.5)	7.1 (0.0 to 13.4)	0.008	0.86
GLS, %	12.4 (10.2 to 13.8)	15.2 (12.8 to 17.4)	3.2 (1.2 to 3.9)	<0.001	11.8 (10.7 to 13.5)	14.7 (14.1 to 17.6)	2.1 (1.0 to 4.2)	<0.001	0.92
LV dimensions									
End-diastolic diameter, mm	51.0 (47.0 to 54.0)	53.0 (47.5 to 55.5)	3.0 (−2.0 to 6.0)	0.038	51.0 (45.8 to 53.2)	49.0 (45.5 to 56.5)	3.0 (−5.0 to 4.0)	0.553	0.42
End-diastolic volume, mL	142.0 (114.8 to 153.8)	119.1 (105.5 to 148.0)	−2.7 (−29.7 to 15.9)	0.551	114.5 (102.0 to 128.0)	112.0 (89.9 to 137.2)	−16.5 (−18.9 to 9.5)	0.126	0.97

Data are presented as stratified by allocated study drug according to the intention-to-treat principle. Data are expressed as median (25%–75%). EF indicates ejection fraction; GLS, global longitudinal strain; and LV, left ventricular.

with anterior STEMI were randomly assigned to the experimental or the control group between October 26, 2017, and September 21, 2020. At 1 year, clinical and echocardiographic follow-up was complete in 100% and 80% of patients, respectively. The mean age of the patients was 61.8±12.6 years, and 41 (82%) were men. Demographic and clinical baseline characteristics have been reported previously.[4] At 1 year, there were no significant differences between the experimental and the control groups with regard to antiplatelet or antithrombotic treatment, nor with regard to treatment with β blockers (81% versus 82%; *P*>0.999), renin-angiotensin system inhibitors (71% versus 82%; *P*=0.49), or angiotensin receptor–neprilysin inhibitors (14% versus 5%; *P*=0.35). Between baseline and follow-up at 1 year, mean LVEF and global longitudinal strain improved in both the experimental group and the control group, with no significant difference between the 2 treatment arms (Table). There were no differences in the change in LV dimensions and volumes between the 2 treatment groups, nor were there any differences in parameters of diastolic dysfunction between the 2 treatment arms. At 1 year, all study participants were alive and in New York Heart Association functional class I or II. One patient in each group had a hospitalization for heart failure. Two patients in the placebo group underwent transcatheter edge-to-edge mitral repair. One patient in the experimental arm underwent modified endoventricular circular plasty (Dor procedure). Four patients in the experimental group and 6 patients in the control group underwent implantation of an internal cardioverter-defibrillator. In this double-blind, placebo-controlled, randomized clinical trial, the extent of LVEF recovery and improvement of global longitudinal strain 1 year after anterior STEMI was comparable in patients treated with a 3-month course of paroxetine or placebo. A greater reduction in late gadolinium enhancement in patients in the experimental compared with the control group documented at 12 weeks by means of cardiac magnetic resonance imaging did not translate into differences in echocardiographic or clinical outcomes at 1 year. Both early revascularization and installation of guideline-directed heart failure treatment may have attenuated a potential effect of GRK2 inhibition as an add-on therapy. The reliability of the reported findings is limited by the modest sample size. In addition, reduction of LVEF at baseline was only moderate, thus attenuating the potential effect of paroxetine on LVEF recovery. In contrast to the assessment at 12 weeks, LV function at 1 year was assessed by use of echocardiocardiography and not by magnetic resonance imaging. Moreover, both LVEF and global longitudinal strain provide an aggregate estimate of LV function, but may not be sensitive enough to assess differences in LV remodeling at a more granular level. Furthermore, GRK2 signaling levels were not

measured in this study. The CARE-AMI study documented no effect of paroxetine on LVEF recovery at 1 year in patients with STEMI.

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