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Circadian-timed quick-release bromocriptine lowers elevated resting heart rate in patients with type 2 diabetes mellitus

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Abstract

Objective: Sympathetic nervous system (SNS) overactivity is a risk factor for insulin resistance and cardiovascular disease (CVD). We evaluated the impact of bromocriptine-QR, a dopamine-agonist antidiabetes medication, on elevated resting heart rate (RHR) (a marker of SNS overactivity in metabolic syndrome), blood pressure (BP) and the relationship between bromocriptine-QR's effects on RHR and HbA1c in type 2 diabetes subjects.

Design and Subjects: RHR and BP changes were evaluated in this post hoc analysis of data from a randomized controlled trial in 1014 type 2 diabetes subjects randomized to bromocriptine-QR vs placebo added to standard therapy (diet ± ≤2 oral antidiabetes medications) for 24 weeks without concomitant antihypertensive or antidiabetes medication changes, stratified by baseline RHR (bRHR).

Results: In subjects with bRHR ≥70 beats/min, bromocriptine-QR vs placebo reduced RHR by −3.4 beats/min and reduced BP (baseline 130/79; systolic, diastolic, mean arterial BP reductions [mm Hg]: −3.6 [P = .02], −1.9 [P = .05], −2.5 [P = .02]). RHR reductions increased with higher baseline HbA1c (bHbA1c) (−2.7 [P = .03], −5 [P = .002], −6.1 [P = .002] with bHbA1c ≤7, >7, ≥7.5%, respectively] in the bRHR ≥70 group and more so with bRHR ≥80 (−4.5 [P = .07], −7.8 [P = .015], −9.9 [P = .005]). Subjects with bRHR <70 had no significant change in RHR or BP. With bHbA1c ≥7.5%, %HbA1c reductions with bromocriptine-QR vs placebo were −0.50 (P = .04), −0.73 (P = .005) and −1.22 (P = .008) with bRHR <70, ≥70 and ≥80, respectively. With bRHR ≥70, the magnitude of bromocriptine-QR-induced RHR reduction was an independent predictor of bromocriptine-QR's HbA1c lowering effect.

Conclusion: Bromocriptine-QR lowers elevated RHR with concurrent decrease in BP and hyperglycaemia. These findings suggest a potential sympatholytic mechanism contributing to bromocriptine-QR's antidiabetes effect and potentially its previously demonstrated effect to reduce CVD events.

KEYWORDS
dopamine, sympathetic nervous system, type 2 diabetes

Trial Registration: ClinicalTrials.gov Identifier: NCT00377676. Registered 18 September 2006.

1 | INTRODUCTION

The sympathetic nervous system (SNS) plays an important role in maintaining normal cardiovascular homeostasis and health by regulating systemic vascular resistance, blood pressure (BP), heart rate, cardiac output and normal vascular endothelial function in response to a multitude of acute environmental, physical and mental status alterations.[1,2] It also regulates normal glucose homeostasis by enhancing hepatic glucose output and adipose-free fatty acid mobilization during fasting periods of the day and in circumstances such as acute hypoglycaemia or prolonged starvation.[3-8] However, chronic overactivity of the SNS leads to cardiovascular as well as metabolic adverse effects.[9-18] Cardiovascular adverse effects of chronically elevated sympathetic tone include vasoconstriction facilitating increased BP, an overactivated renin-angiotensin system potentiating increased BP, increased heart rate and most importantly inflammation and reactive oxygen species (ROS) generation in the micro- and macro-vasculature as well as within the myocardium itself potentiating arterial stiffness, myocardial apoptosis and myocardial ischaemia/reperfusion injury.[2,10,15-23] Less well recognized are the adverse metabolic effects of chronically increased SNS activity, which include increased hepatic gluconeogenesis, decreased hepatic glucose disposal, increased free fatty acid (FFA) mobilization from the adipose tissue, ROS generation and inflammation in adipose and liver, and decreased blood flow to muscle, all potentiating insulin resistance in those tissues and beta cell dysfunction resulting from inflammatory factors, ROS, lipotoxicity and glucotoxicity.[10,12,13,16,18,24-26]

Elevated resting heart rate (RHR) can reflect elevated central sympathetic-to-parasympathetic activity balance[27,28] and has been shown to be a common occurrence in insulin resistance syndrome, independent of high BP or obesity.[29-32] Most importantly, in the insulin resistance syndrome, elevated RHR values are significantly correlated with other measures of SNS activity such as muscle sympathetic nerve activity and serum noradrenaline levels.[12,16,18,29] While clinically RHR between 60 and 100 beats per minute (BPM) is considered the "normal" range for RHR and RHR ≥100 is used as the criteria for defining tachycardia, a large body of evidence from epidemiological and clinical studies suggests that increasing RHR within the "normal" range is associated with increased cardiometabolic risk, particularly above 70-80 beats per minute (BPM). Such elevated RHR has been associated with insulin resistance,[26,33] altered beta cell function,[34] impaired glucose regulation and increased risk of developing type 2 diabetes mellitus[35-37] as well as increased cardiovascular disease (CVD) risk[38-56] and mortality.[38-48,51,52,54,56-65]

Bromocriptine-QR (B-QR), a quick-release formulation of micronized bromocriptine, is the only sympatholytic dopamine-agonist US FDA-approved for the treatment of type 2 diabetes. In several preclinical[66-72] and clinical studies,[73-84] bromocriptine administration has repeatedly been demonstrated to reduce measures of elevated SNS activity such as reduction of elevated sympathetic outflow, plasma norepinephrine, BP and/or conversion of nondipper profile of circadian mean arterial pressure to a dipper profile. A critical aspect of dopaminergic control of autonomic function is via circadian modulation of the central biological clock pacemaker circuit (circadian neuronal afferent signals to and including the suprachiasmatic nuclei [SCN]) (see below).

The biological clock pacemaker circuit (circadian efferent signals to and including the SCN) for the body is a primary regulator of autonomic balance in the body.[85-87] A diminution of the circadian peak in dopaminergic input signalling to this SCN clock system (at daily waking from the sleep cycle) is coupled to and potentiates an increase in hypothalamic pre-autonomic neuronal activities that lead to overactivation of the SNS and metabolic syndrome in animals.[88] The circadian-timed administration of either dopamine agonist systemically or dopamine to the SCN clock area in insulin-resistant animals to induce (mimic) the normal circadian peak of dopaminergic activity at the SCN pacemaker that is diminished in insulin resistance states has been observed to reduce chronic overactivity of SNS pre-autonomic neurons in the hypothalamus and measures of subsequent chronic activation of peripheral sympathetic tone in insulin-resistant states.[66,88-93] Moreover, reduction of brain dopamine synthesis in healthy humans for just a couple of days induces peripheral insulin resistance.[94,95]

Circadian-timed (onset of daily waking) administration of the antidiabetes agent B-QR, a quick-release formulation of micronized bromocriptine, to re-establish the normal circadian peak of central nervous system (CNS) dopaminergic activity that is diminished in insulin-resistant states among mammals has been observed to improve insulin sensitivity and reduce CVD events in type 2 diabetes.[96,97] Therefore, the possibility exists that such B-QR therapy may reduce elevated RHR, a measure of SNS tone in insulin resistance syndrome,[29] that may in part explain the agent's impact to improve glycaemic control[96] and reduce adverse cardiovascular outcomes in type 2 diabetes.[98-101] However, the impact of circadian B-QR therapy on the pathophysiological parameter of elevated RHR and, importantly, its relation to glycaemic control in type 2 diabetes has never been investigated. The primary aim of this present study was twofold: (a) to investigate the effect of B-QR on elevated RHR in type 2 diabetes subjects and (b) to assess the nature of any inter-relationship between B-QR's impact to reduce elevated RHR and to reduce HbA1c in these subjects.

2 | METHODS

2.1 | Study subjects and design

The study population (N = 1014) of type 2 diabetes subjects was derived from the Cycloset Safety Trial (CST). The study protocol and design for the CST have been previously described in detail.[98,102] Briefly, the CST was a multicenter, placebo-controlled, double-blind, parallel-group safety and efficacy study in outpatient type 2 diabetes subjects recruited from general practice and diabetes clinics across 74 clinical centres in the United States and Puerto Rico. Subjects were between the ages of 30 and 80 years and had a body mass index <43 kg/m^2, with established type 2 diabetes by ADA

2003 criteria and HbA1c ≤10.0%. Subjects with New York Heart Classifications I and II congestive heart failure (CHF) were allowed to participate, as were subjects with a history of myocardial infarction (MI) or coronary revascularization occurring >6 months before enrolment. Subjects were required to have maintained a stable diabetes treatment regimen for ≥30 days prior to randomization, consisting of lifestyle interventions of medical nutrition therapy and appropriately prescribed physical activity with or without oral antihyperglycaemic agents (≤2) or insulin either alone or in combination with 1 oral antihyperglycaemic agent.

Following randomization (2:1 active agent vs placebo), the study drug (B-QR or placebo) was titrated from an initial starting dose of 1 tablet daily (0.8 mg B-QR per tablet or matching placebo) by increasing the daily dose by 1 tablet per week until a maximum tolerated daily dose between 2 and 6 tablets once daily (1.6-4.8 mg B-QR/day) was achieved. The study drug was taken with the morning meal, within 2 hours of waking. Subjects were required to continue their established antihyperglycaemic treatments during the first 3 months of the study. However, the dosages of the oral agents or insulin could be modified as deemed appropriate by the study site investigator. After 3 months, alterations in the diabetes treatment regimen were allowed, if deemed necessary by the study site investigator, as long as these changes did not result in a final regimen that exceeded two oral agents or insulin plus one oral agent, exclusive of the study drug. Due to the above study design, the prespecified statistical analysis plan for the CST[102] had specified that data at 24 weeks of treatment be considered for efficacy analyses and therefore were used to assess B-QR's effects on dysglycemia and RHR in the present study.

The study protocol was approved by site-specific or central institutional review boards, and all subjects provided written informed consent to participate in the study before enrolment. The study was conducted in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) 2004 guidelines. This current study and analyses are original and different from any previously reported results from the CST.

The study population for the present study consisted of all subjects from the CST who completed 24 weeks of study drug treatment with no concomitant hypertension medication changes (to avoid confounding arising from BP and/or heart rate effects from changes in concomitant antihypertensive medications during this period) and no antidiabetes medication changes (since the original CST protocol had allowed for changes in dosages and regimens of antidiabetes medications, to avoid any potential confounding arising from the possibility of such diabetes medication changes affecting RHR or BP changes). Subjects on insulin therapy were excluded from this population given the limitations of the database in clearly determining insulin dose changes (and hence ensuring that there were no changes in concomitant diabetes therapies) and also more importantly to control for the potential effects of insulin itself and changes in insulin dose on sympathetic activity given that insulin acts centrally to increase SNS activity.[103,104] A total of 1014 subjects (642 B-QR, 372 placebo) meeting the above criteria constituted the study population for this study.

Resting heart rate was derived from 12-lead electrocardiograms (ECGs) obtained at baseline and at 24 weeks. BP and HbA1c measurements were obtained at the baseline and 24-week study visits.

2.2 | Statistical analyses

To assess the effects of treatment with B-QR on RHR and if baseline RHR influences this effect and determine if there is a RHR threshold at which the treatment effect might first occur, a 2-way analysis of variance was performed to test the interaction of treatment arm (B-QR vs placebo) and baseline RHR subgroup (stratified as RHR <60, 60-69, 70-79 and ≥80) as two independent variables/factors and change in RHR from baseline to week 24 as the outcome variable. The treatment effects within each RHR subgroup were further analysed with *t* tests. Paired sample *t* tests were used to assess within-treatment group changes and Student's *t* test for between-group differences. Based on the findings from these initial analyses, that indicated baseline RHR ≥70 as the threshold above which an effect of B-QR in lowering RHR was evident (Table 2), all further analyses were stratified by a baseline RHR cut-off of <70 vs ≥70 or ≥80 BPM.

In addition to changes in RHR, changes in systolic BP (SBP), diastolic BP (DBP) and mean arterial pressure (MAP) from baseline to 24 weeks were analysed in the study population stratified by baseline RHR < or ≥70 BPM. Multivariable linear regression analyses stratified by RHR <70 and ≥70 BPM were performed with change in RHR from baseline to 24 weeks as the outcome variable and treatment with B-QR vs placebo as a covariate along with age, gender, race, BMI, duration of diabetes, baseline HbA1c, baseline RHR, baseline and changes in SBP and DBP as other covariates included to further evaluate the effect of B-QR treatment on RHR after controlling for potential effects of these other factors on RHR.

Further analyses were then performed to evaluate (a) the relationships between baseline RHR as well as baseline HbA1c and the change in RHR associated with B-QR therapy (vs placebo) and (b) the relationship between B-QR's impact on elevated RHR and its glycaemic control effect.

To evaluate the relationships between baseline RHR, baseline HbA1c and B-QR's impact on RHR, the changes in RHR with B-QR vs placebo were analysed in the baseline RHR <70, ≥70, and ≥80 subgroups stratified by baseline HbA1c (baseline HbA1c ≤7, >7 and ≥7.5).

The nature of the relationship between (a) baseline RHR and B-QR's antidiabetes effect and (b) B-QR's impact on elevated RHR and its antidiabetes effect each was analysed in those subjects with suboptimal glycaemic control (HbA1c ≥7.5%) at baseline (N = 198:125 B-QR, 73 placebo) as described below.

To evaluate if baseline RHR impacts the glycaemic control effects of B-QR, the change in HbA1c from baseline to week 24 with B-QR vs placebo was analysed in subjects with baseline HbA1c ≥7.5 stratified by baseline RHR <70, ≥70, and ≥80.

The relationship between study drug-induced change in elevated RHR and change in HbA1c was analysed in subjects with baseline HbA1c ≥7.5 and baseline RHR ≥70 using Pearson correlation as

well as multivariable linear regression with change in HbA1c from baseline to week 24 as the outcome variable and change in RHR as a covariate along with age, gender, race, baseline HbA1c and other concomitant diabetes medications (metformin, SU and/or TZD, each coded as 0 = no and 1 = yes) as the other variables included in the analysis.

All statistical analyses were performed using SPSS software (Build 1.0.0.1012; IBM Corp). The significance level was set at $P < .05$. Data are presented as mean ± standard error of the mean (SEM) except categorical variables shown as numbers and per cent.

3 | RESULTS

3.1 | Baseline characteristics

The baseline characteristics of the study population are shown in Table 1. Study subjects in the B-QR and placebo treatment arms were well matched at baseline within each RHR subgroup and overall; besides the expected difference in mean RHR, there were no major differences in the baseline characteristics of subjects across the different RHR subgroups. The average blood pressure control was good in all groups but close to 70% of the subjects had a history of hypertension in each group and were on antihypertensive medications. In this regard, it should be re-emphasized that concomitant antihypertensive medication changes did not occur during the course of this study per the study inclusion criteria described in Section 2.

3.2 | RHR threshold for effect of B-QR

Two-way analysis of variance to explore the effect of treatment with B-QR (vs placebo) and baseline RHR on the change in RHR from baseline to week 24 revealed statistically significant interaction between the effects of treatment arm and baseline RHR subgroup on the change in RHR (F [3, 1006] 3.3, $P = .02$), with significant changes in RHR with B-QR therapy seen only in the RHR subgroups with baseline RHR ≥70 BPM (see Table 2 for details). In the baseline RHR between 70 and 79 subgroup, the RHR change from week 0 to week 24 was −3.3 BPM ($P < .001$) within the B-QR treated group and −0.9 ($P = .3$) within the placebo group yielding a between-group difference of −2.4 BPM ($P = .027$). In the baseline RHR ≥80 BPM subgroup, RHR decreased significantly by −7.6 BPM ($P < .001$) in the B-QR-treated group, while the mean RHR change of −2.7 BPM in the placebo group was not statistically significant ($P = .07$) yielding a between-treatment group difference of −4.9 BPM RHR reduction with B-QR relative to placebo ($P = .01$). There were no significant changes in RHR with either B-QR or placebo in the subgroups with

TABLE 1 Baseline characteristics of the study population

	Baseline RHR <70		Baseline RHR ≥70		Baseline RHR ≥80	
	B-QR (n = 399)	Placebo (n = 243)	B-QR (n = 243)	Placebo (n = 129)	B-QR (n = 85)	Placebo (n = 39)
Age (y)	61 ± 0.5	61 ± 0.6	58 ± 0.6	59 ± 0.9	59 ± 1.1	56 ± 1.4
Gender (% male)	61	60	56	47	48	41
Race (% Caucasian)	63	70	65	64	62	69
BMI (kg/m^2)	31.7 ± 0.3	32.2 ± 0.3	32.9 ± 0.3	32.1 ± 0.5	32.2 ± 0.6	32.5 ± 0.9
Duration of diabetes (y)	5.5 ± 03	6.6 ± 0.4*	6.2 ± 0.3	6.1 ± 0.5	7.3 ± 0.7	5.9 ± 0.8
HbA_{1c} (%)	6.64 ± 0.04	6.69 ± 0.06	6.93 ± 0.07	6.92 ± 0.10	7.05 ± 0.11	6.84 ± 0.19
Fasting glucose (mg/dL)	133 ± 1.6	133 ± 2.0	143 ± 2.7	137 ± 3.3	148 ± 5.1	136 ± 6.2
Baseline RHR (bpm)	60 ± 0.3	60 ± 0.4	78 ± 0.5	77 ± 0.6	86.5 ± 0.7	85.4 ± 0.8
Systolic BP (mm Hg)	130 ± 0.7	130 ± 0.8	130 ± 0.8	128 ± 1.1	131 ± 1.5	125 ± 1.9*
Diastolic BP (mm Hg)	77 ± 0.4	77 ± 0.6	79 ± 0.6	78 ± 0.7	78 ± 1.0	77 ± 1.4
eGFR (mL/min/1.73 m^2)	66 ± 0.6	67 ± 0.7	67 ± 0.8	66 ± 1.1	66 ± 1.4	67 ± 1.8
Serum creatinine (mg/dL)	1.1 ± 0.01	1.1 ± 0.01	1.1 ± 0.01	1.1 ± 0.02	1.1 ± 0.02	1.1 ± 0.02
Hypertension history (% yes)	69	70	72	72	72	67

Note: Data shown as mean ± standard error of mean.

Abbreviations: BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; RHR, resting heart rate.

*$P < .05$ for between-treatment group (B-QR vs placebo) within specified baseline RHR category.

baseline RHR <60 or 60-69 (ie RHR <70). Baseline RHR < or ≥70 was therefore used as the cut-off for the subsequent analyses as described below.

3.3 | Effects of B-QR on RHR and BP stratified by baseline RHR ≥70/<70

Among subjects with baseline RHR ≥70 (N = 372:243 B-QR, 129 placebo), RHR decreased from baseline to week 24 on average by −4.8 BPM in the B-QR treated group and by −1.5 in the placebo-treated group yielding a between-group difference of −3.4 BPM (*P* = .001) (see Table 3 for more details). B-QR therapy relative to placebo also reduced SBP by −3.6 mm Hg (*P* = .02), DBP by −1.9 mm Hg (*P* = .05) and MAP by −2.5 mm Hg (*P* = .02) (see Table 3 for more details).

Among subjects with RHR <70 at baseline, there was no reduction in RHR within either treatment group and no significant difference in the RHR change from baseline with B-QR therapy relative to placebo (between-treatment group difference in change in RHR from baseline −0.4, *P* = .5).

Multivariable regression analysis demonstrated that treatment with B-QR (vs placebo) is a significant independent predictor (*P* = .001) of change in RHR, after adjusting for other factors including age, gender, race, BMI, duration of diabetes, baseline HbA1c, and baseline as well as change in SBP and DBP, in subjects with baseline RHR ≥70 but not in those with baseline RHR <70.

3.4 | Effect of baseline HbA1c on B-QR's impact on RHR

The mean change in RHR from baseline to week 24 with B-QR therapy vs placebo among subjects with baseline RHR ≥70 when stratified by baseline HbA1c was −2.7 BPM (*P* = .03) in subjects with baseline HbA1c ≤7, −5.0 BPM (*P* = .002) in subjects with baseline HbA1c >7 and −6.1 BPM (*P* = .002) in those with baseline HbA1c ≥7.5 (Figure 1; Table 4).

TABLE 2 Effects of bromocriptine-QR vs placebo treatment for 24 wk on resting heart rate stratified by baseline resting heart rate

	Bromocriptine-QR (B-QR)			Placebo (PL)			
Baseline RHR subgroups	Baseline	After 24 wk of treatment	B-QR within group change	Baseline	After 24 wk of treatment	PL within group change	B-QR vs PL between-group difference
RHR <60 N = 294 (174 B-QR; 120 P)	54.1 ± 0.3	57.5 ± 0.6	3.4 *P* < .001	55.0 ± 0.3	58.3 ± 0.6	3.3 *P* < .001	0.1 *P* = .90
RHR 60-69 N = 348 (225 B-QR; 123 P)	64.4 ± 0.2	64.7 ± 0.5	0.3 *P* = .61	64.6 ± 0.3	65.3 ± 0.7	0.8 *P* = .26	−0.5 *P* = .55
RHR 70-79 N = 248 (158 B-QR; 90 P)	74.1 ± 0.2	70.8 ± 0.7	−3.3 *P* < .001	73.4 ± 0.3	72.5 ± 0.9	−0.9 *P* = .30	−2.4 *P* = .027
RHR ≥80 N = 124 (85 B-QR; 39 P)	86.5 ± 0.7	78.9 ± 1.1	−7.6 *P* < .001	85.4 ± 0.8	82.7 ± 1.6	−2.7 *P* = .07	−4.9 *P* = .01

Note: Data shown as mean ± standard error of mean.
Abbreviation: RHR, resting heart rate.

TABLE 3 Effects of bromocriptine-QR vs placebo treatment for 24 wk on resting heart rate and blood pressure in subjects with baseline RHR ≥70

	Bromocriptine-QR (B-QR) (N = 243)			Placebo (PL) N = 129			
	Baseline	After 24 wk of treatment	B-QR within group change	Baseline	After 24 wk of treatment	PL within group change	B-QR vs PL between-group difference
RHR (BPM)	78.4 ± 0.5	73.6 ± 0.6	−4.8 *P* < .001	77.0 ± 0.6	75.6 ± 0.9	−1.5 *P* = .06	−3.4 *P* = .001
Systolic BP (mm Hg)	129.9 ± 0.9	127.1 ± 0.9	−2.8 *P* = .002	127.7 ± 1.1	128.5 ± 1.3	0.8 *P* = .6	−3.6 *P* = .02
Diastolic BP (mm Hg)	79.2 ± 0.6	76.8 ± 0.6	−2.4 *P* < .001	78.0 ± 0.7	77.5 ± 0.8	−0.5 *P* = .5	−1.9 *P* = .05
MAP (mm Hg)	96.1 ± 0.6	93.6 ± 0.6	−2.6 *P* < .001	94.6 ± 0.7	94.5 ± 0.8	−0.05 *P* = .9	−2.5 *P* =.02

Note: Data shown as mean ± standard error of mean.
Abbreviations: BP, blood pressure; MAP, mean arterial pressure; RHR, resting heart rate.

The magnitude of the RHR reductions from baseline with B-QR vs placebo was even greater when the analyses were limited to subjects with elevated baseline RHR ≥80 (N = 124:85 B-QR, 39 placebo), with a mean change in RHR from baseline to week 24 with B-QR therapy vs placebo of −4.5 BPM (P = .07) in those with baseline HbA1c ≤7, −7.8 BPM (P = .015) in those with baseline HbA1c >7 and −9.9 BPM (P = .005) in those with baseline HbA1c ≥7.5 (Figure 1; Table 4).

There was no significant change in RHR among subjects with baseline RHR <70 regardless of baseline HbA1c (RHR change week 0 to week 24 with B-QR therapy vs placebo −0.04 [P = .95], −1.4 [P = .26] and −0.9 [P = .59] BPM in subjects with baseline HbA1c ≤7, >7, and ≥7.5, respectively).

3.5 | Effect of baseline RHR on B-QR's glycaemic effect

To assess the relationship between baseline RHR and the antidiabetes effect of B-QR, the change in HbA1c from baseline to week 24 with B-QR therapy vs placebo was analysed in subjects with poor glycaemic control (defined as baseline HbA1c ≥7.5%) at baseline (N = 198:125 B-QR, 73 placebo), stratified by baseline RHR. HbA1c reduction as a function of baseline RHR demonstrated HbA1c reductions with B-QR vs placebo as follows: RHR <70 BPM: −0.50 (P = .04); RHR ≥70 BPM: −0.73 (P = .005), ≥80 BPM: −1.22 (P = .008) (Figure 2).

3.6 | Relationship between B-QR-induced change in RHR and B-QR's antidiabetes effect

The relationship between the B-QR induced change in RHR and change in HbA1c was analysed in the subjects with baseline RHR ≥70 BPM and baseline HbA1c ≥7.5. The change (decrease) in RHR from baseline to week 24 significantly positively correlated with the change (decrease) in HbA1c (Pearson r = .40, P = .001) in subjects treated with B-QR but not placebo. Multivariable regression analysis with change in HbA1c from baseline to week 24 as the outcome variable and change in RHR as a covariate along with age, gender, race, baseline HbA1c, and other concomitant diabetes medications (metformin, SU and/or TZD) as the other variables included in the analysis demonstrated that among the B-QR treated subjects with baseline RHR ≥70 BPM and baseline HbA1c ≥7.5, the magnitude of RHR reduction is a significant independent predictor of B-QR's effect on reducing HbA1c (β .42; P = .001) (see Table 5 for more details).

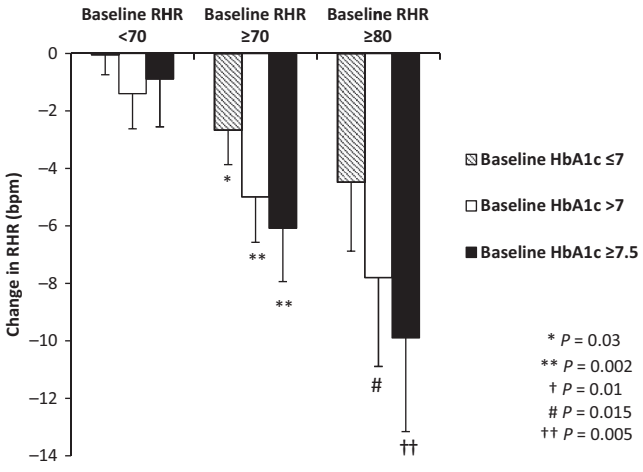

FIGURE 1 Bromocriptine-QR vs placebo reduces elevated resting heart rate (between-group difference in change from baseline) as a function of baseline resting heart and baseline haemoglobin A1c. Data shown as mean ± standard error of mean. RHR, resting heart rate

4 | DISCUSSION

Circadian-timed treatment of type 2 diabetes subjects with B-QR reduced an elevated RHR (≥70 BPM or ≥80 BPM) by between approximately 3-10 BPM relative to placebo dependent upon the baseline RHR and HbA1c level in the study population. The magnitude of this RHR reduction was greater the more elevated the baseline RHR above 70 BPM, with greater reductions seen with baseline RHR ≥80. There was no such B-QR impact to reduce RHR in subjects with baseline RHR below 70 BPM. That is, the B-QR influence to reduce RHR was only observable if the RHR was elevated to a range above 70 BPM, a threshold that has in previous studies been associated with increased risk of insulin resistance, metabolic syndrome, type 2 diabetes and adverse CVD outcomes.[46,47,49-51,61,65] The B-QR-induced reduction in RHR was accompanied also by a concurrent reduction in BP, suggesting an influence to reduce central elevated sympathetic drive to the cardiovascular system.[66,73,74,76,84] Importantly, the magnitude of the B-QR effect to reduce elevated RHR increased also with increasing HbA1c level at baseline which may reflect higher levels of underlying elevated sympathetic activity contributing to both the elevated RHR and higher A1c in these subsets. In addition, the degree of B-QR's impact to reduce elevated RHR was an independent predictor of its effect to reduce HbA1c among subjects with poor glycaemic control (baseline HbA1c ≥7.5). To our knowledge, this is the first demonstration of such an effect on RHR with any FDA-approved antidiabetes medication. This interaction suggests that B-QR therapy may be targeting an aetiologic factor of both elevated RHR and dysglycemia. This aetiologic factor likely is elevated SNS activity, an autonomic imbalance pathology known to both increase RHR and potentiate insulin resistance and dysglycemia.[10,12,13,26] Such a SNS target of B-QR would be consistent with the reported sympatholytic mechanism of action of circadian-timed B-QR therapy to improve glycaemic control and reduce CVD risk in type 2 diabetes subjects.[96,105] However, although SNS innervation of the myocardium is extensive and exerts a prominent control of myocardial function,[106] reduced parasympathetic drive to the heart may also contribute to elevated RHR [107] and central dopamine action can function to reverse this vagal imbalance as well,[108] an effect which may also participate in the observed B-QR effects on elevated RHR in this study.

It is important to appreciate in general and relative to the present investigation in particular that a large body of evidence indicates

TABLE 4 Resting heart rate changes with bromocriptine-QR vs placebo stratified by baseline resting heart rate and baseline haemoglobin A1c

Baseline RHR groups stratified by baseline HbA1c	Bromocriptine-QR (B-QR)		Placebo (P)		Between-treatment group difference in RHR change Week 0-24 (*P*-value)
	RHR at baseline	RHR change Week 0-24	RHR at baseline	RHR change Week 0-24	
Baseline RHR <70 BPM					
HbA1c ≤7 (N = 295 B-QR, 177 P)	60 ± 0.4	1.7 ± 0.4***	60 ± 0.4	1.7 ± 0.5***	0.04 ± 0.7 (*P* = .95)
HbA1c >7 (N = 103 B-QR, 66 P)	61 ± 0.6	1.4 ± 0.8	60 ± 0.6	2.8 ± 0.9**	−1.4 ± 1.2 (*P* = .25)
HbA1c ≥7.5 (N = 60 B-QR, 41 P)	60 ± 0.8	1.1 ± 1.1	61 ± 0.8	2.0 ± 1.2	−0.9 ± 1.7 (*P* = .6)
Baseline RHR ≥70 BPM					
HbA1c ≤7 (N = 148 B-QR, 87 P)	78 ± 0.6	−5.2 ± 0.8***	77 ± 0.7	−2.5 ± 0.9**	−2.7 ± 1.2 (*P* = .03)
HbA1c >7 (N = 95 B-QR, 42 P)	79 ± 0.8	−4.3 ± 0.9***	77 ± 0.9	0.7 ± 1.1	−5.0 ± 1.6 (*P* = .002)
HbA1c ≥7.5 (N = 61 B-QR, 31 P)	79 ± 1.0	−4.5 ± 1.2***	77 ± 1.2	1.6 ± 1.2	−6.1 ± 1.9 (*P* = .002)
Baseline RHR ≥80 BPM					
HbA1c ≤7 (N = 47 B-QR, 29 P)	86 ± 0.0.9	−8.6 ± 1.6***	86 ± 0.7	−4.1 ± 1.8*	−4.5 ± 2.4 (*P* = .07)
HbA1c >7 (N = 38 B-QR, 10 P)	87 ± 1.1	−6.5 ± 1.5***	85 ± 2.2	1.3 ± 1.7	−7.8 ± 3.1 (*P* = .015)
HbA1c ≥7.5 (N = 24 B-QR, 9 P)	86 ± 1.4	−8.1 ± 1.9***	85 ± 2.4	1.8 ± 1.9	−9.9 ± 3.3 (*P* = .005)

Note: Data shown as mean ± standard error of mean.
Abbreviations: HbA1c, haemoglobin A1c; RHR, resting heart rate.
*$P < .05$ for within-treatment group change in RHR.
**$P \leq .01$ for within-treatment group change in RHR.
***$P \leq .001$ for within-treatment group change in RHR.

that while tachycardia is usually defined as heart rate ≥100 BPM, RHR thresholds substantially lower than this traditional tachycardia criterion are also associated with significant increased cardiovascular risks.[39-41,46,47,49-51,53,54,61,62,65] Accumulating evidence from a multitude of large longitudinal epidemiological studies and clinical trials indicate that chronically elevated RHR over a threshold of approximately the >70-80 BPM range is significantly associated with and is a predictor of increased cardiometabolic risk (insulin resistance, metabolic syndrome, type 2 diabetes and CVD) as well as both cardiovascular and all-cause mortality and such associations have been reported in general healthy populations as well as in those with hypertension, coronary artery disease or heart failure.[33-46,48,51-55,57-60,62-64,109,110] RHR ≥70 BPM has therefore been used as the cut-off for defining elevated RHR in previous clinical studies having identified increased CVD risk above this threshold.[45-47,49-51,53,61,62,65,111] Consequently, in the context of these reported findings, the reduction of elevated RHR above 70-80 BPM by 6-10 BPM with circadian-timed B-QR therapy in type 2 diabetes subjects with poor glycaemic control (HbA1c ≥7.5) in the present study can be clinically meaningful. These findings also may relate to (and provide a theoretical mechanistic basis [via reducing elevated SNS tone] for) the 40%-50% reduction in CVD outcomes observed with this therapy in the type 2 diabetes population.[98-101]

The observation that (a) the higher the RHR the greater the B-QR induced reduction in RHR and (b) the magnitude of the elevated RHR reduction with B-QR is an independent predictor of the magnitude of HbA1c reduction with the therapy in type 2 diabetes subjects whose glycaemia is poorly controlled is an interesting and potentially clinically important finding as it may help identify "best responders" to the therapy. An understanding of why the magnitude of the B-QR effect to reduce RHR predicts the magnitude of its effect to reduce HbA1c in type 2 diabetes subjects whose glycemia is poorly controlled may best be obtained by (a) appreciating the relationship between RHR and SNS tone on the one hand and the influence of chronic elevated SNS activity upon cardiometabolic health and glycaemic control on the other and (b) realizing the sympatholytic nature of circadian B-QR therapy upon chronically elevated SNS tone in insulin-resistant states as follows. Importantly, in insulin resistance syndrome, elevated RHR (over 70-80 BPM) is a marker of an increase in cardiac SNS dominance either in absolute terms or in relative terms of SNS/parasympathetic nervous system (PSNS) activity balance [27,28,106] and SNS overactivity is considered to be the most likely central mechanism to explain the association between elevated RHR and adverse cardiometabolic outcomes.[12,18,26,37] While the autonomic imbalance of elevated SNS and depressed PSNS activities to the heart each can contribute to elevated RHR, available evidence suggests that the elevated RHR association with insulin resistance syndrome is most closely coupled to overactive SNS tone that involves several metabolic tissues in addition to the heart.[10,12,16-19,24,25,37,112,113] Both elevated RHR[33-49,51-57] and elevated SNS tone[9-18,114] are associated with and predict the future onset of CVD, insulin resistance, metabolic syndrome and type 2 diabetes. The association of elevated RHR with development of type 2 diabetes has been mainly attributed to increased insulin resistance secondary to elevated SNS activity,[12,16,26,35-37] although elevated RHR has also

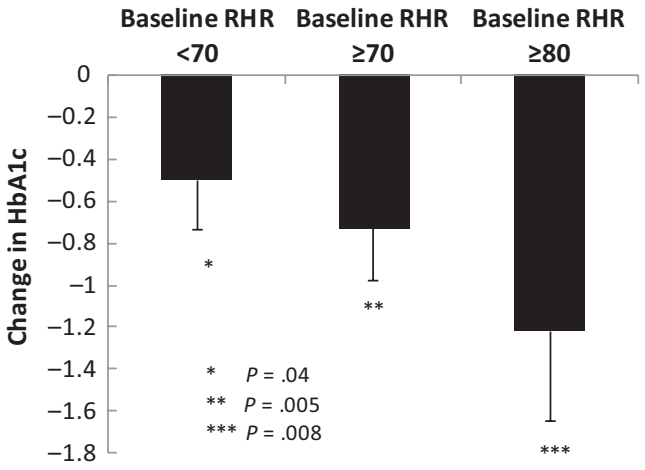

FIGURE 2 Glycaemic control effect of bromocriptine-QR vs placebo (between-group difference in change from baseline HbA1c) in T2DM subjects with suboptimal glycaemic control (baseline HbA1c ≥7.5) stratified by baseline resting heart rate. Data shown as mean ± SEM. RHR, resting heart rate

been reported to be a predictor of beta cell dysfunction and consequent impaired glucose regulation independent of the level of insulin sensitivity.[34]

Chronic SNS overactivity is an important pathophysiological phenomenon that potentiates hypertension, vasoconstriction and vascular insulin resistance,[20,115-118] vascular oxidative stress,[19,119] endothelial dysfunction,[19,120-122] myocardial oxidative and nitrative stress and apoptosis,[15] and renal renin-angiotensin system overactivation,[20-23] as well as metabolic changes such as increased adipose inflammation and lipolysis[3,24,123,124] (inducing hyperaemia, a potent stimulus for central activation of SNS tone[125,126]), increased hepatic oxidative stress, inflammation, lipotoxicity, glucose output, insulin resistance,[66,127] ectopic fat deposition[24,66] and muscle insulin resistance.[128-130] Collectively, these pathophysiologies underlie development of vascular stiffness and arteriosclerosis, atherosclerosis and atherosclerosis progression, cardiac remodelling, occurrence of myocardial ischaemia and arrhythmias, reduced left ventricular function, kidney dysfunction, hypertension and metabolic derangements of obesity, dyslipidemia, metabolic syndrome and type 2 diabetes,[10-13,41,114,131] occurrences often associated with elevated RHR.[10-13,18,26,36,37,41,114,131]

Long-term bromocriptine therapy is well known to reduce elevated sympathetic tone in hypertensive animals and humans.[66-84,132] The present study extends the specifics of these findings on vascular hemodynamics and uncovers an important relationship between B-QR impact on RHR and glycaemic control in type 2 diabetes subjects. Although acute peripheral effects of bromocriptine can function to inhibit noradrenaline release from sympathetic neurons, studies of chronic bromocriptine impact on elevated sympathetic tone implicate a dominant central mechanism of action in this regard.[66,74,82] Insights into how circadian-timed B-QR therapy operates to simultaneously alleviate elevated RHR and dysglycemia in type 2 diabetes subjects may be derived from studies of hypothalamic biological clock circuitry control of autonomic balance and the neuroendocrine axis and dopamine's influence on this system as follows. The CNS biological clock circuitry centred on the SCN co-ordinates autonomic and endocrine system modulation of biochemical metabolic events in the liver, adipose, muscle and other peripheral tissues including the vasculature and heart[85,86,133-135] to generate a whole-body metabolism and to synchronize/co-ordinate metabolism within the individual to the cyclic environment (eg, circadian variations in vascular tone and heart rate associated with the sleep/wake cycle, co-ordination of fuel mobilization with the daily sleep-fasting period, and anabolic fuel

TABLE 5 Relationship of treatment-induced change in resting heart rate with change in haemoglobin A1c

Multivariable regression analysis Outcome: HbA1c change from baseline to week 24 with study drug treatment				
	Bromocriptine-QR		Placebo	
Covariates/Predictors	Standardized β	*P*-value	Standardized β	*P*-value
Age	−.06	.66	.36	.15
Gender (0 = female, 1 = male)	−.16	.23	−.28	.18
Race (0 = non-Caucasian, 1 = Caucasian)	.23	.06	.03	.89
Baseline HbA1c	.01	.92	−.14	.51
Concomitant treatment with metformin (0 = no, 1 = yes)	−.12	.34	−.03	.90
Concomitant treatment with a SU (0 = no, 1 = yes)	.02	.90	−.13	.58
Concomitant treatment with a TZD (0 = no, 1 = yes)	−.10	.42	−.35	.13
Change in RHR from baseline to week 24 with study drug treatment	**.42**	**.001**	.13	.57

Abbreviations: HbA1c, haemoglobin A1c; RHR, resting heart rate.

storage processes with wake-feeding periods of the day). The SCN is the seat of the autonomic nervous system, sending direct and indirect signals to multiple CNS (eg, hypothalamic) centres that are pre-autonomic fibres regulating sympathetic/parasympathetic activity balance from moment to moment and rhythmically over the course of the day.[85-88,135-137]

A series of studies have demonstrated that a diminution of circadian peak dopaminergic activity at the SCN area signals the SCN to send neural messages to several brain centres to activate sympathetic tone and alter glucose and FFA sensing in a manner that potentiates glucose intolerance, insulin resistance, and leptin resistance.[96] Elements of the western lifestyle including high fat/sugar diets, psychological stress and altered sleep/wake architecture all diminish brain dopamine activity and are strongly associated with insulin resistance syndrome.[138-142] Reinstatement of the circadian peak in brain dopaminergic activity in insulin resistance syndrome attenuates these brain (SCN) neural signalling pathways that potentiate the syndrome.[96] Such a reinstatement of CNS dopaminergic effect would be expected to manifest decreases in elevated RHR and dysglycemia in type 2 diabetes subjects as observed herein with circadian-timed B-QR therapy. Moreover, such B-QR treatment would also be expected and has in fact been observed to reduce elevated plasma triglyceride and FFA levels and insulin resistance in type 2 diabetes.[96]

Circadian-timed morning administration of B-QR produces a brief pulse of dopaminergic activity to the body, including the CNS, that would reverse the diminished morning dopaminergic signalling to the CNS[143] (including the biological clock SCN) of the type 2 diabetes patient and resultantly reduce overactivity of pre-autonomic hypothalamic neurons in the brain areas that stimulate increased SNS outflow to the periphery in the manner described above. It should be realized that circadian-timed B-QR therapy may act to reduce sympathetic tone by multiple distinct mechanisms including (a) the above-described action at dopamine receptors at the biological clock (SCN) to reduce its activation of hypothalamic pre-autonomic sympathetic fibres,[72,144] (b) dopamine action directly on paraventricular nuclei pre-autonomic sympathetic fibres to inhibit their SNS activation [93] and (c) peripheral action directly on postganglionic-presynaptic sympathetic fibres to inhibit their noradrenaline release.[75,76,145] It should be appreciated, however, that peripheral effects of dopamine agonism may themselves be regulated by CNS dopamine function.[146] The absence of any significant effect of B-QR on RHR or BP in those type 2 diabetes subjects with RHR <70 suggests that the "resetting" effect of timed B-QR therapy may correct SNS hyperactivity or SNS-to-PSNS dominance to the heart responsible for increased RHR, but does not affect normal RHR/BP in the absence of vascular SNS hyperactivity, while SNS activity may still be elevated and impacted elsewhere (eg, liver, adipose) in the insulin-resistant body.

The limitations of this study include the absence of any additional direct measures of SNS tone, the lack of physical activity/fitness data on the study subjects which may influence RHR and glycaemic control, and the lack of measures of insulin sensitivity to assess correlations between RHR and insulin action. The present findings however suggest that such future studies are warranted.

5 | CONCLUSION

The present study has demonstrated that circadian-timed bromocriptine-QR therapy significantly reduces elevated (but not normal) RHR and blood pressure in type 2 diabetes subjects, the magnitude of which RHR reduction is positively correlated to each of the baseline elevated RHR and HbA1c level. This impact of B-QR to reduce elevated RHR is an independent predictor of its impact to reduce elevated HbA1c (ie the greater the RHR reduction, the greater the HbA1c reduction). These findings lend further support to the reported bromocriptine-QR mechanism of improving glycaemic control in type 2 diabetes in part via reduction of elevated SNS tone.[105] These findings also suggest that type 2 diabetes maximum responder populations to bromocriptine-QR may be those subjects with elevated (>~80 BPM) RHR or other markers of elevated SNS tone. The impact of B-QR to reduce elevated RHR (and the antecedent elevated SNS tone) provides a potential contributing mechanism for the observed marked reduction in CVD outcomes with B-QR therapy.[98-101]

CONFLICT OF INTEREST

BC and ME are employed by VeroScience LLC. AV has received grant support from VeroScience. AHC is employed by and has equity interests in VeroScience LLC.

AUTHOR CONTRIBUTIONS

BC made substantial contributions to the conception/design of the work, analysis and interpretation of data, and drafting the manuscript. AV contributed to the interpretation of the data and critically revising the manuscript for important intellectual content. ME contributed to analysis of the data and drafting the manuscript. AHC made substantial contributions to the conception/design of the work, interpretation of data, and drafting the manuscript. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The Cycloset Safety Trial (CST) study protocol was approved by site-specific or central institutional review boards, and all subjects provided written informed consent to participate in the study before enrolment. The study was conducted in accordance with the International Council for harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) 2004 guidelines. This current post hoc study and analyses are original and different from any previously reported results from the CST.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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