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Opposing Effects of Beta-Blockers and Angiotensin Converting Enzyme Inhibitors on Development of New Onset Diabetes Mellitus in Patients with Stable Coronary Artery Disease

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Abstract

We utilized data from patients with stable coronary artery disease (CAD) to assess the risk of new onset diabetes (NOD) with beta-blockers, and to determine whether angiotensin converting enzyme (ACE) inhibition would modify this risk. The Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial randomized 8290 patients with stable CAD to trandolapril or placebo. The presence of NOD was assessed at each study visit over a median follow-up time of 4.8 years. We examined the risk of NOD associated with beta-blockers use with Cox regression models, adjusting for 25 baseline covariates, and tested whether this risk was modified by randomization to the ACE inhibitor. Of 6910 patients without diabetes mellitus at enrollment (1179 females/5731 males, mean age 64 ± 8 years), 4147 (60%) were taking beta blockers, and 733 (8.8%) developed NOD. We observed a significant interaction between beta-blocker use and randomization to ACE inhibitor with respect to new onset diabetes ($p = 0.028$). Participants taking beta-blockers assigned to the placebo group (N=2090) were at increased risk for NOD adjusting for baseline covariates (HR 1.63, 95% confidence interval 1.29, 2.05, $p<0.001$, while this risk was attenuated in those assigned to trandolapril (N=2057) (HR 1.11, 95% confidence interval 0.87, 1.42; $p=0.39$). Beta blocker use was associated with increased risk for NOD in patients with stable CAD, and this risk was reduced in patients treated concurrently with an ACE inhibitor. In conclusion, these data suggest that ACE inhibition may attenuate the risk for glucose abnormalities observed in patients taking beta blockers.

Keywords

ACE inhibitors; Beta-Blockers; Clinical Trials; Diabetes

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INTRODUCTION

Several classes of common cardiovascular medications have been shown in clinical trials to have disparate effects on blood glucose and the risk for development of new onset diabetes mellitus (NOD). Beta blockers (BB) have been associated with an increased risk for development of NOD.[1,2] Beta-blockers may negatively affect glucose homeostasis through increased hepatic glucose production, blockade of insulin release, and may worsen insulin resistance through reduced peripheral glucose ulitization.[3,4] The effect of angiotensin converting enzyme (ACE) inhibitors on diabetes risk has been more varied. Post-hoc analyses in large trials originally suggested that ACE inhibition might delay or prevent the onset of DM,[2,5,6] while the DREAM trial did not show a benefit on frank development of diabetes, although did show some improvement in glycemic control with ACE inhibitors.[7] Mechanistically, ACE inhibitors may improve insulin sensitivity secondary to kinin accumulation and increased peripheral blood flow.[8–11] The Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial was designed to test the hypothesis that an ACE inhibitor would reduce cardiovascular events in patients with stable coronary artery disease.[12] Trandolapril therapy did not reduce the primary endpoint of death from cardiovascular causes, myocardial infarction, or coronary revascularization, but was associated with a 17% reduction in NOD. We utilized data from PEACE to assess the influence of beta blockers on risk for NOD, and whether this risk was modified by randomization to ACE inhibition.

METHODS

PEACE included patients at least 50 years old, with stable coronary artery disease, defined as history of myocardial infarction, coronary revascularization, or stenosis greater than 50% on angiography, and with normal or mildly reduced left ventricular function (left ventricular ejection fraction > 40%). Patients were excluded from PEACE if at the time of screening coronary artery disease was not stable (i.e. hospitalized for unstable angina in the preceding 2 months, had coronary revascularization within the prior 3 months), had a planned elective coronary revascularization, a serum creatinine value >2.0 mg/dL (177 > μmol/L), or a serum potassium > 5.5 mEq/L. Patients were randomly assigned to receive the ACE inhibitor trandolapril (titrated to a target dose of 4mg daily) or to placebo and followed for a median of 4.8 years, as previously described[13]. The PEACE study protocol was approved by each participating site's institutional review board. All patients provided written informed consent in accordance with established guidelines for the protection of human subjects.

Of the 8290 patients randomized, we included in this analysis 6910 patients who did not have diabetes at baseline, assessed by patient report. The primary outcome variable for this analysis was NOD; diabetic status (i.e. the presence of a new diagnosis of diabetes mellitus), which was assessed by study personnel via patient history at each study visit every 6 months and marked on the case report forms. No other information about the diagnosis of diabetes mellitus was available, including laboratory measurements. Medications were also recorded at baseline and at each visit. Specific beta blockers were not recorded.

Baseline demographics between participants taking or not taking beta blockers were compared to identify potential differences. Between group assessments were performed using t-tests for normally distributed continuous variables or Wilcoxon rank sum tests for non-normally distributed continuous variables, and Chi-Square or Fisher's exact tests, as appropriate, for categorical variables. The risk for NOD associated with beta-blocker use at baseline was examined with Cox proportional hazards models adjusting for baseline covariates as well as randomized treatment interactions. Beta blocker use was also explored as a time dependent covariate. Model covariates, chosen a priori, included age, gender, body

mass index (BMI), tobacco use, systolic & diastolic blood pressure, glomerular filtration rate, left ventricular ejection fraction, baseline cholesterol and potassium concentrations, history of coronary disease on angiography, myocardial infarction, angina, percutanous transluminal coronary arterioplasty, coronary artery bypass graft, stroke, transient ischemic attack, intermittent claudication, Canadian Cardiovascular Society Functional Class and use of lipid lowering agents, digoxin, aspirin or antiplatelets. To test the robustness of multivariable models, we performed a propensity adjusted analysis in which we generated a propensity score for baseline beta-blocker use in a logistic regression of baseline covariates, and then adjusted for this propensity score in the Cox regressions. Since the determination of DM status was assessed every 6 months, we additionally utilized discrete-time proportional hazards models, taking into account the discrete nature of the NOD information captured in the study. The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

Out of 6910 patients without diabetes included in these analyses, 4147 (60%) were taking beta blockers (figure 1) at baseline. Of 4147 taking beta blockers, 2090 were assigned to the treatment group and 2057 were assigned to the placebo group. Baseline characteristics of all the analyzed subjects, broken down by beta blocker use, are shown in Table 1. Participants taking beta blockers were more likely to be younger in age, have a higher BMI, a history of coronary disease, documented myocardial infarction (MI), and were more likely to have undergone coronary interventions, compared with patients not taking beta-blockers.

There were 733 cases of NOD reported over the trial follow-up time of 4.8 years (event rate 2.0%/year). Randomization to trandolapril was associated with a 17% reduction of the risk for development of NOD (Hazard ratio 0.83, 95% confidence interval 0.71, 0.95, p=0.009) as previously reported (Figure 2). In univariate analyses, beta-blocker use was associated with a 44% increased overall risk for development of NOD (HR 1.44, 95% confidence interval 1.23, 1.68; p<0.001), and remained associated with an increased risk for NOD after adjustment for baseline covariates and randomized treatment (HR 1.36, 95% confidence interval 1.15, 1.61). We observed a significant interaction between treatment assignment to trandolapril and the use of beta blockers on NOD in both univariate (p-interaction = 0.021) and multivariable adjusted models (p-interaction = 0.028); participants taking beta-blockers assigned to the placebo group (N=2090) had an adjusted increased risk for NOD (HR 1.63, 95% confidence interval 1.29, 2.05, p<0.001, figure 3), while this risk was attenuated in those assigned to trandolapril (N=2057) (HR 1.11, 95% confidence interval 0.87, 1.42; p=0.39). Adjusted analyses in which beta-blocker use throughout the trial were included as time-dependent covariates yielded qualitatively similar results (placebo group: HR 1.40, 95% confidence interval 1.12, 1.75; trandolapril group: HR 1.02, 95% confidence interval 0.81, 1.29). Propensity adjusted analyses yielded similar results (trandolapril group, HR 1.59, 95% confidence interval 1.26, 2.00; placebo group, HR 1.06, 95% confidence interval 0.83, 1.34). Additional predictors of NOD in adjusted models are shown in Table 2. The results from discrete-time proportional hazards models (not shown) were similar to those from the standard Cox's regression models reported above.

DISCUSSION

We found that in patients with stable coronary artery disease, use of beta blockers was associated with an increased risk for development of NOD in traditional, propensity adjusted, and time-dependent analyses. Moreover, we observed a significant interaction between ACE inhibitor treatment assignment and beta blocker use with respect to NOD risk,

such that the risk for NOD associated with beta-blockers was attenuated in participants randomized to ACE inhibitor.

Prior studies have raised concern that beta blockers contribute to the risk of NOD.[1,2,14–17] We found that beta blocker use was associated with increased risk of NOD in univariate analyses, an effect that was minimally changed following traditional multivariable or propensity score adjustment. These results are similar to those observed in other studies, including the ASCOT-BPLA study[1] comparing combination of beta blocker (atenolol) plus a thiazide diuretic to an ACE inhibitor plus dihydropyridine calcium channel blocker in high risk hypertensive individuals, in which the atenolol-based regimen was associated with a 30% higher incidence of development of diabetes compared to the amlodipine-based regimen. Similarly, the Atherosclerosis Risk in Communities study reported a 28% increased likelihood of developing diabetes in patients taking a beta blocker.[14] Nonselective (β1/β2) blockade by conventional beta blockers leads to unopposed α1-mediated vasoconstriction, thereby reducing blood flow to muscles and glucose uptake in peripheral tissues.[18] Beta blockers also interfere with β2 mediated pancreatic insulin release.[3,19,20] Additionally, reduced insulin release and blockade of hepatic β2 adrenergic receptors elevates glucose production following meals.[4] Beta-blockers have also been shown to increase weight,[21] which is associated with development of diabetes.

Several studies have shown that not all beta blockers negatively affect glucose metabolism. Carvedilol is thought to have neutral or even beneficial effects on insulin resistance. The GEMINI study randomized patients with diabetes and hypertension to receive metoprolol tartrate or carvedilol.[22] Carvedilol did not worsen HbA1c, improved insulin resistance, and slowed the development of microalbuminuria compared with metoprolol. In a post-hoc analysis of the COMET trial, a study in heart failure patients that examined the effect of metoprolol tartrate and carvedilol on mortality, metoprolol was associated with a 20% increased risk for new onset diabetes compared to carvedilol.[23] We do not have data about specific beta blocker use in the PEACE trial, and as such cannot comment on whether certain beta blockers conferred a higher risk for NOD in this cohort.

Numerous post-hoc analyses of clinical trials data have suggested that inhibitors of the RAAS may have beneficial effects on glycemic control. These include the Captopril Prevention Project (CAPPP) [24], in which captopril therapy was associated with a 14% reduction in development of diabetes compared with conventional therapies, and the Heart Outcomes Prevention Evaluation (HOPE) study[25] in which ramipril was associated with a 34% risk reduction in the development of diabetes.[5] In contrast, the DREAM trial,[7] which was prospectively designed to test this hypothesis, showed minimal difference in new onset diabetes between patients receiving ramipril versus placebo, although patients receiving ramipril were more likely to have regression to normoglycemia. Of note, the use of beta-blockers in the DREAM population was only 17%, which was substantially lower than in PEACE and HOPE. That ACE inhibitors might demonstrate some benefit with regard to glycemic control is not inconsistent with the results of DREAM, which did show a benefit with respect to glycemic control. ACE inhibitors may reduce vasoconstrictive and pro-fibrotic actions of angiotensin II in the pancreas, thus protecting pancreatic vasculature and beta cells,[26] and may also improve insulin sensitivity through increased blood flow to skeletal muscle, while kinin accumulation resulting from ACE inhibition may also improve hemodynamics and augment glucose utilization.[27]

While our data suggest that ACE inhibitors may attenuate the increased risk of NOD associated with beta-blockers, in PEACE the benefit of the ACE inhibitor with respect to NOD appears essentially limited to those patients taking beta-blockers. Prior studies that have demonstrated a reduction in NOD associated with ACE inhibitors have not reported

whether this benefit was limited to patients taking beta-blockers. We cannot determine from these hypothesis-generating data whether this attenuation is simply due to opposing effects or indicates a more complex interaction between beta-blocker and ACE inhibitor use. Nevertheless, these disparate effects of beta blockers and ACE inhibitors may provide a compelling rationale for combination use in patients with coronary disease requiring beta-blocker therapy. Similarly, trials of angiotensin receptor blockers have also reported a reduction in NOD,[28,29] but whether ARBs attenuate the effects of beta blockers on NOD has not been reported. These data may be relevant in a high risk population of patients taking multiple medications who are potentially at risk for development of diabetes.

This study has several limitations. The determination of NOD was made only on the basis of patient report at baseline and 6-month visits, and not confirmed with laboratory testing, a limitation of the data collected in this multicenter clinical trial. Unfortunately, the PEACE study consent forms do not allow for contact with study participants or for collecting additional data in retrospect. Nevertheless, this endpoint was assessed prospectively at study visits, an advantage over other studies in which the identification of NOD was made only if reported. Moreover, fasting blood glucose and HbA1c levels were not available and we thus could not adjust our statistical models for this variable, which has been shown to be associated with development of NOD.[30]

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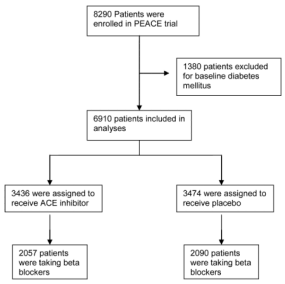

Figure 1.
Study subjects included in analyses

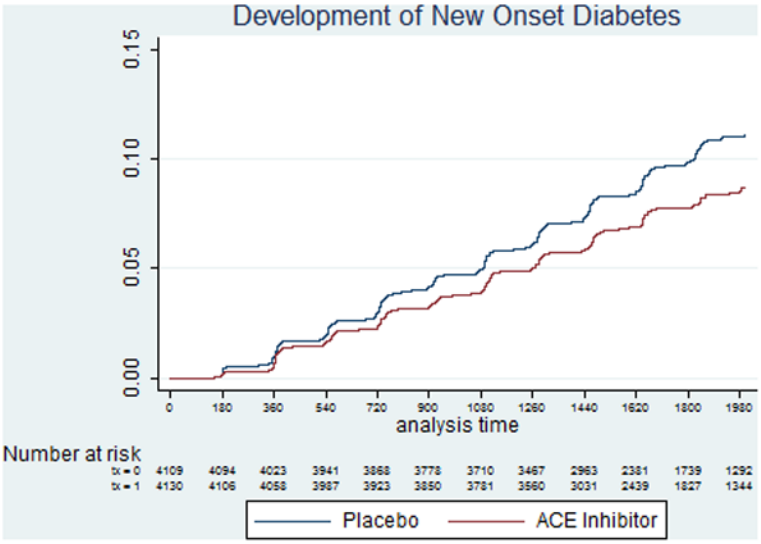

Figure 2.
Development of New Onset Diabetes (NOD) in patients assigned to trandolapril and placebo.

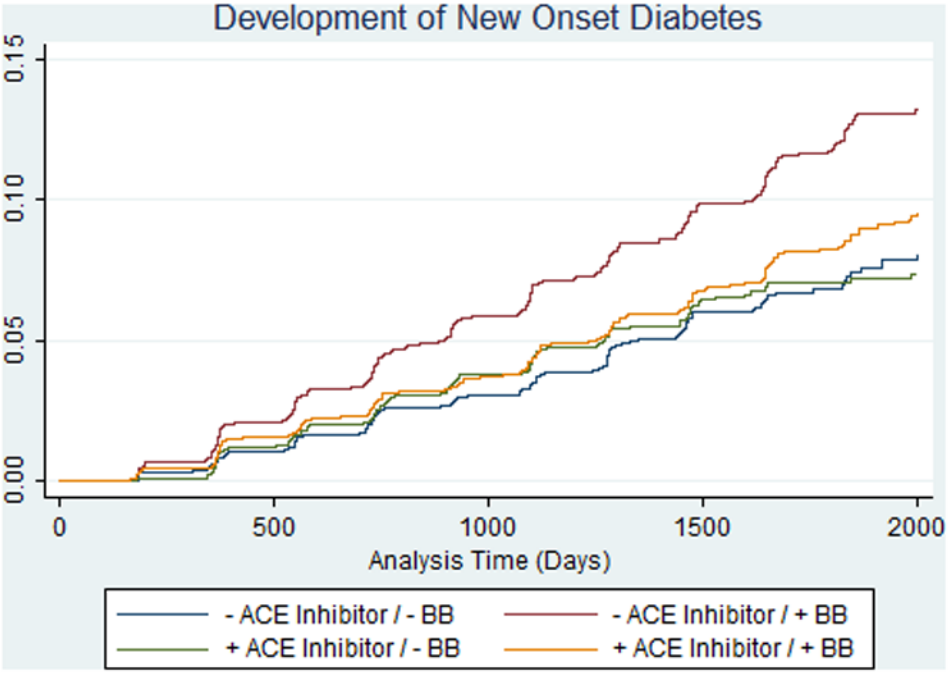

Figure 3.
Risk for new onset diabetes (NOD) by beta-blocker and randomization to ACE inhibitor. Interaction p-value = 0.03.

Table I

Subject Characteristics

		Beta Blocker		
Variable	**All subjects (N=6910)**	**YES (N=4147)**	**NO (N=2763)**	**P value**
Age (years) (± SD)	64 ± 8	64 ± 8	65 ± 8	<0.001
Women	17%	18%	16%	0.05
Body Mass Index (Kg/m^2)	28.1	28.4	27.6	<0.001
Current tobacco use	14%	14%	15%	0.49
Ejection fraction (%)	58 ± 9	58 ± 9	58 ± 9	0.31
Hypertension	44%	49%	36%	<0.001
Documented myocardial infarction	56%	58%	52%	<0.001
Coronary disease on angiography	60%	65%	54%	<0.001
Angina pectoris	69%	71%	65%	<0.001
Coronary artery bypass grafting	37%	35%	41%	<0.001
Stroke	4%	4%	4%	0.44
Medicines				
Calcium channel blocker therapy	35%	28%	44%	<0.001
Beta blocker	60%	100%	0%	N/A
Diuretic	12%	12%	12%	0.97
Aspirin/antiplatelet	91%	92%	90%	0.008
Lipid lowering agent	71%	74%	66%	<0.001
Anticoagulant	5%	4%	5%	0.05
Digoxin	3%	3%	4%	0.97
Antiarrhythmic	2%	1%	3%	<0.001

Table II

Other confounders that predict New Onset Diabetes, ordered by strength of multivariable association.

Variable	Univariate HR (95% confidence interval)	Multivariable HR (95% confidence interval)	Chi-Square
Body mass index (per kg/m^2)	1.1 (1.09, 1.11)	1.1 (1.08, 1.09)	13.3
Beta blocker	1.44 (1.24, 1.68)	1.56 (1.24, 1.95)	3.83
Seated systolic blood pressure (per mmHg)	1.01 (1.0, 1.01)	1.0 (1.0, 1.01)	2.96
Use of lipid lowering agents	0.8 (0.67, 0.94)	0.81 (0.69, 0.97)	2.26
Use of potassium sparing diuretics	1.8 (1.29, 2.54)	1.51 (1.06, 2.18)	2.25
Use of other diuretics	1.52 (1.22, 1.9)	1.24 (0.98, 1.57)	1.8
Seated diastolic blood pressure (per mmHg)	1.0 (0.96, 1.01)	0.99 (0.98, 1.0)	1.74
History of Coronary Disease on Angiography	1.32 (1.13, 1.54)	1.16 (0.98, 1.37)	1.73
Use of aspirin or antiplatelet	0.94 (0.73, 1.2)	0.81 (0.6, 1.07)	1.46
Canadian Cardiovascular Society functional class	1.18 (1.07, 1.3)	1.08 (0.97, 1.2)	1.43
History of percutaneous transluminal coronary arterioplasty	0.98 (0.84, 1.13)	0.89 (0.76, 1.05)	1.36
Use of angiotensin converting enzyme inhibitors	0.83 (0.72, 0.96)	1.03 (0.79, 1.34)	1.34