

# Effect of Rosiglitazone and Ramipril on $\beta$ -Cell Function in People With Impaired Glucose Tolerance or Impaired Fasting Glucose

## The DREAM trial

ANTHONY J. HANLEY, PHD<sup>1,2,3</sup>  
BERNARD ZINMAN, MD<sup>1,2,3</sup>  
PATRICK SHERIDAN, PHD<sup>4</sup>  
SALIM YUSUF, MD<sup>4</sup>

HERTZEL C. GERSTEIN, MD<sup>4</sup>  
FOR THE DIABETES REDUCTION ASSESSMENT  
WITH RAMIPRIL AND ROSIGLITAZONE  
MEDICATION (DREAM) INVESTIGATORS

**OBJECTIVE** — The objective of this study was to determine the degree to which ramipril and/or rosiglitazone changed  $\beta$ -cell function over time among individuals with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) who participated in the Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) Trial, which evaluated whether ramipril and/or rosiglitazone could prevent or delay type 2 diabetes in high-risk individuals.

**RESEARCH DESIGN AND METHODS** — The present analysis included subjects ( $n = 982$ ) from DREAM trial centers in Canada who had oral glucose tolerance tests at baseline, after 2 years, and at the end of the study.  $\beta$ -Cell function was assessed using the fasting proinsulin-to-C-peptide ratio (PI/C) and the insulinogenic index (defined as 30–0 min insulin/30–0 min glucose) divided by homeostasis model assessment of insulin resistance (insulinogenic index [IGI]/insulin resistance [IR]).

**RESULTS** — Subjects receiving rosiglitazone had a significant increase in IGI/IR between baseline and end of study compared with the placebo group (25.59 vs. 1.94,  $P < 0.0001$ ) and a significant decrease in PI/C ( $-0.010$  vs.  $-0.006$ ,  $P < 0.0001$ ). In contrast, there were no significant changes in IGI/IR or PI/C in subjects receiving ramipril compared with placebo (11.71 vs. 18.15,  $P = 0.89$ , and  $-0.007$  vs.  $-0.008$ ,  $P = 0.64$ , respectively). The impact of rosiglitazone on IGI/IR and PI/C was similar within subgroups of isolated IGT and IFG + IGT (all  $P < 0.001$ ). Effects were more modest in those with isolated IFG (IGI/IR: 8.95 vs. 2.13,  $P = 0.03$ ; PI/C:  $-0.003$  vs.  $-0.001$ ,  $P = 0.07$ ).

**CONCLUSIONS** — Treatment with rosiglitazone, but not ramipril, resulted in significant improvements in measures of  $\beta$ -cell function over time in pre-diabetic subjects. Although the long-term sustainability of these improvements cannot be determined from the present study, these findings demonstrate that the diabetes preventive effect of rosiglitazone was in part a consequence of improved  $\beta$ -cell function.

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**P**ancreatic  $\beta$ -cell dysfunction plays a central role in the pathogenesis of type 2 diabetes (1). It is present in people at high risk for type 2 diabetes, including those with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (2,3), and it predicts the development of type 2 diabetes in prospective studies of

people with these disorders (4,5).  $\beta$ -Cell function is also known to decline steadily over the course of type 2 diabetes, highlighting the progressive nature of this disorder (6). It is therefore crucial to understand the factors that erode or preserve  $\beta$ -cell function across the spectrum of glucose tolerance. Relatively little information is available, however, regarding the determinants of  $\beta$ -cell dysfunction in humans (1).

Recent evidence suggests that thiazolidinediones (TZDs) and ACE inhibitors may preserve  $\beta$ -cell function (7,8). Although TZDs have been demonstrated to improve glucose control and  $\beta$ -cell function in type 2 diabetes (9–11), very little is known about the effect of TZDs on  $\beta$ -cell function in people with hyperglycemia in the nondiabetic range, namely those with IGT and/or IFG (12–15). Similarly, while it has been hypothesized that ACE inhibitors may lower glucose via direct effects on the  $\beta$ -cell (16), studies have not been conducted in people with IGT and/or IFG.

The objectives of this study, therefore, were to determine the degree to which ramipril (an ACE inhibitor) and/or rosiglitazone (a TZD) changed  $\beta$ -cell function over time among individuals with IFG and/or IGT who participated in the Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) Trial, which evaluated whether ramipril and/or rosiglitazone could prevent or delay diabetes in high-risk individuals. We also aimed to determine the degree to which changes in indexes of  $\beta$ -cell function over time were modified by baseline glucose tolerance status and whether ramipril and/or rosiglitazone's effect on diabetes incidence was mediated by treatment-induced changes in  $\beta$ -cell function.

## RESEARCH DESIGN AND METHODS

— The design and principal findings of the DREAM trial have been

From the <sup>1</sup>Department of Nutritional Sciences, University of Toronto, Toronto, Canada; the <sup>2</sup>Leadership Sinai Centre for Diabetes, Mount Sinai Hospital, Toronto, Canada; the <sup>3</sup>Division of Endocrinology, Department of Medicine, University of Toronto, Toronto, Canada; and the <sup>4</sup>Division of Endocrinology and Metabolism and the Population Health Research Institute, Department of Medicine, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada.

Corresponding author: Anthony Hanley, anthony.hanley@utoronto.ca.

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presented in previous publications (17). Briefly, the DREAM trial was a large, international, multicenter, double-blind, randomized controlled trial designed to determine whether ramipril and/or rosiglitazone could prevent or delay the development of type 2 diabetes in people with IFG or IGT, metabolic states that indicate very high risk for eventual progression to diabetes (17). Eligibility for the DREAM trial included a diagnosis of IFG, IGT, or both IFG and IGT based on a screening 75-g oral glucose tolerance test (OGTT) (17). A total of 5,269 participants with these disorders were recruited and randomized to either ramipril and/or rosiglitazone using a two-by-two factorial design and followed for a median of 3 years after randomization. Participants were assessed at regular intervals to ascertain the occurrence of the primary outcome, which included new-onset diabetes or all-cause mortality. As part of a substudy, 982 DREAM trial participants attending Canadian study centers had OGTTs at baseline, after 2 years, and at the end of the study, with blood samples drawn fasting as well as 30 and 120 min after the glucose challenge.

The primary outcome variable in the present study was change in  $\beta$ -cell function over the course of follow-up.  $\beta$ -Cell function was assessed using two measures: the insulinogenic index (IGI) and proinsulin (PI) concentration, with IGI defined as  $(30\text{-min insulin} - \text{fasting insulin}) / (30\text{-min glucose} - \text{fasting glucose})$ . Both indexes have previously been validated against gold-standard measures of insulin secretion (18,19) and have been shown to be significant predictors of incident diabetes in large epidemiological studies. To account for the compensatory response of insulin secretion in relation to background insulin resistance, IGI was divided by the homeostasis model assessment of insulin resistance index (HOMA-IR) (defined as  $\text{fasting glucose} \times \text{fasting insulin} / 22.5 [20]$ ) (IGI/IR) for univariate analysis or adjusted for HOMA-IR in multivariate analysis. Similarly, PI concentration was divided by C-peptide concentration (i.e., the PI/C-peptide ratio [PI/C]) for univariate analysis or adjusted for insulin secretion using C-peptide as a covariate in multivariate analysis. Although the PI-to-insulin ratio is often used to identify disproportionate elevations in PI, C-peptide offers advantages over insulin as a denominator for PI because it is cosecreted with insulin in an equimolar ratio, but unlike insulin it is not extracted by the

liver and thus it has a constant peripheral clearance.

Glucose concentration was determined using an enzymatic reference method on a Roche Hitachi 917 Instrument and a Roche reagent kit (Roche Diagnostics, Indianapolis, IN). Serum insulin and C-peptide were measured on the Roche Elecsys 2010 immunoassay analyzer using an electrochemiluminescence immunoassay. The insulin assay had a sensitivity of 1.39 pmol/L, an interassay coefficient of variation (CV) of <4.6% at all levels, and <0.05% cross-reactivity with human C-peptide and PI. The C-peptide assay had a sensitivity of 3.0 pmol/L, an interassay CV of <3% at all levels, and <0.005% cross-reactivity with human insulin. PI concentration was measured using a sandwich enzyme-linked immunosorbent assay manufactured by Linco Research (Linco Research, St. Charles, MO). This assay had a sensitivity of 2.0 pmol/L, an interassay CV of <9% at all levels, and no cross-reactivity with human insulin or des (31,32) split PI, although this assay does cross-react with human des (64,65) split PI.

### Statistical analysis

Statistical analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC), and  $P$  values <0.05 were considered statistically significant. The distributions of continuous variables were assessed for normality, and transformations of skewed variables were used in the analysis as appropriate. Means and SDs for primary  $\beta$ -cell function measures (IGI/IR and PI/C) were calculated for each time point (baseline, at 2 years, and final visit), according to the marginal treatment group. Change was calculated as baseline minus final visit value.  $P$  values for change were based on a  $t$  test of the average change being different from zero, while  $P$  values for treatment difference were calculated using the Wilcoxon's rank-sum test. Similar analyses were conducted within subgroups of isolated IFG (IIFG), isolated IGT (IIGT), and combined IFG and IGT (IFG+IGT). As there was no significant interaction between ramipril and rosiglitazone's effect on  $\beta$ -cell function, main-effects analyses were conducted according to marginal randomization groups (i.e., rosiglitazone versus placebo, ramipril versus placebo).

Longitudinal analyses of the associations between treatments and changes over time in  $\beta$ -cell function measures were examined using random-effects

models in PROC MIXED, which provides appropriate options for handling the covariance structure of the repeated-measures (longitudinal) data. Specifically, we ran four models, which assessed the impact of treatment group on 1) IGI, with age and HOMA-IR as covariates; 2) IGI/HOMA-IR, with age as a covariate; 3) PI, with age and C-peptide as covariates; and 4) PI/C, with age as a covariate.

Finally, using Cox proportional hazards regression, we assessed whether the impact of ramipril and/or rosiglitazone treatment on diabetes incidence was independent of baseline levels and changes over the course of the trial in  $\beta$ -cell function. The outcome variable in these analyses was diabetes status at the final visit, and the primary exposures were the marginal treatment groups (rosiglitazone, ramipril). In separate models, we assessed the impact of treatment on diabetes incidence, adjusting for either baseline  $\beta$ -cell function (including baseline IGI and HOMA-IR or baseline PI and C-peptide as covariates) or change over the course of the trial in  $\beta$ -cell function (including changes in the above-mentioned covariates). Baseline models were also adjusted for age and baseline waist circumference, fasting glucose, triglycerides, and HDL, while change models were also adjusted for age and changes in these covariates.

**RESULTS** — Baseline characteristics of participants in this DREAM substudy are presented in Table 1. The average age and BMI were 54 years and 31.5 kg/m<sup>2</sup>, respectively, and 60% of participants were female. The majority (81%) were of European origin, and substantial proportions had a family history of diabetes or a history of gestational diabetes (61 and 16%, respectively), characteristics that were consistent with the recruiting strategy for the DREAM trial (17). There were no significant differences between the marginal randomization groups for any of the baseline characteristics other than family history of diabetes in the ramipril versus placebo marginal group ( $P = 0.02$ ) (Table 1).

Changes in markers of  $\beta$ -cell function in marginal randomization groups are presented in Table 2. Participants receiving rosiglitazone versus placebo had a significant increase in IGI/IR during the study (25.59 vs. 1.94,  $P < 0.0001$ ) and a significant decrease in PI/C ( $-0.010$  vs.  $-0.006$ ,  $P < 0.0001$ ). In contrast, there were no significant changes in IGI/IR or PI/C in participants receiving ramipril

Table 1—Baseline characteristics of participants with measures of  $\beta$ -cell function overall and by allocation

	Overall	Randomization (marginal groups)			
		Rosiglitazone	Placebo	Ramipril	Placebo
n	982	505	477	494	488
Age (years)	54.36 $\pm$ 10.64	54.81 $\pm$ 10.49	53.9 $\pm$ 10.79	53.96 $\pm$ 10.47	54.77 $\pm$ 10.81
BMI (kg/m <sup>2</sup> )	31.49 $\pm$ 5.45	31.36 $\pm$ 5.33	31.63 $\pm$ 5.58	31.25 $\pm$ 5.35	31.74 $\pm$ 5.54
Waist-to-hip ratio	0.89 $\pm$ 0.09	0.89 $\pm$ 0.09	0.9 $\pm$ 0.09	0.89 $\pm$ 0.09	0.9 $\pm$ 0.09
Systolic blood pressure (mmHg)	135.07 $\pm$ 16.85	135.4 $\pm$ 15.92	134.71 $\pm$ 17.79	134.75 $\pm$ 16.52	135.39 $\pm$ 17.18
Diastolic blood pressure (mmHg)	82.79 $\pm$ 9.89	82.88 $\pm$ 9.5	82.69 $\pm$ 10.29	82.57 $\pm$ 10.06	83 $\pm$ 9.72
Females	593 (60.39)	298 (59.01)	295 (61.84)	297 (60.12)	296 (60.66)
IIFG	97 (9.88)	49 (9.7)	48 (10.06)	49 (9.92)	48 (9.84)
IIGT	609 (62.02)	312 (61.78)	297 (62.26)	310 (62.75)	299 (61.27)
IFG and IGT	276 (28.11)	144 (28.51)	132 (27.67)	135 (27.33)	141 (28.89)
Gestational diabetes	93 (15.68)	52 (17.45)	41 (13.9)	51 (17.17)	42 (14.19)
Family history diabetes	597 (60.79)	296 (58.61)	301 (63.1)	318 (64.37)	279 (57.17)
European	795 (80.96)	416 (82.38)	379 (79.45)	400 (80.97)	395 (80.94)
Other ethnicity	187 (19.04)	89 (17.62)	98 (20.55)	94 (19.03)	93 (19.06)
Statin	56 (15.89)	77 (15.25)	79 (16.56)	73 (14.78)	83 (17.01)
Blood pressure medications	168 (17.11)	93 (18.42)	75 (15.72)	82 (16.6)	86 (17.62)
Fasting glucose (mmol/l)	5.76 $\pm$ 0.66	5.77 $\pm$ 0.66	5.74 $\pm$ 0.67	5.75 $\pm$ 0.66	5.77 $\pm$ 0.67
30-min glucose (mmol/l)	10.45 $\pm$ 1.74	10.55 $\pm$ 1.74	10.35 $\pm$ 1.73	10.41 $\pm$ 1.74	10.5 $\pm$ 1.74
2-h glucose (mmol/l)	8.78 $\pm$ 1.35	8.8 $\pm$ 1.29	8.76 $\pm$ 1.4	8.74 $\pm$ 1.36	8.82 $\pm$ 1.33
Fasting insulin (pmol/l)	88.92 $\pm$ 2.67	88.36 $\pm$ 2.66	89.52 $\pm$ 2.67*	86.5 $\pm$ 2.61	91.43 $\pm$ 2.72*
30-min insulin (pmol/l)	438.44 $\pm$ 3.53	435.11 $\pm$ 3.44	442.0 $\pm$ 3.63*	436.31 $\pm$ 3.51	440.6 $\pm$ 3.55*
IGI	78.38 $\pm$ 2.93	75.78 $\pm$ 2.99	81.22 $\pm$ 2.86*	79.8 $\pm$ 2.82	76.97 $\pm$ 3.04*
IGI/IR	30.56 $\pm$ 22.78	29.43 $\pm$ 20.26	31.75 $\pm$ 25.16	31.52 $\pm$ 23.18	29.59 $\pm$ 22.36
Fasting PI (pmol/l)	13.47 $\pm$ 1.92	13.56 $\pm$ 1.93	13.37 $\pm$ 1.91*	13.13 $\pm$ 1.9	13.82 $\pm$ 1.94*
Fasting C-peptide (pmol/l)	1,011.32 $\pm$ 454.96	1,005.15 $\pm$ 450.93	1,017.84 $\pm$ 459.56	999.98 $\pm$ 452.87	1,022.82 $\pm$ 457.24
PI/C	0.02 $\pm$ 2.98	0.02 $\pm$ 3.01	0.02 $\pm$ 2.94*	0.02 $\pm$ 2.99	0.02 $\pm$ 2.97*

Data are means  $\pm$  SD or n (%). No significant differences between rosiglitazone versus placebo or ramipril versus placebo other than family history of diabetes in the ramipril versus placebo group ( $P = 0.02$ ). \*Indicates that statistical testing was performed using geometric means.

versus placebo (11.71 vs. 18.15,  $P > 0.05$ , and  $-0.007$  vs.  $-0.008$ ,  $P > 0.05$ , respectively) (Table 2). In the rosiglitazone group, changes in the  $\beta$ -cell function measures were more substantial between the baseline and 2-year visits compared with changes that occurred between the 2-year and final visits (Table 2). The impact of rosiglitazone on IGI/IR and PI/C was similar within subgroups of IIGT and IFG + IGT (IIGT, IGI/IR: 27.74 vs. 2.76,  $P < 0.0001$ ; PI/C:  $-0.009$  vs.  $-0.008$ ,  $P < 0.001$ ; IFG + IGT, IGI/IR: 27.39 vs.  $-0.70$ ,  $P < 0.0001$ ; PI/C:  $-0.014$  vs.  $-0.002$ ,  $P < 0.0001$ ), although effects were more modest in those with IIFG (IGI/IR: 8.95 vs. 2.13,  $P = 0.03$ ; PI/C:  $-0.003$  vs.  $-0.001$ ,  $P > 0.05$ ) (supplemental Table, available at <http://care.diabetesjournals.org/cgi/content/full/dc09-1579/DC1>).

We further assessed the impact of treatment on markers of  $\beta$ -cell function by utilizing longitudinal data from multiple study time points in mixed-model

analyses. Compared with placebo, rosiglitazone significantly increased IGI after adjustment for age and HOMA-IR ( $P = 0.015$ ) (Table 3). In contrast, ramipril did not significantly affect adjusted IGI ( $P > 0.05$ ). Similar findings were seen using PI concentration as a measure of  $\beta$ -cell function. Specifically, rosiglitazone significantly reduced PI concentrations over time after adjustment for age and C-peptide concentration ( $P = 0.0064$ ) (Table 3). In contrast, ramipril did not significantly change adjusted PI concentrations ( $P > 0.05$ ).

We assessed whether the impact of ramipril and/or rosiglitazone on diabetes incidence was independent of baseline levels or changes in indexes of  $\beta$ -cell function with time (Fig. 1). After accounting for baseline  $\beta$ -cell function as measured by either IGI or PI in models that adjusted for insulin resistance and other covariates, rosiglitazone significantly reduced the risk of developing diabetes (hazard ratio 0.32 [95% CI 0.22–0.45],

$P < 0.001$ , and 0.33 [0.23–0.47],  $P < 0.001$ , in IGI and PI models, respectively). Adjusting for the change in  $\beta$ -cell function as measured by IGI attenuated the preventive effect of rosiglitazone on incident diabetes (0.53 [0.28–0.99],  $P = 0.046$ ). Such attenuation was not noted when the change in  $\beta$ -cell was measured using PI (0.28 [0.18–0.42],  $P < 0.0001$ ) (Fig. 1, model 2). Ramipril showed smaller, nonsignificant reductions in diabetes risk.

**CONCLUSIONS**— Rosiglitazone, but not ramipril, improved measures of  $\beta$ -cell function over time in people with IFG and/or IGT. Specifically, rosiglitazone increased IGI/IR and reduced PI/C by 86 and 42%, respectively. These findings were consistent across glucose tolerance subgroups (IIFG, IIGT, and IFG+IGT), although there was the suggestion of a more modest effect in the subgroup with IIFG. Finally, rosiglitazone's effect on diabetes prevention persisted after adjust-

Table 2—Changes in markers of  $\beta$ -cell function

	Study visit	[(Ins <sub>30</sub> –Ins <sub>0</sub> )/(Gluc30–Gluc0)]/HOMA-IR			PI/C		
		n	P	Means $\pm$ SD	n	P	Means $\pm$ SD
A: rosiglitazone marginal group							
Placebo	Baseline	357		34.0 $\pm$ 22.82	449		0.022 $\pm$ 0.04
	2 years	350		41.74 $\pm$ 43.94	422		0.019 $\pm$ 0.03
	Final	357		35.94 $\pm$ 38.42	449		0.016 $\pm$ 0.02
	Change*	357		1.94 $\pm$ 36.37	449		–0.006 $\pm$ 0.04
	P†		0.31			0.0044	
Rosiglitazone	Baseline	429		29.95 $\pm$ 20.44	480		0.024 $\pm$ 0.04
	2 years	417		59.82 $\pm$ 82.93	463		0.018 $\pm$ 0.03
	Final	429		55.53 $\pm$ 125.14	480		0.014 $\pm$ 0.02
	Change*	429		25.59 $\pm$ 125.22	480		–0.010 $\pm$ 0.04
	P†		<0.0001			<0.0001	
Treatment difference	P‡		<0.0001			<0.0001	
B: ramipril marginal group							
Placebo	Baseline	383		30.72 $\pm$ 21.17	461		0.023 $\pm$ 0.04
	2 years	372		50.26 $\pm$ 72.91	440		0.017 $\pm$ 0.02
	Final	383		48.87 $\pm$ 128.97	461		0.014 $\pm$ 0.01
	Change*	383		18.15 $\pm$ 128.93	461		–0.008 $\pm$ 0.04
	P†		0.0062			<0.0001	
Ramipril	Baseline	403		32.80 $\pm$ 22.04	468		0.023 $\pm$ 0.04
	2 years	395		52.80 $\pm$ 64.20	445		0.020 $\pm$ 0.04
	Final	403		44.51 $\pm$ 48.48	468		0.015 $\pm$ 0.03
	Change*	403		11.71 $\pm$ 48.18	468		–0.007 $\pm$ 0.05
	P†		<0.0001			0.0009	
Treatment difference	P‡		0.89			0.64	

Data are means  $\pm$  SD and are reported for marginal treatment groups. \*Change was calculated as baseline minus final visit value. †P value for change were based on a *t* test of the average change being different from zero. ‡P values for treatment difference were calculated using the Wilcoxon rank-sum test.

ment for baseline  $\beta$ -cell function. The demonstration that an agent that reduces diabetes incidence also improves  $\beta$ -cell function invites the hypothesis that measures of change in  $\beta$ -cell function in response to therapy are indexes of that

therapy's ability to reduce the incidence of diabetes. The modest attenuation of rosiglitazone's effect after accounting for the change in  $\beta$ -cell function suggests that some but not all of the effect of rosiglitazone on diabetes prevention/delay is me-

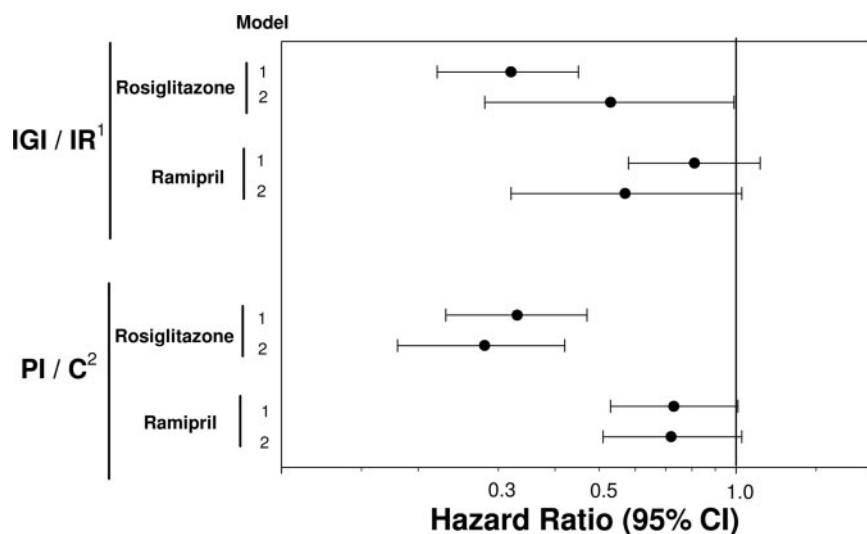
diated through its effects on  $\beta$ -cell function.

Whereas a number of previous studies (9–11) have documented improvements in  $\beta$ -cell function with TZD treatment in people with diabetes, only four studies (12–15) have investigated this question in people with IFG and/or IGT. The results of these studies have been inconsistent, with two studies (12,15) indicating a significant improvement in measures of  $\beta$ -cell function with TZD treatment and two studies (13,14) reporting no change. These studies all had small sample sizes ( $n \leq 30$ ), and the methods used to assess  $\beta$ -cell function varied widely from intensive approaches (insulin responses to glucose infusion [12,14]) to simple fasting-based indexes (HOMA-B [13,15]). Interestingly, the complexity of the method used to assess  $\beta$ -cell function did not appear to explain the differences in findings of these previous studies (12,14). Finally, in a diabetes prevention trial among Hispanic women with previous gestational diabetes, ~70% of whom had IGT at enrollment, treatment with troglitazone resulted in significant improvements in the frequently

Table 3—Longitudinal changes in markers of  $\beta$ -cell function in DREAM trial: analysis of slopes using mixed-model analysis

	Slope	SE	P	Slope difference
Rosiglitazone versus placebo				
PI				
PI/C (adjusted for age)	–0.003	0.0005	0.25	0.0008
PI (adjusted for age, fasting C-peptide)	–1.0524	0.1344	0.0064	0.5308
IGI				
IGI/HOMA-IR (adjusted for age)	9.0674	1.115	<0.0001	–7.0191
IGI (adjusted for age and HOMA-IR)	5.2814	1.3232	0.015	–4.7305
Ramipril versus placebo				
PI				
PI/C (adjusted for age)	–0.0028	0.0005	0.57	0.0004
PI (adjusted for age, fasting C-peptide)	–0.7796	0.14	0.87	0.0329
IGI				
IGI/HOMA-IR (adjusted for age)	5.2084	1.1522	0.5	1.1206
IGI (adjusted for age and HOMA-IR)	2.7603	1.3517	0.73	0.6681

Analysis in table are based on full data; results essentially unchanged when analysis repeated on subjects with information from all visits.



**Figure 1**—Association of treatment allocation with risk of diabetes: impact of baseline levels and changes in  $\beta$ -cell function. <sup>1</sup>For IGI/IR models: model 1 adjusted for age and baseline IGI, HOMA-IR, fasting glucose, waist circumference, triglyceride, and HDL; model 2 adjusted for age and changes in IGI, HOMA-IR, fasting glucose, waist circumference, triglyceride, and HDL. <sup>2</sup>For PI/C models: model 1 adjusted for age and baseline PI, C-peptide, fasting glucose, waist circumference, triglyceride, and HDL; model 2 adjusted for age and changes in PI, C-peptide, fasting glucose, waist circumference, triglyceride, and HDL.

sampled intravenous glucose tolerance-determined disposition index after 3 months (21).

Our results suggest a significant improvement in  $\beta$ -cell function with TZD treatment in pre-diabetic subjects. These findings extend the literature in a number of important ways. First, the sample size of our study ( $n = 982$ ) was much larger than previous investigations. Second, we demonstrated improvements in  $\beta$ -cell function under TZD treatment using two validated, widely used proxy measures of  $\beta$ -cell function, namely IGI and PI. Third, in our analysis we accounted for the compensatory impact on  $\beta$ -cell function of background insulin resistance. Specifically, in analyses of IGI we used HOMA-IR either as a covariate in multivariate analysis or as the denominator in the IGI-to-HOMA-IR ratio. C-peptide was used in a similar fashion in analyses of PI. Accounting for background insulin resistance is crucial to the interpretation of  $\beta$ -cell function measures in this study because TZDs improved insulin sensitivity, thus reducing pancreatic  $\beta$ -cell demand.

The exact mechanisms responsible for the increases in IGI/IR and the reductions in PI/C documented in the present study are not known, although a number of possibilities exist. The reduction in insulin resistance with TZDs would be expected to reduce insulin secretory demand on the  $\beta$ -cells and thus reduce

$\beta$ -cell stress. In addition, TZDs such as rosiglitazone may improve  $\beta$ -cell function indirectly by ameliorating a number of pathogenic processes that have been shown to be detrimental to the  $\beta$ -cells, including lipotoxicity, glucotoxicity, and inflammation (7,8). TZDs lower free fatty acids (22), elevated levels of which result in excess deposition of lipid within  $\beta$ -cells, which in turn leads to increases in ceramide and the stimulation of nitric oxide-mediated  $\beta$ -cell apoptosis. As well, the glucose-lowering effect of TZDs may reduce the impact of reactive oxygen species on the  $\beta$ -cells, which are known to be especially susceptible to oxidative damage (23). Finally, TZDs have been demonstrated to reduce levels of inflammatory cytokines (24), which may induce  $\beta$ -cell apoptosis when chronically elevated. TZDs may also impact  $\beta$ -cell function directly by maintaining  $\beta$ -cell proliferation and/or reducing  $\beta$ -cell apoptosis (25).

In the HOPE study, treatment with ramipril was shown to reduce the incidence of diabetes in middle-aged individuals with vascular disease. In the DREAM trial, although ramipril did not significantly reduce the incidence of diabetes in people with IFG and/or IGT, it did significantly increase regression to normoglycemia. The mechanism by which ramipril might reduce glucose levels and/or prevent/delay diabetes is unknown, although vascular and metabolic effects on the muscle and

pancreatic  $\beta$ -cell have been proposed (16). The results of the present study suggest that ramipril does not have significant effects on  $\beta$ -cell function compared with placebo in people at high risk for diabetes, and thus its glucose-lowering effects may operate through other metabolic mechanisms. The improvement in  $\beta$ -cell function in the placebo arm of the ramipril marginal group analysis may be explained by the fact that under the factorial design of the DREAM trial, half of the participants on ramipril placebo were receiving active rosiglitazone.

The major strengths of the present study include the large sample size, the randomized, double-blind design, and the completeness of follow-up (92.6%). Further, participants were thoroughly characterized in terms of glucose tolerance status and were all in the pre-diabetic range (either IIFG, IIGT, or IFG+IGT). The major limitation of the present study is the lack of detailed measures of  $\beta$ -cell function, such as those obtained from the hyperglycemic clamp technique or the frequently sampled intravenous glucose tolerance test. Notwithstanding, we used two proxy measures of  $\beta$ -cell function that have been extensively validated and used in previous studies including the Diabetes Prevention Program and the American Diabetes Association Genetics of Type 2 Diabetes Study (in the case of IGI/IR) and the IRAS study (in the case of PI).

In conclusion, rosiglitazone, but not ramipril, resulted in significant improvements in measures of  $\beta$ -cell function over time. These findings demonstrate that the diabetes preventive effect of rosiglitazone may in part be a consequence of improved  $\beta$ -cell function.

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## References

- Prentki M, Nolan CJ. Islet beta cell failure in type 2 diabetes. *J Clin Invest* 2006;116:1802–1812
- van Haefen TW, Pimenta W, Mitrokaou A, Korytkowski M, Jenssen T, Yki-Jarvinen H, Gerich JE. Disturbances in  $\beta$ -cell function in impaired fasting glycemia. *Diabetes* 2002;51(Suppl. 1):S265–S270
- Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of  $\beta$ -cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. *Diabetes Care* 2006;29:1130–1139
- Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 1999;104:787–794
- Hanley AJG, D'Agostino R Jr, Wagenknecht LE, Saad MF, Savage PJ, Bergman R, Haffner SM. Increased proinsulin levels and decreased acute insulin response independently predict the incidence of type 2 diabetes in the Insulin Resistance Atherosclerosis Study. *Diabetes* 2002;51:1263–1270
- UKPDS 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes* 1995;44:1249–1258
- Decker M, Hofflich H, Elias AN. Thiazolidinediones and the preservation of beta-cell function, cellular proliferation and apoptosis. *Diabetes Obes Metab* 2008;10:617–625
- Bell DS. Beta-cell rejuvenation with thiazolidinediones. *Am J Med* 2003;115(Suppl. 8A):20S–23S
- Prigeon RL, Kahn SE, Porte D Jr. Effect of troglitazone on B cell function, insulin sensitivity, and glycemic control in subjects with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 1998;83:819–823
- Wallace TM, Levy JC, Matthews DR. An increase in insulin sensitivity and basal beta-cell function in diabetic subjects treated with pioglitazone in a placebo-controlled randomized study. *Diabet Med* 2004;21:568–576
- Smith SA, Porter LE, Biswas N, Freed MI. Rosiglitazone, but not glyburide, reduces circulating proinsulin and the proinsulin: insulin ratio in type 2 diabetes. *J Clin Endocrinol Metab* 2004;89:6048–6053
- Cavaghan MK, Ehrmann DA, Byrne MM, Polonsky KS. Treatment with the oral antidiabetic agent troglitazone improves beta cell responses to glucose in subjects with impaired glucose tolerance. *J Clin Invest* 1997;100:530–537
- Osei K, Gaillard T, Kaplow J, Bullock M, Schuster D. Effects of rosiglitazone on plasma adiponectin, insulin sensitivity, and insulin secretion in high-risk African Americans with impaired glucose tolerance test and type 2 diabetes. *Metabolism* 2004;53:1552–1557
- Hung YJ, Hsieh CH, Pei D, Kuo SW, Lee JT, Wu LY, He CT, Lee CH, Fan SC, Sheu WH. Rosiglitazone improves insulin sensitivity and glucose tolerance in subjects with impaired glucose tolerance. *Clin Endocrinol (Oxf)* 2005;62:85–91
- Hung YJ, Lin SH, Pei D, Kuo SW, Hsieh CH, He CT, Hsing Lee C, Fan SC, Sheu WH. Rosiglitazone improves insulin sensitivity in nonobese subjects with impaired glucose tolerance: the role of adiponectin and C-reactive protein. *Metabolism* 2006;55:439–444
- Carlsson PO, Berne C, Jansson L. Angiotensin II and the endocrine pancreas: effects on islet blood flow and insulin secretion in rats. *Diabetologia* 1998;41:127–133
- DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators, Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, Shaw J, Zinman B, Holman RR. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006;368:1096–1105
- Wareham NJ, Phillips DI, Byrne CD, Hales CN. The 30 minute insulin incremental response in an oral glucose tolerance test as a measure of insulin secretion. *Diabet Med* 1995;12:931
- Mykkanen L, Haffner SM, Hales CN, Ronnema T, Laakso M. The relation of proinsulin, insulin, and proinsulin-to-insulin ratio to insulin sensitivity and acute insulin response in normoglycemic subjects. *Diabetes* 1997;46:1990–1995
- Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412–419
- Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP. Preservation of pancreatic  $\beta$ -cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 2002;51:2796–2803
- Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, Mari A, DeFronzo RA. Thiazolidinediones improve beta-cell function in type 2 diabetic patients. *Am J Physiol Endocrinol Metab* 2007;292:E871–E883
- Robertson RP, Harmon J, Tran PO, Poitout V.  $\beta$ -Cell glucose toxicity, lipotoxicity, and chronic oxidative stress in type 2 diabetes. *Diabetes* 2004;53(Suppl. 1):S119–S124
- Haffner SM, Greenberg AS, Weston WM, Chen H, Williams K, Freed MI. Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. *Circulation* 2002;106:679–684
- Finegood DT, McArthur MD, Kojwang D, Thomas MJ, Topp BG, Leonard T, Buckingham RE.  $\beta$ -Cell mass dynamics in Zucker diabetic fatty rats: rosiglitazone prevents the rise in net cell death. *Diabetes* 2001;50:1021–1029