SUPPLEMENTAL MATERIAL

For

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Rosiglitazone and Outcomes for Patients with Diabetes and Coronary Artery Disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial

SUPPLEMENTAL MATERIALS

Models for Propensity Score Matching

The goal of this analysis was to determine the likelihood (or propensity) of prescribing rosiglitazone to patients in BARI 2D. As expected the likelihood of prescribing rosiglitazone in BARI 2D was strongly linked to study randomly-assigned treatment strategy (insulin-providing (IP) vs. insulin-sensitizing (IS)). This treatment assignment was used in our propensity score calculation since our goal was to estimate the probability that an IS patient was intended for rosiglitazone therapy and match them with a "similar" IP patient who was not intended for rosiglitazone. The use of rosiglitazone at study entry (baseline) also had a large influence on future rosiglitazone use. Thus, we created two separate propensity scores, one for patients receiving rosiglitazone at baseline and another for patients not receiving rosiglitazone at baseline. The rationale and results for these scores are presented below.

Supplemental Table 1A: Intention-to-treat classification

Patients were classified according to whether early drug prescriptions during the study indicated that clinicians intended to treat (a) with rosiglitazone or (b) without any thiazolidinedione. Of the 2207 participants who survived at least 6 months and had a clinic visit documented at 4-6 months after randomization, patients were categorized in the rosiglitazone treated group (n=748) if they: (1) had not been receiving a thiazolidinedione prior to study entry and were prescribed rosiglitazone at any time during the first 6 monthly visits (n=563); (2) had been receiving a thiazolidinedione prior to study entry, were randomized to the insulin sensitization strategy, and were prescribed rosiglitazone at any time during the first 6 monthly visits (n=171); (3) had been receiving a thiazolidinedione prior to study entry, were randomized to the insulin provision strategy, and were prescribed rosiglitazone at the last visit during the first 6 months (n=12); or, (4) were prescribed rosiglitazone at any time during the first 6 monthly visits and pre-study thiazolidinedione was unknown (n=2). Of the remaining 1459 patients, 96 patients were prescribed pioglitazone during the first 6 months after study entry and were excluded from

analysis, leaving 1363 patients who did not receive any thiazolidinedione during the first 6 months after study entry who comprised the group of participants not prescribed a thiazolidinedione.

The following table presents the number of patients classified as intended treatment with rosiglitazone compared with intended treatment with no thiazolidinedione by assigned treatment group (IP versus IS) and baseline rosiglitazone use.

		(a) Rosiglitazone (RSG) treated group			(b) No thiazolidinedione prescription group		
		Total	IP	IS	Total	IP	IS
Rosiglitazone at baseline	Unknown	2	0	2	3	3	0
	Yes	128	8	120	90	89	1
	No	618	10	608	1270	982	288
Total		748	18	730	1363	1074	289

Supplemental Table 1B:

Propensity score matching among patients on rosiglitazone at baseline

Among patients on rosiglitazone at baseline, 89 IP patients in the No thiazolidinedione group were matched to a suitable subset of 120 IS patients in the rosiglitazone group (refer to Supplemental Table 1A above).

Rationale: Among the 97 patients on rosiglitazone at baseline who were randomized to the IP arm, 89 ended up in the No thiazolidinedione group and 8 ended up in the rosiglitazone group. For these patients the probability that thiazolidinedione would be withdrawn was high, roughly 89/97 = 0.92. With a logistic regression model, we identified baseline characteristics associated with thiazolidinedione withdrawal, and we used this model to calculate the individual probability that the patient was taken off thiazolidinedione. We also use this same model to similarly calculate such a probability among the 120 patients on rosiglitazone at baseline who were randomized to the IS arm and who went on to receive rosiglitazone treatment. The aim was to find 89 patients among these 120 IS patients who had the same probability of going without a

thiazolidinedione as the 89 IP patients who actually went without thiazolidinedione. That made the two groups comparable in their 'propensity' to have thiazolidinedione withdrawn in an IP setting, and as a result the two groups differ only in the randomized assignment.

The matching was based on the linear coefficient calculated from the logistic regression model below:

Characteristic	Beta
Intercept	4.6793
From the United States	-2.6784
On sulfonylurea at baseline	-2.4948
Patient either has LDL≥130 mg/dl or is on statins	2.3117
HDL <40 mg/dl in men and <50 mg/dl in women	-2.2441
Obese: BMI ≥ 30 kg/m²	3.9561
Never smoked	-1.9550

The linear coefficient for a given patient was calculated as the sum of the Betas for the characteristics that are present in that patient. The probability that an IP patient who was on rosiglitazone at baseline was able to go without any thiazolidinedione once the study started, was then calculated by the formula:

probability = exp{linear coefficient} / (1+ exp{linear coefficient}),

where exp{} is the exponential function.

Supplemental Table 1C:

Propensity score matching among patients NOT on rosiglitazone at baseline

Among patients not on rosiglitazone at baseline, 608 IS patients in the rosiglitazone group were matched to a suitable subset of 982 IP patients in the No thiazolidinedione group (refer to Supplemental Table 1A above).

Rationale: Among the 896 patients NOT on rosiglitazone at baseline who were randomized to the IS arm, 608 ended up in the rosiglitazone group and 288 ended up in the No thiazolidinedione group. Thus, for about 2/3 of these patients rosiglitazone therapy was considered feasible despite the fact that they were not on that drug coming into the study. With a logistic regression model, we identified baseline characteristics associated with receiving rosiglitazone therapy, and we used this model to calculate the individual probability that the patient received rosiglitazone therapy. We also used this same model to similarly calculate such a probability among the 982 patients NOT on rosiglitazone at baseline who were randomized to the IP arm and who stayed off any thiazolidinedione treatment. The aim was to find 608 patients among these 982 IP patients who had the same probability of receiving rosiglitazone therapy as the 608 IS patients who actually received it. That made the two groups comparable in their 'propensity' to receive rosiglitazone therapy in an IS setting, and as a result the two groups differ only in the randomized assignment.

The matching was based on the linear coefficient calculated from the logistic regression model below:

Characteristic	Beta
Intercept	-4.9585
On insulin at baseline	1.3035
On sulfonylurea at baseline	1.5767
On metformin at baseline	0.4866
From Canada	-0.5369
From Brazil	0.6804
Known history of TIA/non-coronary artery disease	0.4347
Known history of CHF	-0.9391
Patient either has triglycerides≥150 mg/dl or is on fibrates	0.3066
Duration of diabetes (per year)	0.0208
HbA1c (per % unit)	0.5434

The linear coefficient for a given patient was calculated as the sum of the Betas described in the table for that patient. The probability that an IS patient who was not on rosiglitazone at baseline

would receive rosiglitazone therapy once the study started, as previously defined, was then calculated with the formula:

probability = exp{linear coefficient} / (1+ exp{linear coefficient}),

where exp{} is the exponential function.

Supplemental Table 1D: Final count of matches found for various outcomes

A total of 89 matches were sought among patients on rosiglitazone at baseline, plus 608 matches among patients not on rosiglitazone at baseline, for a total of 697 possible matches (equal number of IS patients in the rosiglitazone group and IP patients in the No thiazolidinedione group). But the actual number of matches analyzed was smaller than 697, for two reasons: (i) for outcomes other than death, patients having those outcome during the first 6 months were excluded, and (ii) no matches were available for some patients with either very large or very small propensity scores. The following table summarizes, for each outcome, the number of matches found, out of the maximum number of matches sought:

Analysis of outcome	Theoretical maximum number of matches	Actual number of matches found*
Death	697	686
MI	683	668
Stroke	696	686
Death/MI/Stroke	682	667
CHF	522	512
Fractures	691	681

*These numbers appear as the denominators in Table 4

Supplemental Table 1E:

Baseline Characteristics of Matched Patients for Mortality Comparison

Baseline Characteristic	Total (n=1372)	No TZD (n=686)	Rosiglitazone (n=686)	p-value
Female, %	29.4	28.6	30.3	
Age, mean±SD	62.0±8.8	62.1±8.4	61.9±9.2	
Race, %				
Non-Hispanic, White	67.1	67.6	66.6	
Non-Hispanic, Black	17.1	16.9	17.2	
Hispanic	12.0	11.8	12.1	
Asian + Other	3.9	3.6	4.1	
Education, %				
< High School	38.6	38.8	38.3	
High School Graduate	21.6	21.7	21.6	
Some Post-High School	23.0	24.6	21.4	
Bachelor Degree or Higher	16.8	14.9	18.7	
Geography, %				
USA	60.3	62.1	58.5	
Canada	13.9	12.8	15.0	
Mexico	3.9	3.4	4.4	
Brazil	19.0	19.1	19.0	
Czech Republic/Austria	2.9	2.6	3.2	
BMI, %				
Normal (<25)	9.4	9.7	9.1	
Overweight (25 to <30)	33.7	33.7	33.8	
Class 1 Obesity (30 to <35)	31.8	31.2	32.5	
Class 2 Obesity (35 to <40)	16.0	15.8	16.3	
Class 3/4 Obesity (≥40)	9.0	9.7	8.3	
Cigarette Smoking, %				
Never Smoked	33.8	33.4	34.1	
Former Smoker	54.8	56.1	53.5	
Current Smoker	11.5	10.5	12.4	
Family History of coronary artery disease/sudden cardiac death	42.7	42.6	42.8	

Baseline Characteristic	Total (n=1372)	No TZD (n=686)	Rosiglitazone (n=686)	p-value
Prior PCI, %	20.0	20.6	19.4	
Prior CABG, %	6.6	5.7	7.4	
History of Angina within the last 6 weeks, %	59.6	58.7	60.5	
History of MI, %	31.5	31.1	31.9	
History of stroke or TIA, %	9.4	9.8	8.9	
History of Carotid Artery Disease, %	7.4	8.2	6.6	
Atrial fibrillation, %	0.9	1.1	0.7	
Left ventricular dysfunction, %	15.6	15.3	15.9	
History of congestive heart failure, %	5.3	5.7	4.8	
History of Hypertension, %	89.0	89.9	88.0	
On statins, %	75.4	74.9	75.9	0.07
Total cholesterol ≥ 200 mg/dl, %	21.4	21.0	21.9	
High total cholesterol or on statin, %	84.7	84.0	85.4	0.05
LDL-C ≥ 130 mg/dl, %	15.2	15.7	14.7	
High LDL-C or on statin, %	82.7	82.5	82.8	
HDL-C < 40 mg/dl men or < 50 mg/dl women, %	71.9	69.9	73.9	<0.10
On Fibrate, %	8.2	9.1	7.3	
Triglycerides ≥ 150 mg/dl, %	52.5	52.5	52.5	
High triglycerides or on fibrate, %	54.4	54.4	54.5	
On Gemfibrozil, %	3.3	3.9	2.6	
Duration of diabetes, mean±SD	11.1±8.3	11.5±8.7	10.7±7.9	0.08
Glycated hemoglobin, mean±SD	7.91±1.6	7.88±1.5	7.94±1.6	
Prior amputation, %	1.2	1.5	1.0	
Albuminuria, %				
No albuminuria	66.1	67.2	64.9	
Micro albuminuria	23.5	22.1	24.9	
Macro albuminuria	10.4	10.7	10.2	
Serum creatinine, mean±SD	1.04±0.28	1.05±0.28	1.03±0.29	

Supplemental Table 2. Association Of Fractures with Use of Rosiglitazone In BARI 2D Among Propensity Matched Participants Prescribed vs. Not Prescribed a Thiazolidinedione Within 6 Months of Study Entry.

	Rosiglitazone		No Thiazolidinedione					
	No. of Fractures/ Patients	**Rate**	**No. of Fractures/ Patients**	**Rate**	**Unadjusted RR**	**P Value**	**Adjusted RR**	**P Value**
All Patients	52/681	9.1	45/681	6.3	1.23	0.30	1.24	0.33
Men	21/470	4.8	27/470	5.6	0.76	0.34	0.84	0.56
Women	29/210	17.3	18/210	7.2	1.95	0.03	2.03	0.07

Supplemental Table 3. Effect of Co-administration of Select Medications During Treatment with Rosiglitazone on the Relative Risk of the Composite Rate of Death, Myocardial Infarction, and Stroke

Drug	Pt on drug	Patient-Years	RR of Rosiglitazone vs. No Thiazolidinedione*	95% CI	p value	Interaction p value
Insulin	Y	688	061	0.38, 0.96	0.03	0.38
	N	2081	0.77	0.57, 1.04	0.08	
Metformin	Y	2249	0.74	0.53, 1.03	0.08	0.74
	N	520	0.68	0.45, 1.02	0.06	
Gemfibrozil	Y	46	0.86	0.17, 4.32	0.86	0.79
	N	2723	0.69	0.53, 0.90	0.005	
Fibrate	Y	543	0.78	0.45, 1.33	0.36	0.66
	N	2226	0.68	0.51, 0.90	0.007	
Sulfonylurea	Y	574	0.60	0.34, 1.05	0.07	0.45
	N	2195	0.75	0.57, 0.99	0.04	
Any Nitrates	Y	881	0.76	0.53, 1.08	0.13	0.49
	N	1888	0.65	0.47, 0.89	0.008	
ACE	Y	1758	0.70	0.51, 0.95	0.02	0.93
	N	1011	0.68	0.46, 1.01	0.05	

*Adjusted for differences in baseline characteristics and use of other anti-diabetic medications.

Supplemental Table 4. Effect of Co-administration of Select Medications During Treatment with Rosiglitazone on the Relative Risk of the Congestive Heart Failure

Drug	Pt on drug	Patient-Years	RR of Rosiglitazone vs. No Thiazolidinedione*	95% CI	p value	Interaction p value
Insulin	Y	627	1.09	0.68, 1.74	0.72	0.75
	N	1955	1.19	0.80, 1.78	0.39	
Metformin	Y	2123	0.85	0.52, 1.38	0.50	0.03
	N	459	1.89	1.10, 3.24	0.02	
Gemfibrozil	Y	40	1.29	0.25, 6.80	0.76	0.87
	N	2542	1.13	0.81, 1.56	0.48	
Fibrate	Y	526	1.32	0.68, 2.56	0.41	0.61
	N	2056	1.10	0.78, 1.56	0.58	
Sulfonylurea	Y	522	1.62	0.92, 2.87	0.10	0.19
	N	2060	1.08	0.76, 1.54	0.65	
Any Nitrates	Y	784	1.03	0.66, 1.62	0.89	0.58
	N	1797	1.20	0.82, 1.74	0.35	
ACE	Y	1647	1.28	0.88, 1.86	0.20	0.22
	N	935	0.91	0.56, 1.48	0.70	

*Adjusted for differences in baseline characteristics and use of other anti-diabetic medications.