

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Hazard Ratios for Pioglitazone in Subgroup without Pre-diabetes by US/ADA Criteria and Interaction P-values for Comparison with HRs in Subgroup with Pre-diabetes by US/ADA Criteria

	Hazard Ratio (95% CI) (p)	Interaction P-value
Adherence \geq 80% (n=534)		
Stroke or myocardial infarction	0.85 (0.49, 1.47) (0.55)	0.24
Stroke	1.09 (0.60, 1.97) (0.78)	0.15
Acute coronary syndrome	0.55 (0.21, 1.42) (0.22)	0.78
Stroke/MI/hospitalized HF	0.93 (0.54, 1.58) (0.78)	0.20
Diabetes	0.40 (0.04, 3.89) (0.43)	0.48
Intention-to-Treat (n=991)		
Stroke or myocardial infarction	0.80 (0.55, 1.15) (0.23)	0.56
Stroke	0.86 (0.56, 1.31) (0.48)	0.50
Acute coronary syndrome	0.69 (0.40, 1.19) (0.18)	0.88
Stroke/MI/hospitalized HF	0.82 (0.58, 1.16) (0.26)	0.80
Diabetes	0.60 (0.18, 2.06) (0.42)	0.68

eTable 2. Change in risk factors from baseline with pioglitazone vs. placebo, among participants with adherence $\geq 80\%$

Risk factor	Pioglitazone n = 644	Placebo n = 810	p
Continuous variables			(ANOVA)
Fasting glucose (mg/dL)	-1.55 ± 15.20	4.11 ± 17.71	0.0001
Systolic pressure (mmHg)	-4.09 ± 19.12	-1.47 ± 17.68	0.008
Diastolic pressure (mmHg)	-5.79 ± 11.23	-2.27 ± 10.9	0.0001
Total cholesterol (mg/dL)	0.13 ± 1.03	0.07 ± 0.99	0.214
Triglycerides (mg/dL)	-0.32 ± 0.72	-0.06 ± 0.75	0.0001
HDL-C (mg/dL)	0.24 ± 0.31	0.10 ± 0.27	0.0001
LDL-C (mg/dL)	0.03 ± 0.91	-0.005 ± 0.86	0.428
Categorical variables			Chi-Square
Became diabetic (%)	2.0%	10.1%	0.0001
Smoker at end (%)	17.6%	14.0%	0.064

HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol

Conversion to SI units: multiply blood glucose x 0.0555; multiply total cholesterol, HDL-C and LDL-C x 0.0259; multiply triglycerides x 0.0113.

eTable 3. Baseline Characteristics of Participants with Pre-Diabetes by WHO/Canadian Criteria

	Adherence \geq 80%			Intention-to-Treat		
	Pioglitazone n = 300	Placebo n = 385	p	Pioglitazone n = 709	Placebo n = 701	p
Continuous variables	Mean \pm SD					
Age	64.21 \pm 9.97	64.98 \pm 10.26	0.32	64.1 \pm 10.49	64.48 \pm 10.67	0.50
Fasting glucose	104.86 \pm 10.86	103.98 \pm 10.54	0.28	104.33 \pm 10.54	103.99 \pm 10.91	0.55
A1C %	6.1 \pm 0.28	6.09 \pm 0.28	0.78	6.11 \pm 0.27	6.11 \pm 0.28	0.88
HOMA-IR	6.17 \pm 3.44	5.64 \pm 2.67	0.02	6.14 \pm 3.44	5.94 \pm 3.21	0.24
Systolic pressure	135.09 \pm 17.79	133.93 \pm 16.56	0.38	134.71 \pm 17.91	134.25 \pm 17.01	0.63
Diastolic pressure	80.15 \pm 11.06	78.83 \pm 10.12	0.10	79.46 \pm 11.04	79.08 \pm 10.5	0.51
Total cholesterol	157.17 \pm 36.37	158.36 \pm 34.87	0.66	161.21 \pm 38.87	162.15 \pm 36.69	0.64
Triglycerides	142.8 \pm 74.85	138.7 \pm 60.51	0.43	144.04 \pm 81.22	140.79 \pm 64.33	0.41
HDL-C	45.12 \pm 11.56	46.81 \pm 11.73	0.06	46.51 \pm 12.47	46.76 \pm 12.28	0.71
LDL-C	83.71 \pm 30.56	83.79 \pm 30.34	0.97	86.15 \pm 31.82	87.18 \pm 31.11	0.54
BMI	30.43 \pm 5.27	29.95 \pm 4.97	0.22	30.55 \pm 5.88	30.36 \pm 5.24	0.53
Categorical variables	%					
Men	74.0%	69.4%	0.18	65.2%	63.6%	0.55
Smoker	15.1%	11.7%	0.20	17.7%	15.8%	0.35

Units for blood analytes are mg/dL; blood pressure in mmHg, age in years

HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol,

HOMA-IR = Homeostasis Model Assessment of Insulin Resistance score

eTable 4. Outcome Rates by Treatment Group and Hazard Ratios for Pioglitazone in Participants with Pre-Diabetes by WHO/Canadian Criteria

Outcome	Pioglitazone	Placebo	Hazard Ratio (95% CI)	P
Adherence > 80%				
	n=300	n=385		
Stroke or myocardial infarction	8.3%	11.7%	0.68 (0.42, 1.12)	0.13
Stroke	6.0%	8.8%	0.66 (0.37, 1.16)	0.15
Acute coronary syndrome	4.0%	4.9%	0.78 (0.38, 1.61)	0.50
Stroke/MI/Hospitalized HF	9.0%	11.7%	0.74 (0.46, 1.19)	0.21
New onset diabetes	2.3%	14.3%	0.15 (0.07, 0.32)	<.0001
Intention-to-Treat				
	n=709	n=701		
Stroke or myocardial infarction	9.6%	13.7%	0.70 (0.51, 0.95)	0.02
Stroke	7.2%	10.6%	0.68 (0.48, 0.97)	0.03
Acute coronary syndrome	4.1%	5.4%	0.76 (0.47, 1.23)	0.26
Stroke/MI/Hospitalized HF	11.9%	14.8%	0.80 (0.60, 1.07)	0.13
New onset diabetes	7.2%	14.7%	0.47 (0.34, 0.66)	<.0001

eTable 5. Baseline Characteristics of Participants with Pre-Diabetes by US/ADA Criteria, by Treatment Group (Intention-to-Treat)

	Pioglitazone n = 1456	Placebo n = 1429	p
Continuous variables Mean ± SD			ANOVA
Age	63.66 ±10.54	63.76 ±10.55	0.80
Fasting glucose	100.85 ±9.83	100.76 ±9.83	0.81
A1C %	5.92 ±0.33	5.92 ±0.34	0.96
HOMA-IR	5.72 ±2.91	5.63 ±2.83	0.42
Systolic pressure	134.26 ±17.99	133.42 ±17.31	0.20
Diastolic pressure	79.74 ±10.95	78.91 ±10.38	0.04
Total cholesterol	162.14 ±38.30	162.48 ±37.71	0.81
Triglycerides	141.34 ±73.31	139.28 ±68.07	0.43
HDL-C	46.52 ±12.11	47.07 ±12.27	0.23
LDL-C	87.54 ±31.68	87.58 ±31.72	0.97
Body mass index	30.05 ±5.58	30.22 ±5.31	0.41
Categorical variables %			χ-Square
Men	66.9%	63.5%	0.06
Smoker	17.1%	15.7%	0.32

Units for blood analytes are mg/dL; blood pressure in mmHg, age in years
HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol, HOMA-IR = Homeostasis Model Assessment of Insulin Resistance score

eFigure. Time to Event for Participants with Pre-Diabetes by WHO/Canadian Criteria and $\geq 80\%$ Adherence

A. Stroke or myocardial infarction; B. Stroke; C. Acute Coronary Syndrome; D. Stroke/Myocardial Infarction/Hospitalization for heart failure; E. New-onset Diabetes

