

Effect of Pioglitazone and Ramipril on Biomarkers of Low-Grade Inflammation and Vascular Function in Nondiabetic Patients with Increased Cardiovascular Risk and an Activated Inflammation: Results from the PIOace Study

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Abstract

Aims:

This study investigated the effects of pioglitazone (PIO), ramipril (RAM), or their combination (PIRA) on low-grade inflammation in nondiabetic hypertensive patients with increased cardiovascular risk.

Methods and Results:

Patients enrolled in this placebo-controlled, double-blind, randomized, parallel trial (72 male, 77 female, aged 60 ± 9 years, body mass index 30.4 ± 4.7 kg/m², duration of hypertension 9 ± 8 years) were treated with either 30/45 mg PIO (dose titration), 2.5/5 mg RAM, or their combination for 12 weeks. A reduction in high-sensitivity C-reactive protein was observed with PIO (-0.89 ± 1.98 mg/liter; -25%) and PIRA (-0.49 ± 2.11 mg/liter; -16%), while an increase was seen with RAM (0.58 ± 2.13 mg/liter; +20%, $p < .05$ vs PIO and PIRA). The 24-hour blood pressure profile showed a small increase with both monotherapies but a decrease with PIRA ($p < .05$ vs PIO). Improvements in biomarkers of chronic systemic inflammation and insulin resistance (IR) were observed in the PIO and PIRA arms only [PIO/RAM/PIRA: homeostasis model of assessment of IR: -0.78 ± 1.39 (-29%)/ 0.15 ± 1.03 (+5%)/ -1.44 ± 2.83 (-40%); adiponectin: 8.51 ± 5.91 (+104%)/ 0.09 ± 2.63 (+1%)/ 8.86 ± 6.37 mg/liter (+107%); matrix metalloproteinase-9: -48 ± 127 (-12%)/ -1 ± 224 (0%)/ -60 ± 210 ng/ml (-13%), $p < .05$ for RAM vs PIO or PIRA in all cases].

Conclusions:

Our 3-month study in nondiabetic hypertensive patients showed a decrease in biomarkers of IR and chronic systemic inflammation with the PIO monotherapy and the PIRA combination only, which may help to explain some findings in other cardiovascular outcome trials.

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Abbreviations: (ACE) angiotensin-converting enzyme, (ACT NOW) Actos Now for Prevention of Diabetes, (ANCOVA) analysis of covariance, (B) β -cell function, (DREAM) Diabetes REduction Assessment with ramipril and rosiglitazone Medication, (ELISA) enzyme-linked immunosorbent assay, (eNOS) endothelial nitric oxide synthase, (HbA1c) hemoglobin A1c, (HDL) high-density lipoprotein, (HOMA) homeostatic model assessment, (HOPE) Heart Outcomes Prevention Evaluation, (hs-CRP) high-sensitivity C-reactive protein, (IR) insulin resistance, (JUPITER) Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin, (LDL) low-density lipoprotein, (LOCF) last observation carried forward, (MAPK) mitogen-activated protein kinase, (MCP-1) macrophage chemoattractant protein-1, (MMP9) matrix metalloproteinase-9, (NO) nitric oxide, (OGTT) oral glucose tolerance test, (oxLDL) oxidized low-density lipoprotein, (PIO) pioglitazone, (PIRA) pioglitazone+ramipril, (PPAR γ) peroxisome proliferator-activated receptor- γ , (RAM) ramipril, (RAS) renin-angiotensin system, (S) insulin sensitivity, (SAE) serious adverse event, (SD) standard deviation

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