

Effects of Pioglitazone on Major Adverse Cardiovascular Events (MACE) and Myocardial Infarction: Results From PROactive

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Composite endpoints of cardiovascular (CV) events are standard measures for comparing treatments in large CV outcome studies and are referred to as major adverse cardiovascular events (MACE). Patients with type 2 diabetes (T2D) are at high risk of macrovascular events. In PROactive, we evaluated the effects of pioglitazone (PIO) on the prespecified endpoints of fatal/nonfatal myocardial infarction (MI; excluding silent MI) and a MACE1 composite of CV death, nonfatal MI (excluding silent MI), or nonfatal stroke; and on a *post-hoc* MACE2 composite of all-cause mortality, nonfatal MI (excluding silent MI), nonfatal stroke, or acute coronary syndrome in high-risk patients with T2D.

PROactive was a double-blind, placebo-controlled CV outcome study in which 5,238 patients were randomized to PIO (titrated to 45 mg od) or placebo (PBO), in addition to their existing glucose-lowering and CV medication. Mean follow-up was 34.5 months.

A Cox proportional hazards model showed statistically significant risk reductions with PIO compared with PBO for the MI (23%; HR=0.77; 95%CI=0.60,1.00; P=0.046), MACE1 (18%, HR=0.82; 95% CI=0.70,0.97; P=0.020), and MACE2 endpoints (17%; HR=0.83; 95%CI=0.72,0.96; P=0.010). At study end, 339 (13.0%) patients in the PIO group had a first event that contributed to the MACE2 endpoint, compared with 409 (15.5%) in the PBO group and 108 (4.1%) PIO patients and 140 (5.3%) PBO patients had an MI (excluding silent MI). A similar result occurred when non-CV deaths were excluded from the MACE2 endpoint (HR=0.80; 95%CI=0.69,0.94; P=0.005).