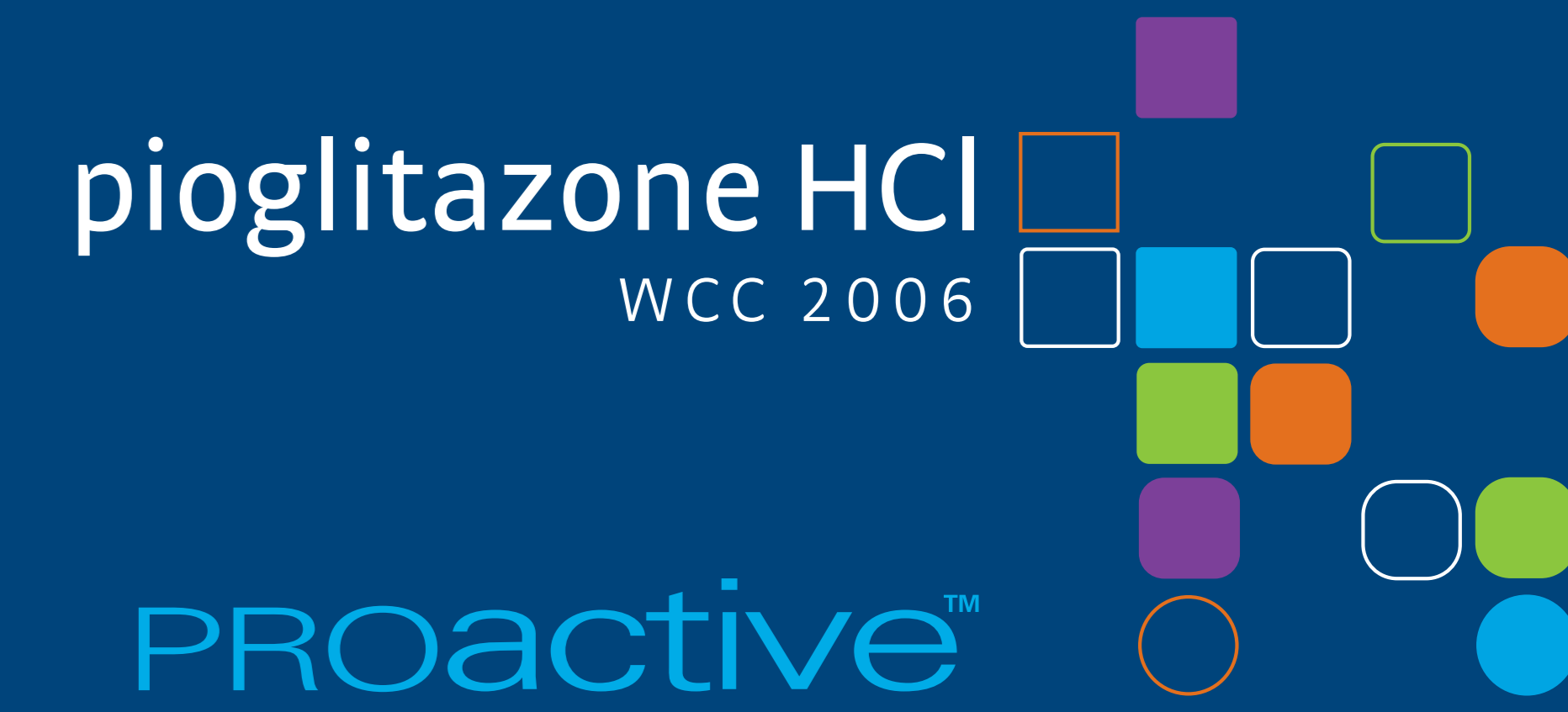


An Analysis from PROactive on the Effects of Pioglitazone on Myocardial Infarction and Major Adverse Cardiovascular Events (MACE) in Patients with Type 2 Diabetes

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ABSTRACT

Composite endpoints of cardiovascular (CV) events, referred to as major adverse cardiovascular events (MACE), are commonly used to compare treatments in large CV outcome studies. Patients with type 2 diabetes (T2D) have an increased incidence of CV events compared with the general population. This analysis from PROactive evaluated the effects of pioglitazone (PIO) on the prespecified endpoints of fatal/non-fatal myocardial infarction (MI; excluding silent MI) and a MACE1 composite of CV death, non-fatal MI (excluding silent MI), or non-fatal stroke; and on two post-hoc MACE composites.

PROactive was a double-blind, placebo-controlled CV outcome study in which 5,238 patients were randomised to PIO (titrated to 45 mg od) or placebo (PBO), in addition to their existing glucose-lowering and concomitant CV medication. Patients started with 15 mg/day PIO, titrated to maximal tolerated doses in 15 mg increments up to 45 mg. Mean follow up was 34.5 months.

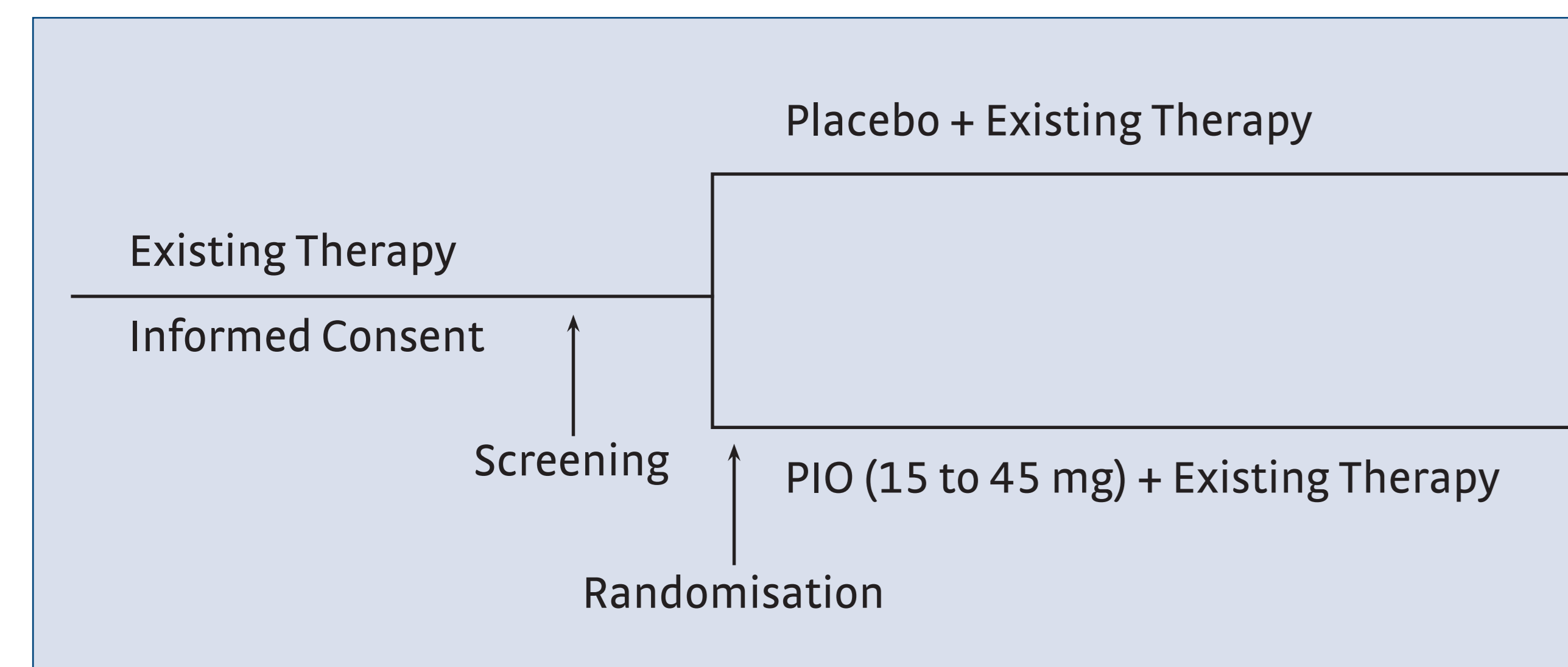
A Cox proportional hazards model showed statistically significant risk reductions for the MI and MACE endpoints with PIO compared with PBO. PIO treatment resulted in a 23% significant risk reduction in time to first fatal or non-fatal MI events and up to 20% risk reduction in time to MACE compared with PBO in this population of patients with T2D at high risk for CV events.

INTRODUCTION

- Composite endpoints of CV events are standard measures for comparing therapies in large CV outcome studies and are referred to as major adverse CV events (MACE).
- PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) is a CV outcomes study in a high-risk type 2 diabetes population. (1)
- Here, we report the results of prespecified analyses on a MACE endpoint of CV death, non-fatal MI (excluding silent MI), or non-fatal stroke and total MI (fatal and non-fatal, excluding silent MI) (MACE1).
- To allow further comparison to other landmark CV outcome trials, we also conducted *post-hoc* analyses on six additional MACE endpoints.

STUDY DESIGN AND METHODS

Design: Multicentre, randomised, double-blind, placebo-controlled, parallel-group study.



STUDY DESIGN AND METHODS (continued)

Duration: Mean follow-up was 34.5 months.

Inclusion criteria:

- Male or female, 35 to 75 years of age, inclusive
- HbA_{1c} above the upper limit of normal (local equivalent of 6.5%)
- Established history of macrovascular disease

Exclusion criteria:

- Signs of type 1 diabetes
- Established insulin therapy
- MI, stroke, CABG, or PCI in the 6 months prior to enrollment
- Heart failure defined as NYHA class II or above
- Significantly impaired hepatic function
- Hypersensitivity to or current use of a thiazolidinedione

Event Adjudication Process:

An independent and treatment blinded Endpoint Adjudication Committee reviewed all events that could potentially contribute to the primary endpoint. The following definitions apply to those events included in the MACE endpoints:

Death – all cases of death adjudicated and classified as either death or CV-related death

MI – at least 2 of the following criteria:

- Ischaemic symptoms ≥30 min
- ECG evidence
- Cardiac enzyme evidence

Stroke – at least one of the following:

- Acute focal neurological deficit for >24 h, or resulting in death if <24 h
- Cerebral, vascular origin
- Imaging data supportive

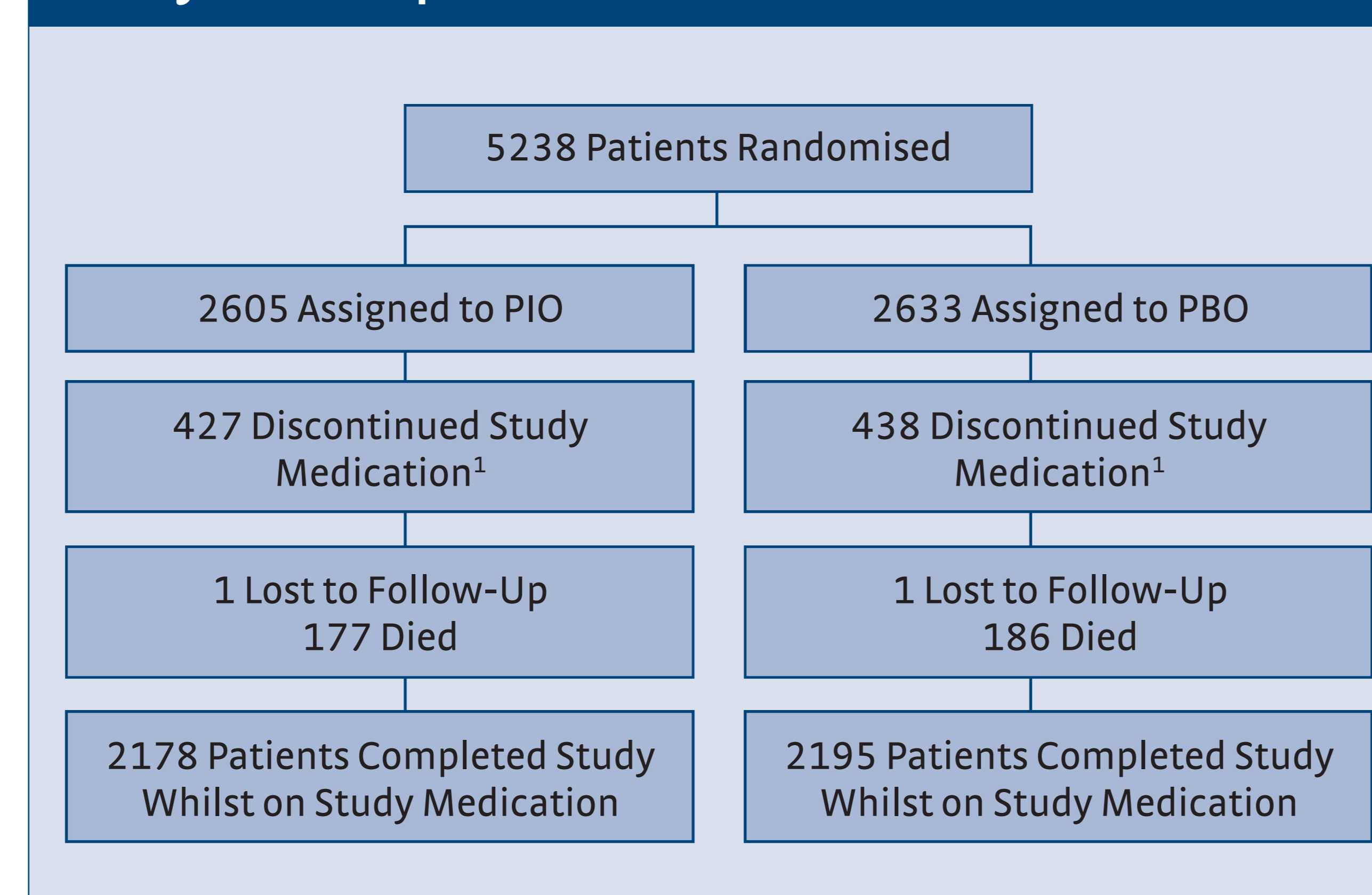
Acute coronary syndrome – at least one of the following:

- Ischemic symptoms ≥5 min
- ECG evidence
- Cardiac enzyme evidence

RESULTS

Subject disposition was similar between treatment groups.

Subject Disposition



¹The most common reasons for discontinuation were adverse events (PIO, n=235; PBO, n=202) and withdrawal of consent (PIO, n=171; PBO, n=179).

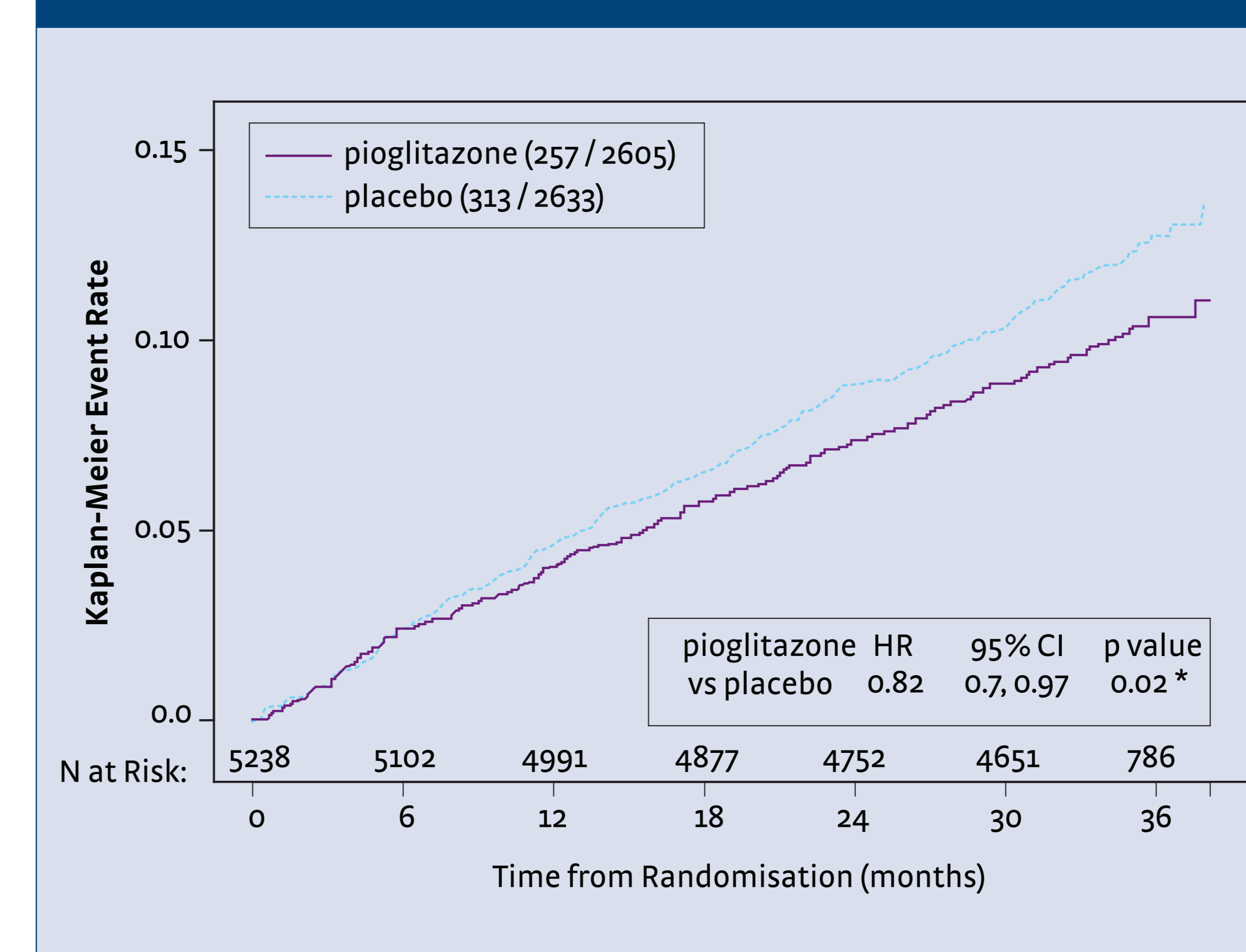
RESULTS (continued)

- The randomised treatment groups were well matched with regard to demographic characteristics.
- Baseline medical history was consistent with a study population with long-standing type 2 diabetes (mean duration of 9.5 years since diagnosis) and significant underlying CV disease (eg, 75% had hypertension, 47% had a prior MI, and 19% had a prior stroke).
- Patient population was two-thirds male and predominantly Caucasian.
- At least two macrovascular disease-related entry criteria were met by 48% of the study population.

MACE Endpoints

- For the MACE1 composite endpoint, 257 (9.95%) patients in the PIO group experienced an event compared to 313 (11.9%) patients in the PBO group.
- A Cox proportional hazards model indicated that the risk to PIO-treated patients for this composite endpoint was significantly reduced by 18% compared with PBO (HR, 0.82; 95% CI: 0.70, 0.97; P=0.020).

MACE1: Time to CV Death, Non-fatal MI (excl. Silent MI) or Stroke



Time to MI or MACE1 Endpoint (a)

	PIO N=2605 n (%)	PBO N=2633 n (%)
Fatal/Non-fatal MI (excl. silent MI)		
1 year	51 (2.0%)	54 (2.1%)
2 year	83 (3.2%)	104 (3.9%)
3 year	107 (4.1%)	139 (5.3%)
MACE1 composite of CV death, non-fatal MI (excl. silent MI), or non-fatal stroke		
1 year	105 (4.0%)	121 (4.6%)
2 year	191 (7.3%)	231 (8.8%)
3 year	256 (9.8%)	311 (11.8%)

(a) Prespecified endpoints

Frequency of Composite Event

Event	n (%)		Hazard Ratio ^a		
	PIO N=2605	PBO N=2633	Est	95% CI	P-value
MACE1 (CV mortality, non-fatal MI, or stroke)	257 (9.9%)	313 (11.9%)	0.82	(0.70, 0.97)	0.0201
MACE2 (Any death, non-fatal MI, stroke, or ACS)	339 (13.0%)	409 (15.5%)	0.83	(0.72, 0.96)	0.0103
MACE3 (CV mortality, non-fatal MI, stroke, or ACS)	295 (11.3%)	267 (13.9%)	0.80	(0.69, 0.94)	0.0051
MACE4 (Cardiac mortality, non-fatal MI, or stroke)	242 (9.3%)	301 (11.4%)	0.81	(0.68, 0.95)	0.0120
MACE5 (Cardiac mortality, non-fatal MI, or ACS)	205 (7.9%)	259 (9.8%)	0.79	(0.66, 0.95)	0.0132
MACE6 (Cardiac mortality, non-fatal MI, stroke, or ACS)	282 (10.8%)	356 (13.5%)	0.79	(0.68, 0.93)	0.0034
MACE7 (Cardiac mortality or non-fatal MI)	164 (6.3%)	202 (7.7%)	0.82	(0.66, 1.00)	0.0517

^a PIO versus PBO, from a Cox proportional hazards model with a treatment explanatory variable

CONCLUSIONS

- The PROactive study is the first prospective study evaluating the effects of thiazolidinedione therapy on CV outcomes in patients with type 2 diabetes who are at high risk for first or recurrent CV events.
- Consistent benefit of effect with pioglitazone was demonstrated for a variety of MACE endpoints in PROactive.
- Therapy with PIO resulted in a 23% decrease in MI and an 18% to 23% decrease in MACE composite endpoints relative to placebo.
- These benefits were observed on top of existing treatment for diabetes and CV conditions.
- These endpoints incorporate the most clinically important and objectively measurable CV events in this high-risk patient population and allow for a comparison of PROactive results with those of other CV outcome studies.

REFERENCE

1. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled study. *Lancet* 2005;366:1279-89.