

Effects of Pioglitazone in patients with
or without a history of stroke
— an analysis of PROactive

Discussion

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The original publication

Dormandy et al. *Lancet* October 8 2005;366:1279

Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial

John A Dormandy, Bernard Charbonnel, David J A Eckland, Erland Erdmann, Massimo Massi-Benedetti, Ian K Moules, Allan M Skene, Meng H Tan, Pierre J Lefebvre, Gordon Sirtori, László Korányi, Markku Tuomi, Guntram Schernthaner

Summary

Background Patients with type 2 diabetes have an increased risk of cardiovascular morbidity and mortality. Pioglitazone is a thiazolidinedione that improves insulin sensitivity and has been shown to reduce cardiovascular morbidity and mortality in patients with type 2 diabetes.

Interpretation

Pioglitazone reduces the composite of all-cause mortality, non-fatal myocardial infarction and stroke in patients with type 2 diabetes who have high risk of macrovascular events

The original publication

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Already known

Stroke – one of the most influenced endpoints

John A Dormandy, Bernard Charbonnel, David J A Eckland, Erland Erdmann, Massimo Massi-Benedetti, Ian K Moules, Allan M Skene, Meng H Tan, Pierre J Lefebvre, Gordon D Murray, Eshwar S Ganji, Robert C Wilcox, Lars Wilhelmsen, John Battarée, Károly Dósa, Alain Colquhoun, Robert J Heineke, László Kovács, Güntram

Summ
 Backgro
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First events			Total events	
Pioglitazone (n=2605)	Placebo (n=2633)	HR (95% CI)	Pioglitazone	Placebo

Variable	Pioglitazone	Placebo	HR (95% CI)
Stroke	86	107	0.81 (0.67-1.07)

Coronary revascularisation	169	193	0.88 (0.72-1.08)	195	240
Leg revascularisation	80	65	1.25 (0.90-1.73)	115	92
Total	803	900

The present finding



Why perform this analysis
What does it mean

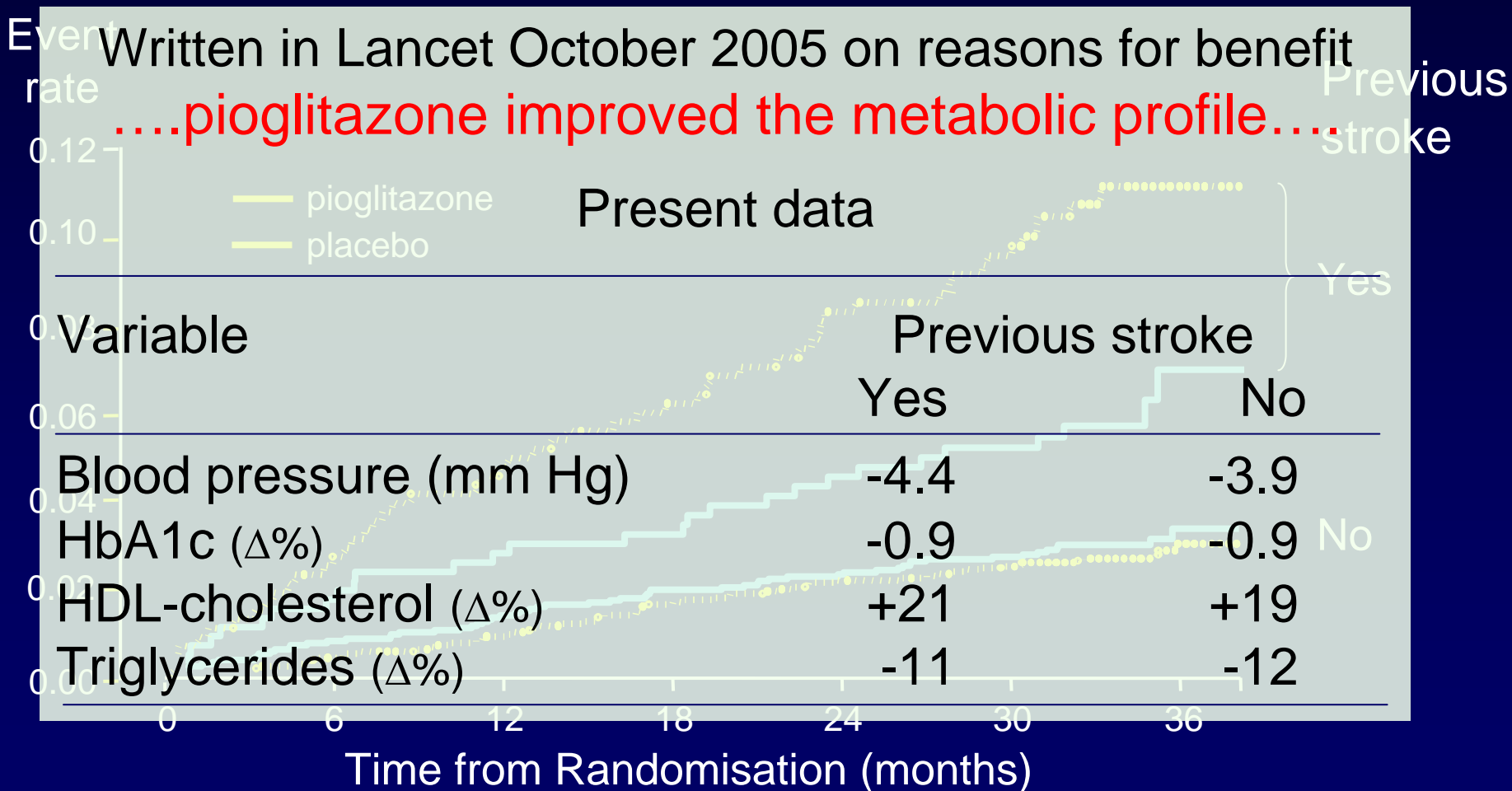
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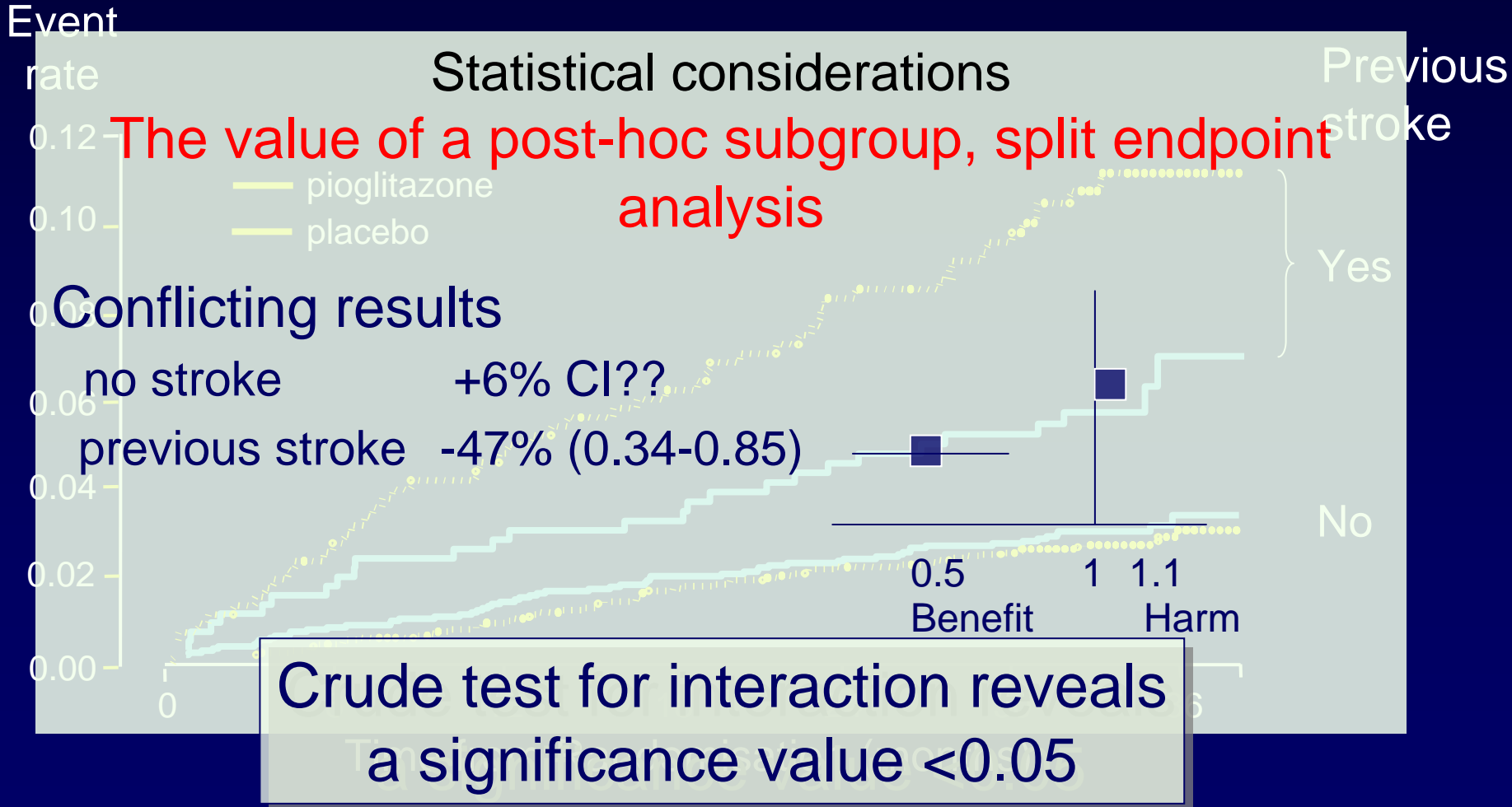
or a
b

e risk

Time to fatal or non-fatal stroke



Time to fatal or non-fatal stroke



My concern

The present outcome difficult to understand

- ✓ No reasonable biological explanation
- ✓ An obvious risk for confounding factors

Astrology and clinical trials

Subgroup analysis in clinical trials
fun to look at but don't believe them

"One of the perhaps most important results in ISIS II....

.....when patients were divided in 12 astrological
subgroups ASA had adverse effects in those born in the
sign of Gemini and Libra."

Sleight P. Curr Control Trials Cardiovasc Med 2000; 1:25

In my opinion

Time to death, non-fatal MI and stroke



The best estimate of treatment effects for any subgroup is the estimate of the hazard ratio for the overall trial

Remain pleased with it –
it is encouraging enough!!