

ACUTE CORONARY SYNDROMES ALEGLITAZAR TRIAL FINDINGS REPORTED

The findings from AleCardio, the first large-scale, cardiovascular outcomes trial of a dual PPAR activator, indicate that aleglitazar therapy does not reduce cardiovascular risk in patients with type 2 diabetes mellitus who have experienced an ACS. “This study may well mark the end of this class of drug being tested clinically,” says Dr Michael Lincoff, who presented the trial findings at the 2014 ACC Scientific Sessions.

PPAR- α agonists have beneficial effects on serum lipid levels, and PPAR- γ agonists reduce hyperglycaemia. Therefore, dual PPAR agonists have been considered a promising therapeutic strategy for patients with both diabetes and dyslipidaemia. In phase II trials, the potent dual PPAR agonist aleglitazar was associated with significantly reduced levels of glycated haemoglobin, triglycerides, and LDL cholesterol, as well as increased HDL-cholesterol concentration. The phase III AleCardio trial was designed to assess the affect of adding aleglitazar to standard therapy on the risk of ‘hard’ cardiovascular outcomes in patients with diabetes who have experienced an ACS.

In 2010–2012, 7,226 patients with diabetes, who were hospitalized for an ACS at one of 720 centres in 26 countries, were enrolled in the study. Treatment was scheduled to continue until patients had been followed up for at least 2.5 years; however, the trial was terminated for futility in July 2013, after recommendation by the independent data and safety monitoring board. Median follow-up was 104 weeks.

Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke—the primary efficacy end point—occurred in 9.5% and 10.0% of the aleglitazar and placebo groups, respectively ($P=0.57$). The aleglitazar group experienced more gastrointestinal haemorrhage, heart failure, hypoglycaemia, peripheral oedema, renal dysfunction, and weight gain than controls.

The AleCardio investigators speculate that “favourable lipid and metabolic effects of aleglitazar may have been negated by adverse effects of the drug”. They also point out that “the possibility that other, unmeasured adverse consequences of PPAR activation contributed to the neutrality of the primary results cannot be excluded, given the multiplicity of genes regulated by PPAR transcription factors”.

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Original article Lincoff, A. M. *et al.* Effect of aleglitazar on cardiovascular outcomes after acute coronary syndrome in patients with type 2 diabetes mellitus: the AleCardio randomized clinical trial. *JAMA* doi:10.1001/jama.2014.332