

## Avandia: Cardiovascular Safety Concern Remains

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### Introduction

Avandia or rosiglitazone is widely used for the treatment of Type-2 diabetes (T2D), marketed by the GlaxoSmithKline Pharmaceuticals. It has several beneficial effects on the pathogenesis of diabetes as well as its complications: 1) By improving insulin resistance Avandia has been successfully used to achieve glycemic control in a manner that is at least as effective as sulfonylureas and metformin; 2) via PPAR $\gamma$  Avandia regulates adipocyte proliferation and lipid storage, improving lipid profile; 3) Avandia interferes with the foam cell formation and inflammatory response, reduces lipid deposition in the vessel wall, and thus attenuates the development of atherosclerosis [1-3].

In 2007, a large meta-analysis suggests a 43% increase in risk for myocardial infarction and a possible increase in risk for cardiovascular death with Avandia treatment [4]. This was followed by a number of clinical trials. Because results from these studies were rather inconsistent, the Food and Drug Administration (FDA) decided not to withdraw the drug from the market in 2007 and 2010. Meanwhile a safety alert was issued, warning a possibly increased risk of ischemic cardiovascular events in patients using Avandia. Subsequently, the FDA required a reevaluation of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial. With new RECORD data, the FDA has lifted use restrictions of Avandia in November, 2013 [5]. A recent article in New England Journal Medicine concluded: "From a cardiovascular perspective, rosiglitazone, saxagliptin, and alogliptin appear to be relatively safe [1]."

However, the RECORD trials were designed to evaluate whether in the treatment of T2D Avandia was inferior to metformin/sulfonylurea on cardiovascular outcomes [6]. Although such inferiority was not found, the RECORD results should not be interpreted as Avandia does not elevate cardiovascular risks. The RECORD results only suggest that the cardiovascular risks in Avandia users are about the same as in metformin/sulfonylurea users. Indeed, a recent metaanalysis of randomized clinical trials indicates that the use of sulfonylureas in T2D is associated with increased mortality and a higher risk of stroke [7].

Experimental evidence from bench research suggests that Avandia has adverse effects on the vascular wall, compromising vasodilation responses to circulating hormones and neurotransmitters as well as metabolites. Such adverse effects are independent of PPAR $\gamma$  and involve the vascular KATP channel that is inhibited by Avandia and sulfonylureas [8-10]. Since the RECORD trials only compared cardiovascular risks between Avandia and sulfonylureas/ metformin,

the RECORD results should be interpreted with great precautions.

The information of the novel vascular target seems to explain several adverse cardiovascular effects of Avandia and may be helpful for physicians and diabetic patients to use the drug more properly by taking the advantage of its metabolic benefits and avoiding potential cardiovascular risks [11]. The finding should not be considered as evidence to indicate that Avandia is a bad drug, as no drugs are completely free of side-effects including widely used Aspirin, Prozac and Vitamins.

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