Australian Diabetes Society

A.B.N. 13 053 787 965 A.C.N. 053 787 965

The Peak Medical and Scientific Health Professional Body for Diabetes in Australia

ADS Position Statement on rosiglitazone (AVANDIA ®) and cardiovascular outcomes.

Updated September 2010

This is a revision of our previous position statement concerning rosiglitazone and cardiovascular outcomes in light of recent regulatory changes with respect to this drug. ADS recognise that this is an important issue of concern. The purpose of this statement is to provide guidance to Australian doctors. ADS Council has considered a number of key research articles [some of which are listed at the end of this document], their accompanying editorials and other publications in formulating this position statement.

The recent changes in regard to rosiglitazone have been 1) the decision of the European Medicines Agency to suspend sales, and 2) the decision by the US Food and Drug Administration (FDA) to restrict prescribing in the USA to physicians who are part of a registry certifying that they are familiar with the heart risks associated with rosiglitazone and that they are prescribing it only because their patients have exhausted all other medications to help control their blood sugar. For completeness, the US Department of Veteran Affairs withdrew rosiglitazone from its formulary in 2007.

It is clear and undisputed that thiazolidinediones (TZDs) can cause heart failure, but there has been controversy about the association between TZDs, particularly rosiglitazone, and other cardiovascular outcomes.

Two meta-analyses have examined the association between rosiglitazone and cardiovascular death. The first included 14,376 patients from many small studies and the DREAM and ADOPT studies. There was a 1.43 OR for myocardial infarction (p=0.03) and an OR of 1.64 for cardiovascular death (p=0.06) (1). The second, which included 20,191 patients, found no increased risk of cardiovascular death with either rosiglitazone or pioglitazone with RR 0.93 (2).

Since these two papers, the ACCORD (3), ADVANCE (4) and RECORD (5) studies have been published. In the ACCORD trial, a significantly increased risk of all-cause mortality and death from cardiovascular death in the intensively treated group was observed. The study was designed to achieve near-normal glycaemia in a population of people with relatively long-standing diabetes. In the intensively treated group, 92% of patients received a TZD, predominantly rosiglitazone. No increase in mortality was seen with intensive therapy in the ADVANCE trial with a 58% rate of TZD use. The RECORD study was an open label study of 4,447 patients who received either addition of rosiglitazone as dual therapy with metformin or sulfonylurea *or* metformin+sulfonylurea. Hazard ratio was 1.14 (p=ns) for myocardial infarction, and 0.84 for cardiovascular death (p=ns).

There have already been many commentaries published on this issue, as editorials or statements. Regulatory authorities including the FDA, the European Medicines Agency and the Australian Therapeutic Goods Administration have stated their position. Professional bodies including the (American) Endocrine Society, American Association of Clinical Endocrinologists and jointly the American Diabetes Association, American Heart Association and American College of Cardiology and Diabetes Australia have also released statements.
A review of the statements from the above bodies reveals agreement that:

1. The possible association between TZDs and cardiovascular events is of extreme importance.
2. The currently available evidence does not allow a definitive statement on the safety or risk of TZDs, particularly rosiglitazone, in this context.
3. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study did not confirm a significant cardiovascular risk with rosiglitazone.

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RECOMMENDATIONS:-

General comments

Discussion with patients should address the proven value of glycaemic control in reducing the risk of microvascular complications of diabetes. ADS emphasises that comprehensive management of diabetes should always include cardiovascular risk assessment and treatment.

The current PBS guidelines in Australia support the use of TZDs for "*Type 2 diabetes, in combination with either metformin or a sulfonylurea, in a patient whose HbA1c is greater than 7% prior to initiation of a thiazolidinedione (glitazone) despite treatment with either metformin or a sulfonylurea and where a combination of metformin and a sulfonylurea is contraindicated or not tolerated.*"

Australian PBS guidelines do not support the use of TZDs alone, with insulin, or for initiation for triple oral therapy.

Patients already taking rosiglitazone

Patients should not stop rosiglitazone without consultation with their doctor because of the risk of uncontrolled hyperglycaemia.

ADS strongly recommends that doctors fully discuss the various study results with their patients. ADS further recommends that the options for management be discussed with patients. These options include:

1. Discontinuation of rosiglitazone and maintenance of glycaemic control by the initiation of alternative agents.

Or

2. In patients already taking rosiglitazone, continuation of therapy. ADS council considers that this may be a reasonable option at this time in fully informed patients who are well controlled on therapy, with no history of heart failure or cardiovascular disease.

While ADS do not consider the current evidence allows a definitive recommendation on the discontinuation of rosiglitazone except in the setting of known heart failure, it is prudent practice to advise alternative management if a patient has ongoing concerns after discussion.

Rosiglitazone 'naïve' patients

ADS recommends that in the setting of heart failure or prior heart disease, it is prudent to consider other classes of agent to control blood glucose.

Otherwise, if it is considered that the patient has significant insulin resistance, and there is intolerance or inadequate therapeutic efficacy with diet and exercise and the other therapeutic classes (metformin, sulfonylureas, DPP IV inhibitors, acarbose, GLP-1 agonists, insulins), then there may still be a role for TZDs in management of type 2 diabetes. It is recommended that this step only be considered under specialist advice.

Potential conflict of interest statements relevant to rosiglitazone (Avandia): The ADS Annual Scientific Meeting received support from GSK as a principal sponsor and has had standard commercial arrangements with GSK to display at the ADS Scientific Meeting. Ashim Sinha, Jenny Gunton, Michael d'Emden, Sof Andrikopoulos, and N. Wah Cheung have received honoraria, travel support or payment for participation in GSK advisory committees.

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1. Nissen SE, Wolski K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. N Engl J Med. 2007 Jun 14;356(24):2457-71
2. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. Lancet. 2007; 370: 1129-1136.
3. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545-59
4. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes.N Engl J Med 2008;358:2560-72.
5. Home DM et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD). Lancet 2009; 373: 2125-2135.