Diabetes mellitus constitutes an important risk factor of ischemic cardiopathy that confers to the patients a similar risk as having suffered a previous cardiovascular event. Nevertheless, at present, there are still many doubts about which are the best pharmacological strategies of prevention and treatment of the cardiovascular disease in patients with diabetes. The thiazolidinediones, rosiglitazones and pioglitazones, introduced in the market in 2000, seemed to exert beneficial effects from the cardiovascular point of view. However, the concern about the use of these drugs is still increasing after its commercialization, due to its association with the development of congestive heart failure (CHF) and more recently, with the increase of the acute myocardial infarction risk (AMI)–in the case of the rosiglitazone–. Several meta-analysis published in 2007 warned about an increase of the AMI risk over 40% and confirmed the much higher risk of CHF in this group of patients. Although the incidence of AMI during the follow-up was low (lower than 1.5%) and the mortality was similar in both groups, the data were still worrying and the authors advised against the clinical use of the rosiglitazone. These findings motivated the performance of an intermediate analysis of the RECORD study during the same year, which did not show differences in patients treated with rosiglitazone compared to the control group, therefore the trial continues as it was foreseen and the final results were published in June 2009.

The objective of the RECORD study was to evaluate the cardiovascular events risk in diabetic patients treated with rosiglitazone. It was a multicenter, open-label clinical study in which 4,447 recruited patients under treatment with metformin or sulphonylurea in monotherapy at maximum doses and who were randomized to receive rosiglitazone or a double treatment with sulphonylurea and metformin. During a mean follow-up period of 5.5 years, no differences were observed as regards to the death risk or hospitalization due to cardiovascular cause, complying besides with the rosiglitazone non-inferiority criterion. However, the patients treated with this drug showed, as expected, a higher incidence of CHF and of distal fractures compared to the control group. The levels of HbA1c were reduced more in the rosiglitazone group, with a relevantly higher proportion of patients who reached levels below 7%. The objective of the RECORD study was to clarify the influence of the drug in the AMI development, but the number of events was less than expected, probably due to the fact that most of the patients received an adequate cardiovascular prevention strategy; therefore, the study did not result conclusive.

Another recent clinical trial, the BARI-2D provided valuable information regarding to the treatment of diabetic patients, in this case with determined coronary disease but asymptomatic or paucisymptomatic. The intention was to compare, on one hand, an interventionist strategy (percutaneous or surgical, according to the medi-
cal criterion) with the conservative treatment and, on the other hand, the insulin treatment as regards to the treatment with insulin sensibilizing drugs. The survival after 5 years of follow-up was similar in all the groups and was in the region of 88%. The secondary objective of the study, the risk of major cardiovascular events was either different between the groups, except in patients proposed for revascularization surgery. In this stratum of patients who showed a more serious coronary disease, the risk of major cardiovascular events during the follow-up period was lower with the invasive strategy (22.4 versus 30.5%; p = 0.002), mainly dependent on the reduction of the non-fatal AMI risk. Though 42.1% of the patients corresponding to the medical treatment group suffered changes in their clinical condition that obliged the performance of a revascularization procedure, the conservative strategy demonstrated to be a good initial option in diabetic patients with ischemic cardiopathy. Even though the objective of the BARI-2D study was not to evaluate the cardiovascular risk of rosiglitazone, 52% of patients of the insulin-sensibilizing group received the drug. The incidence of CHF in this group, which included also patients treated with other antidiabetic drugs, was only slightly higher, compared to the group of patients assigned to insulin therapy, though it seems probable to be attributed to the use of rosiglitazone. As we have commented previously, no relevant differences were observed regarding to the development of ischemic events. On the other hand, the serious hypoglycemia events were more frequent in the group of patients treated with insulin.

The results of both clinical trials do not seem to confirm the increase of the AMI risk associated to the use of glitazones—and especially of rosiglitazone—though the low rate of AMI development might have conditioned these findings. Taking into account the CHF risk, both the rosiglitazone and the pioglitazone should be used with caution or be avoided in patients at high risk of developing such pathology. In this sense, in spite of the fact that the results of the meta-analysis and the observational studies suggest that the pioglitazone show a better cardiovascular safety profile, probably both drugs should be considered similar and corresponding to the same pharmacology class.

In conclusion, though the promising cardiovascular effects of rosiglitazone on carbohydrate metabolism seem to be outshined by the deleterious effects on water balance and lipid metabolism, the results of the RECORD and BARI-2D studies do not constitute a definitive proof to advise against the use of this drug in the treatment of the diabetic patients.

Declaration of potential conflict of interests
The authors state that there are no conflicts of interest as regards to the content of this article.

References