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Insulin Sensitizers and Heart Failure: An Engine Flooded with Fuel:

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Abstract

Rating—Of Importance

Introduction—In 2007, a meta-analysis of 42 randomized controlled trials involving the thiazolidinedione (TZD) rosiglitazone reported a 1.4 fold increase in the risk of acute myocardial infarction (AMI) compared with non-TZD therapies. Subsequently, another meta-analysis of 19 randomized controlled trials involving the TZD pioglitazone found a significant reduction in the composite outcome of nonfatal AMI, stroke, and all-cause mortality, thereby suggesting a potential difference in cardiovascular risk between the two TZDs.

Aims—To determine if the risk of serious cardiovascular harm is increased by rosiglitazone compared with pioglitazone.

Methods—The study was designed as a nationwide observational, retrospective, inception cohort of 227,571 Medicare beneficiaries aged 65 years or older (mean age, 74.4 years) who initiated treatment with rosiglitazone or pioglitazone through a Medicare Part D prescription drug plan from July 2006-June 2009 and who underwent follow-up for up to three years after TZD initiation. Individual and composite end points of AMI, stroke, heart failure, and all-cause mortality were assessed using the following: incidence rates by TZD, attributable risk, number needed to harm, Kaplan-Meier plots of time to event, and Cox proportional hazard ratios for time to event. Data were adjusted for potential confounding factors, with pioglitazone as a reference.

Results—A total of 8,667 end points were observed during the study period. The adjusted hazard ratio for rosiglitazone compared with pioglitazone was 1.06 (95% CI, 0.96-1.18) for AMI; 1.27 (95% CI, 1.12-1.45) for stroke; 1.25 (95% CI, 1.16-1.34) for heart failure; 1.14 (95% CI, 1.05-1.24) for death; and 1.18 (95% CI, 1.12-1.23) for the composite of AMI, stroke, heart failure, or death. The attributable risk for this composite end point was 1.68 (95% CI, 1.27-2.08) excess events per 100 person-years of treatment with rosiglitazone compared with pioglitazone. The corresponding number needed to harm was 60 (95% CI, 48-79) treated for one year.

Discussion—This study contributes to the rising tide of retrospective analyses suggesting post-marketing cardiovascular complications from the insulin sensitizing group of agents known as TZDs, especially rosiglitazone. In this study, rosiglitazone was associated with an increased risk of stroke, heart failure, and death and the composite of AMI, stroke, heart failure, or death. Limitations of the present study include the absence of randomization, a potential for misclassification, and a potential for unmeasured confounding factors. Still, we consider this work important for the following reasons.

Since the FDA approved rosiglitazone in May 1999, there have been concerns about adverse lipid effects, edema and increased cardiovascular risk.[1] Nissen and Wolski's 2007 meta-analysis of 42 clinical trials drew special attention to increased death and disability from

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cardiovascular complications in patients treated with rosiglitazone; thus many questions have been raised regarding the safety of this drug.[2] In 2007, the FDA revealed similar results in a separate meta-analysis showing a statistically significant increase in cardiovascular risk with the use of rosiglitazone.[3] The manufacturers of rosiglitazone therefore felt compelled to release an interim analysis of the RECORD Trial in 2007, with final results published in 2009. The RECORD Trial supports that the addition of rosiglitazone to glucose-lowering therapy in people with type 2 diabetes does indeed increase the risk of heart failure. However, the data were inconclusive about any possible effect on myocardial infarction, and it suggested no increased risk of overall cardiovascular morbidity or mortality in those treated with rosiglitazone compared with standard glucose-lowering drugs.[4] The RECORD Trial was criticized as being underpowered and flawed by the publication of unblinded, preliminary data.[5] In June 2009, the FDA therefore mandated an adequately powered cardiovascular outcomes study for rosiglitazone known as the TIDE Trial.

In July 2010, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee joint meeting with the Drug Safety and Risk Management Advisory Committee convened. At this meeting, Dr. Nissen (Cardiovascular Medicine Chairman of the Cleveland Clinic) presented an updated meta-analysis which again demonstrated an increased risk of AMI associated with rosiglitazone.[6] In addition, Dr. Graham (Associate Director of the FDA's Office of Drug Safety) presented the results of the retrospective cohort study discussed here, also suggesting adverse cardiovascular events associated with the use of rosiglitazone. A representative from the manufacturers of rosiglitazone was also present at the joint meeting to defend its product utilizing results from the RECORD Trial. One week following the advisory committee meeting, the FDA announced that the TIDE Trial has been placed on partial clinical hold, with no new patients eligible for enrollment until further notice. In addition, the FDA has instructed the manufacturers of rosiglitazone to update their investigators, institutional review boards and ethics committees involved in the TIDE Trial regarding any new safety information, along with information concerning the deliberations and votes of the FDA joint advisory committee meeting. The FDA is currently still evaluating all available information on rosiglitazone's safety, in conjunction with discussions of the recent advisory committee meeting, and will update the public on the outcome of its review and its implications for both the TIDE Trial and rosiglitazone.

Editor's comments

At the time of their introduction into clinical practice, TZDs were considered a major breakthrough for the management of type 2 (insulin resistant) diabetes mellitus. In hindsight, a better appreciation of the physiology of insulin resistance and the metabolic principles of insulin sensitizing agents seemed to be in order. The question herein lies: what is the possible mechanism, and are these adverse effects drug or class specific? In terms of adverse cardiovascular effects from TZDs, heart failure was arguably the earliest known and most widely accepted, leading to a FDA labeled precaution for TZD induced heart failure in 2002. Heart failure appears to be a class specific adverse effect, with studies suggesting the use of both rosiglitazone and pioglitazone associated with heart failure.[7] In 2007, a meta-analysis showed that pioglitazone was associated with increased heart failure without an associated increase in mortality.[8] However, these two drugs seem to have different cardiovascular event profiles, and mechanisms to explain these drug specific differences requires further investigation.

Now that both drugs have been shown to increase the risk of heart failure, some explanation is warranted. Why should a glucose lowering agent adversely affect the heart? Intuitively, one would expect the opposite. In a study designed to examine the relationship between

glycosylated hemoglobin (HbA1C) and adverse outcomes in diabetic patients with established heart failure, it was shown that patients with modest glucose control (7.1% < HbA1C < 7.8%) had the lowest risk of death in comparison to lower and higher HbA1C levels.[9] These data are consistent with that found in the ACCORD trial, which displayed an unexpected increase in mortality, without reduction in cardiovascular events, in diabetic patients assigned to the intensive glucose control treatment arm, targeting normal levels of HbA1C (below 6%).[10]

What if we were to speculate that insulin resistance actually protects the heart from being flooded with fuel? What if insulin resistance was viewed as a marker rather than a mediator of premature death and disability from cardiovascular disease? A dysregulated fuel supply would certainly impair cardiac function. Here we will present lines of evidence to suggest a cardioprotective role of insulin resistance. The first was traditionally considered anecdotal and paroxysmal. Consider the likes of Queen Victoria and Winston Churchill who lived well beyond their 80's despite evident morbid obesity, which is frequently associated with insulin resistance. Glucose lowering pharmacological agents were not known at the time as insulin was not discovered until 1921. Some studies have identified certain paradoxical patterns between cardiovascular risk factors and clinical outcomes in those with heart failure. For example, higher levels of body weight or cholesterol were associated with increased survival in patients with established heart failure.[11] A second line of evidence comes mainly from physiologic observations. It has been shown that the myocardium of patients with non-insulin dependent diabetes expresses a competent insulin-response system with respect to glucose metabolism, unlike that seen in the peripheral tissues and vasculature. In essence, this suggests that insulin resistance is mediated at the level of individual organs through distinct mechanisms.[12] Lastly, from a biochemical perspective, obesity itself may limit access of tissue to insulin by preventing interstitial dispersion, apart from its indirect downstream effects on insulin signaling.[13] Intracellularly, both fatty acids and glucose inhibit each other as they enter their pathways of oxidation.[14]

In closing, insulin and insulin-sensitizing agents enhance substrate uptake by a heart already flooded with nutrients, including fats and sugars. Current therapies should aim more at lowering substrate supply as opposed to promoting substrate uptake. As insulin sensitizing agents, TZDs have many effects on metabolic homeostasis, including increased substrate uptake by insulin responsive tissues, such as the heart. The consequence of fuel overload in the heart muscle cell is an imbalance of substrate uptake and oxidation. However, it seems easy to reason that the ultimate consequence is contractile dysfunction and, inevitably, heart failure.

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