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Letter by Musso et al Regarding Article, "Cardiac Outcomes After Ischemic Stroke or Transient Ischemic Attack: Effects of Pioglitazone in Patients With Insulin Resistance Without Diabetes Mellitus"

Giovanni Musso[1]M.D., Maurizio Cassader[2] Ph.D., Roberto Gambino[2] Ph.D.

[1]*Gradenigo HUMANITAS, Italy*

[2]*Department of Medical Sciences, University of Turin, Italy*

Corresponding author:

Giovanni Musso

Gradenigo HUMANITAS, Turin

C.so R. Margherita 8

10132 Turin, Italy

Phone: +39-11-8151283

E-mail: giovanni_musso@yahoo.it

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To the Editor

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we read with interest the article by Young et al[1], reporting a secondary analysis of the results from the Insulin Resistance Intervention after Stroke(IRIS) trial, reporting the effects of pioglitazone on cardiac outcomes after Ischemic Stroke or TIA in nondiabetic insulin resistant patients with prior acute cerebrovascular disease.

Notably, the IRIS is the first trial showing that a drug reduced the risk of diabetes[2] while simultaneously decreasing cardiovascular disease. As insulin resistance is not a disease entity but a condition predisposing to other diseases and pioglitazone does have unwanted effects, an important challenge will be to identify which insulin resistant nondiabetic patients would benefit most from this drug, in order to limit pioglitazone exposure to the subgroup at higher cardio-metabolic risk.

In the IRIS trial, the benefit of pioglitazone was more remarkable in patients with more pronounced metabolic derangement, like those with metabolic syndrome2. We recently observed similar, prominent benefits of pioglitazone on liver disease in nondiabetic patients with nonalcholic steatohepatitis (NASH), in whom this drug reversed steatohepatitis and, unique among all drugs evaluated in NASH to date, also advanced hepatic fibrosis[3]. NASH is the most common chronic liver disease in the world, is the hepatic manifestation of metabolic syndrome and may predispose to both diabetes and cardiovascular disease via different pathogenic mechanisms[4]. Hence, it would be important to assess if the presence of NASH (as assessed by liver enzyme elevation and/or abdomen ultrasound) identified those patients who had most benefit from pioglitazone with respect to their cardio-metabolic risk in the IRIS trial, similar to what has been observed with statins in the Greek Atorvastatin and Coronary Heart Disease Evaluation(GREACE) Study[5].

Disclosures

No author has any present or past conflict of interest to disclose

1 Young LH, Viscoli CM, Curtis JP, Inzucchi SE, Schwartz GG, Lovejoy AM, Furie KL, Gorman MJ, Conwit RA, Abbott JD, Jacoby DL, Kolansky DM, Pfau SE, Ling FS, Kernan WN; IRIS Investigators. Cardiac Outcomes After Ischemic Stroke or TIA: Effects of Pioglitazone in Patients with Insulin Resistance Without Diabetes. Circulation. 2017 Feb 28.pii: CIRCULATIONAHA.116.024863. doi: 10.1161/CIRCULATIONAHA.116.024863. [Epub ahead of print]

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3 Musso G, Cassader M, Paschetta E, Gambino R. Thiazolidinediones and Advanced Liver Fibrosis in Nonalcoholic Steatohepatitis: A Meta-analysis. JAMA Intern Med. 2017 Feb 27. doi: 10.1001/jamainternmed.2016.9607

4Musso G, Cassader M, Gambino R. Non-alcoholic steatohepatitis: emerging molecular targets and therapeutic strategies. Nat Rev Drug Discov. 2016; 15:249-74.

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