EDITORIAL

Can drugs influencing the renin–angiotensin system prevent diabetes mellitus? A lesson from randomized clinical trials

Krzysztof J. Filipiak

1st Department of Cardiology, Warsaw Medical University, Warsaw, Poland

Al-Mallah et al. [1] present in the current issue of *Cardiology Journal* a new meta-analysis studying the impact of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) on the incidence of new onset diabetes mellitus (DM). In 18 carefully selected randomized controlled trials, they report this endpoint with ACEI or ARB therapy *vs* comparators in more than 100,000 patients. ACEI/ARB use was associated with a decrease in new onset DM of around 22% for ACEI and 20% for ARB. So, one of the conclusions to be drawn from this meta-analysis is that this effect does not differ between ACEIs and ARBs. This fully accords with the results of the prospective, landscape trial of head-to-head ramipril *vs* telmisartan (the ONTARGET trial), in which the new incidences of DM were very similar in both groups [2].

In 1999, Yusuf et al. [3] reported a decrease in new cases of DM in the HOPE trial in those taking ramipril 10 mg daily *vs* placebo, although this was a *post hoc* analysis. In the DREAM trial, ramipril 15 mg daily did not prevent new cases of DM. However, such a primary endpoint was reached in the subgroup of those < 50 years old, and ramipril was statistically significantly better than placebo as far as regression from glucose intolerance was studied. It also tended to be better in those with lower body mass index, lower waist-to-hip ratio and those whose systolic blood pressure was below 140 mm Hg [4]. Thus, it could be concluded that ramipril 15 mg

daily may prevent DM in the very early stages of metabolic syndrome.

The meta-analysis of Al-Mallah et al. [1] was carried out in 2009, without knowing about the NAVIGATOR trial results. It is interesting to look at the carefully selected trials in their meta-analysis. From those trials with ACEIs (captopril, enalapril, lisinopril, quinapril, ramipril and trandolapril) only quinapril did not reach statistical significance in DM prevention in its only trial reporting this endpoint. Thus, the DM prevention by ACEIs might be interpreted as the class effect of all those drugs. However, if the regulatory agency was to one day consider the potential indications for any ACEI in DM prevention, only five ACEIs could be discussed: captopril, enalapril, lisinopril, trandolapil and ramipril. These are, by the way, the ACEIs with the strongest evidence for the reduction of the most important endpoint in clinical trails — total mortality.

When we look at the trials selected for ARBs (candesartan, losartan, telmisartan and valsartan), only candesartan, losartan and valsartan might be considered for DM prevention by regulatory agencies, although from the pharmacological point of view, telmisartan seems very interesting in terms of DM prevention. It is the ARB which has the most potent peroxisome proliferators-activated receptor-gamma (PPAR-γ) activity, with potential additional insulin-sensitizing/antidiabetic effect [5]. It is very hard to explain why these pharmacological properties of telmisartan do not differentiate this drug from its relatives in the ARB family as far as the results of the clinical trials published to date are concerned.

Address for correspondence: Krzysztof J. Filipiak, MD, PhD, FESC, 1st Department of Cardiology, Warsaw Medical University, Banacha 1a, block D, 02–097 Warsaw, Poland, tel: + 48 22 599 18 18, fax: + 48 22 599 19 57, e-mail: krzysztof.filipiak@wum.edu.pl

If we consider solely the positive trials for DM prevention, and narrow our focus onto only those where DM prevention was the pre-specified end-point, only candesartan (ALPINE, CASE) and valsartan (VALUE, NAVIGATOR — not included in this meta-analysis) meet the potential new indication according to European (EMEA) or American (FDA) regulatory agencies, in my opinion. Of those two drugs, valsartan is probably closer to such an indication, due to the recently published NAVIGATOR trial where this endpoint was a pre-specified and primary one [6].

The Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research study (NAVIGATOR), presented in March 2010 at a meeting of the American College of Cardiology, was a multinational, double blind and randomized trial that enrolled patients between January 2002 and January 2004. One of the three primary endpoints of NAVIGATOR was to look for reductions in the incidence of new onset type 2 diabetes combined with a reduction in postprandial hyperglycemia, a blockade of the renin–angiotensin system, or both. Contrary to the failure of nateglinide, valsartan *vs* placebo significantly reduced the incidence of DM by 14% during follow-up. The results of this trial support the meta-analysis presented in the current issue of *Cardiology Journal*, and if these results were to be incorporated in the meta-analysis, it probably would not the change the outcome. So we can conclude that ACEIs and ARBs decrease the probability of new cases of DM by up to 20%.

Acknowledgements

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