Rev Clin Esp. 2017;xxx(xx):xxx–xxx

Revista Clínica Española

www.elsevier.es/rce

REVIEW

Cardiovascular safety of noninsulin antidiabetic drugs: Facts and promises☆

A. García-Lledó[a,b,*], A.M. de Santiago-Nocito[c,d], F.J. de Abajo[e,f]

[a] *Servicio de Cardiología, Hospital Universitario Príncipe de Asturias, Spain*
[b] *Departamento de Medicina y Especialidades Médicas, Facultad de Medicina y Ciencias de la Salud, Universidad de Alcalá, Alcalá de Henares, Madrid, Spain*
[c] *EAP Cogolludo, Guadalajara, SESCAM, Spain*
[d] *Cátedra SEMERGEN-Universidad de Alcalá, Alcalá de Henares, Madrid, Spain*
[e] *Unidad de Farmacología Clínica, Hospital Universitario Príncipe de Asturias, Spain*
[f] *Departamento de Ciencias Biomédicas, Facultad de Medicina y Ciencias de la Salud, Universidad de Alcalá, Alcalá de Henares, Madrid, Spain*

Received 23 November 2016; accepted 4 February 2017

KEYWORDS
Diabetes mellitus;
Cardiovascular risk;
Oral diabetes drugs

Abstract Non insulin antidiabetic drugs are widely used in patients with type 2 diabetes. However, the drugs' effect in terms of reducing cardiovascular risk has been the subject of controversy. In 2008, based on the evidence of cardiovascular risk resulting from the use of a number of non insulin antidiabetic drugs, the US Food and Drug Administration published directives on the need to perform cardiovascular safety studies. These directives have helped obtain more evidence, such that at present there are 2 families of drugs that can reduce cardiovascular risk. These recent data have helped us add the reduction of cardiovascular morbidity and mortality to the objective of controlling blood glucose. Nevertheless, research continues with the development of new long-term studies.

PALABRAS CLAVE
Diabetes mellitus;
Riesgo cardiovascular;
Antidiabéticos orales

Seguridad cardiovascular de los antidiabéticos no insulínicos: hechos y promesas

Resumen Los antidiabéticos no insulínicos son fármacos de uso muy extendido en los pacientes con diabetes tipo 2, cuyo efecto sobre la reducción del riesgo cardiovascular ha sido objeto de controversia. En el año 2008, ante la evidencia del riesgo cardiovascular derivado del uso de algunos antidiabéticos no insulínicos, la *Food and Drug Administration* americana publicó una

☆ Please cite this article as: García-Lledó A, de Santiago-Nocito AM, de Abajo FJ. Seguridad cardiovascular de los antidiabéticos no insulínicos: hechos y promesas. Rev Clin Esp. 2017. http://dx.doi.org/10.1016/j.rce.2017.02.007
* Corresponding author.
E-mail address: alberto.garcia-lledo@uah.es (A. García-Lledó).

directriz sobre la necesidad de realizar estudios de seguridad cardiovascular. Ello ha contribuido a disponer de más evidencia, de manera que en el momento actual existen dos familias de fármacos que podrían reducir el riesgo cardiovascular. Estos datos recientes nos permiten añadir, al objetivo de controlar la glucemia, el de reducir la morbimortalidad cardiovascular. No obstante, la investigación continúa con el desarrollo de nuevos estudios a largo plazo.

Background

Type 2 diabetes mellitus (DM2) affects 13.8% of the population of Spain, although 6.8% of those with DM2 are unaware of it.[1] DM2's association with age, physical inactivity and excess weight explains the increase in its prevalence.[2] The microvascular damage makes DM2 the leading cause of blindness, end-stage renal failure and, due to the neuropathy, nontraumatic leg amputation.[3] The mortality of patients with diabetes is increasing, with 60% corresponding to cardiovascular causes.[4,5] Approximately 30% of patients with stable or acute ischemic heart disease have DM2,[6,7] as well as a poorer outcome.[7]

Surprisingly, there are few noninsulin antidiabetic drugs (NIAD) that have been shown to reduce the cardiovascular risk (CVR), and there are questions about the safety of a number of NIADs. For years, it has been accepted that controlling blood glucose is beneficial in and of itself. The alerts for drugs such as muraglitazar[8] and rosiglitazone[9] that, while controlling blood glucose, increase the CVR motivated the US Food and Drug Administration (FDA) to issue a directive requiring pharmaceutical companies to conduct cardiovascular safety studies with the new antidiabetic drugs (Table 1).[10] The directive required noninferiority studies with narrower statistical margins, more patients, longer study periods and the inclusion of patients with high CVR. In the following 3 years, the number of trials doubled, and the number of patients included in these trials increased 6-fold.[11] The emerging results are creating enormous expectations but also some degree of controversy.

Table 1 Summary of the food and drug administration directives for the assessment of cardiovascular risk in new antidiabetic therapies.

For studies with new designs
For phase 2 and 3 studies, there should be an independent prospective adjudication committee for cardiovascular events. The minimum cardiovascular events to be recorded are defined.
Phase 2 and 3 studies should include patients with high cardiovascular risk, long-standing diabetes, advanced age and kidney damage.
A longer duration is proposed for safety studies (at least 2 years).
Phase 2 and 3 studies should be designed to facilitate their subsequent inclusion in a meta-analysis.
The sponsors should deliver a protocol that describes the statistical methods of the proposed meta-analyses.
Recommendations are made on the types of studies and identifiers for variables to be included.
The differences and similarities of the events by subgroup should be examined, when possible, indicating as examples sex, race and age.
For completed studies, before submitting them for evaluation
The statistical margins for the confidence interval are narrowed in the noninferiority studies regarding cardiovascular events. When it is not possible to demonstrate them with meta-analyses, new studies should be performed.
If the premarketing request shows clinical data outside the previous demands but within less demanding predefined ranges and the overall risk–benefit analysis supports the approval of the drug, a specific study may be requested to demonstrate the safety adjusted to the new required limits, once the drug has been marketed.
The characteristics these studies must have for their evaluation and inclusion in meta-analyses are defined.

Source: U.S. Department of Health and Human Services.[10]

Trials with noninsulin antidiabetic drugs in type 2 diabetes mellitus

In 1970, the University Group Diabetes Program study was published,[12] the first randomized study on DM2 designed to demonstrate the usefulness of treating asymptomatic hyperglycemia. The study included branches with insulin, tolbutamide, phenformin and placebo. The study showed no overall benefit and suggested an increase in cardiovascular mortality in the sulfonylurea branch. The study design was widely criticized.[13] Nevertheless, it has been shown that treatment with sulfonylureas blocks the myocardial adenosine triphosphate-sensitive K+ channels and impedes ischemic preconditioning in the long term, a protective mechanism whose block would explain the excess mortality.[14] These potential harmful effects have been supported by a Danish registry that included more than 100,000 patients followed for up to 9 years.[15] The registry showed an excess of total mortality, cardiovascular mortality and ischemic events in the patients treated with