

Metformin: Should it be the first therapeutic option in the patient with high-risk diabetes?

Metformina: ¿Debería ser la primera opción terapéutica en el paciente con diabetes de alto riesgo?

Agonist

HUGO DANIEL SANABRIA¹

Diabetes mellitus (DM) is classically defined as a metabolic disorder characterized by the presence of hyperglycemia secondary to defects in insulin secretion or action. Type 2 diabetes (DM2), the most prevalent entity, is frequently associated with other components of the metabolic syndrome and its etiopathogenesis shows different pathophysiological alterations, insulin resistance being one of the central mechanisms.

Diabetes mellitus is undoubtedly one of the cardiovascular risk factors with greatest impact, and cardiovascular disease is the most frequent cause of death among patients with diabetes. Although the role of glycemic control on cardiovascular effect is controversial, there is a well known association between intensified control and the reduction of other complications with a high burden of morbidity and mortality, such as retinopathy, peripheral nephropathy and diabetic nephropathy.

Metformin is one of the most widely used drugs as first-line treatment for the management of hyperglycemia in patients with DM2, due to its proven efficacy in lowering blood glucose (it reduces HbA1c between 1% and 2%, depending on its initial value), added to its adequate safety profile without risk of hypoglycemia and with few serious adverse events observed after more than 60 years of experience in its use. It has few relevant drug interactions in routine clinical practice and its low cost allows wide access as the first tool for metabolic control.

Metformin reduces blood glucose by improving peripheral insulin sensitivity, mainly decreasing hepatic glucose production and increasing glucose uptake by the skeletal muscle. These effects are produced through the regulation of the energy balance and redox potential at the mitochondrial level. In addition, it exerts an important action on the gastrointestinal tract, modulating GLP-1, bile acid content and microbiota composition. On the other hand, it would modulate inflammation by direct and indirect effects on cells of the immune system in different organs such as the liver, muscle and digestive tract, all mechanisms

favoring the reduction of insulin resistance typical of DM2. (1) These mechanisms allow including the use of metformin as a preventive strategy for DM2. (2, 3)

Besides the normoglycemic effect described, metformin has been associated with a beneficial impact on the vascular endothelium by restoring reduced nitric oxide production in hyperinsulinemic and hyperglycemic states. A favorable effect has been observed even on the lipid profile and, in experimental studies, on cardiomyocyte metabolism, platelet function and cell proliferation, in addition to the aforementioned anti-inflammatory effect. (4)

Taking into account its effectiveness in glycemic control, its insulin-stabilizing action and its pleiotropic effects, one could ask: is metformin associated with a reduction in cardiovascular events? Various observational studies link metformin with a reduction in cardiovascular events when compared with a diet plan, sulfonylureas, or insulin therapy. (5) For example, the REACH registry that evaluated 19691 patients with DM2 observed a lower rate of cardiovascular death (HR 0.79; 95% CI 0.65-0.96) and overall mortality (HR 0.76; 95% CI 0.65-0.89) in patients who used metformin. Similar results were observed in the subgroup of patients of the same registry with diabetes and heart failure. (6) Of course, it is not possible to rule out that the observed benefit was secondary to an increase in cardiovascular events of the comparator drugs.

Evidences available from randomized clinical trials are scarcer. One of them is the UKPDS study that evaluated 1704 patients with newly diagnosed DM and overweight assigned to intensive control with metformin, sulfonylureas or insulin vs. conservative treatment with a diet plan. After 10 years of follow-up, intensive glycemic control based on metformin was associated with a significant reduction of myocardial infarction (HR 0.61 [95% CI 0.41-0.89]), death related to diabetes (HR 0.58 [95% CI 0.37-0.91]) and overall mortality (HR 0.64 [95% CI 0.45-0.91]) when compared with conservative treatment. (7) Even when the various strategies were compared in the intensive con-

trol group of the UKPDS study, patients on metformin treatment presented lower incidence of stroke and overall death. Moreover, in a subsequent open-label follow-up of 10 years, patients initially treated with metformin continued to present a lower incidence of infarction and mortality despite achieving similar glycemic controls. (8) It should be considered that it was an open-label study comparing treatment strategies, and this analysis, although prespecified, was performed on a selected group (overweight patients) incorporating only 342 patients into the metformin group. Besides, it was a population at low cardiovascular risk, with patients with recent diagnosis and no previous events.

Other randomized clinical trials and different meta-analyses have been less conclusive on the cardiovascular impact of metformin, and have not shown significant benefits. (9) (10) However, it should be clarified that none of these clinical trials incorporated more than 350 patients in the metformin arm and their follow-up period was very uneven, ranging from 6 months to 4 years. There is an evident difference when compared to modern cardiovascular safety studies involving 3000-17 000 patients. A modern clinical trial evaluating the cardiovascular impact of metformin vs. placebo with enough statistical power to generate definitive conclusions would hardly be carried out.

Considering the evidence of the cardiovascular benefit of SGLT2i inhibitors (SGLT2i) and GLP-1 receptor agonists (GLP-1ra), should we replace metformin with these drugs as first-line treatment in DM2 patients and high cardiovascular risk?

Once again, the ultimate answer would only be obtained from a clinical trial evaluating the cardiovascular impact of a first-line strategy based on metformin vs. SGLT2i or GLP-1ra which will require thousands of patients and extended follow-ups greater than 5 years, which probably will not be performed. Therefore, I propose to observe, in order to give an answer, the inclusion criteria of the studies and the characteristics of the populations included in the cardiovascular safety clinical trials with SGLT2i and GLP-1ra (Tables 1 and 2).

We can see that most of the patients included had more than 10 years of disease progression (range between 10 and 15 years) and inadequate glycemic controls (mean HbA1c in most studies between 8% and 9%). Less than 1% of the patients included were without concomitant antidiabetic treatment, and metformin was the most widely used drug. From this observation, it appears that the antidiabetic drugs evaluated in these studies were not incorporated as first-line treatment (they were second- and even third-line treatment). Although, based on some group

Table 1. Baseline characteristics of the clinical trials demonstrating cardiovascular benefits with GLP-1 receptor agonists

	HARMONY (11) Albiglutide vs. placebo	LEADER (12) Liraglutide vs. placebo	SUSTAIN-6 (13) Semaglutide SC vs. placebo	REWIND (14) Dulaglutide vs. placebo
Patients(n)	10 793	9340	3297	9901
Age (years)	64	64	65	66
PCD (%)	100	81	83	31.5
High CD risk without previous events (%)	0	19	17	68.5
A1c inclusion criteria (%)	≥7	≥7	≥7	≤9.5
Mean HbA1c (%)	8.7	8.7	8.7	7.3
Time of DM progression (years)	14.1	12.8	14.3	10.5
Previous Metformin (%)	73	76.5	73.3	81

PCD: Previous cardiovascular disease. DM: Diabetes mellitus.

Table 2. Baseline characteristics of clinical trials demonstrating cardiovascular benefits with SGLT-2 inhibitors

	EMPAREG (15) Empagliflozin vs. placebo	CANVAS (16) Canagliflozin vs. placebo	DECLARE (17) Dapagliflozin vs. placebo	CREDENCE (18) Canagliflozin vs. placebo
Patients(n)	7020	10 142	17 160	4401
Age (years)	63	63	64	63
PCD (%)	100	67	40.6	50
High CD risk without previous events (%)	0	34.4	59	50
A1c inclusion criteria (%)	7-10	7-10.5	6.5-12	6.5-12
Mean HbA1c (%)	8.1	8.2	8.3	8.3
DM time of evolution (years)	57% > 10	13.5	11	15.8
Previous Metformin (%)	74.1	78	78.5	57.8

PCD: Previous cardiovascular disease. DM: Diabetes mellitus.

sub-analyses, there seems to be an agreement that the cardiovascular benefit observed is independent of baseline HbA1c, the duration of diabetes and the presence or absence of metformin, perhaps the final clinical impact is probably not exactly the same in recently diagnosed patients with not so high hemoglobin and, especially, in those who have not developed cardiovascular events.

On the other hand, patients with DM2 at higher cardiovascular risk, where the benefit of SGLT2i and GLP1ra is more clinically relevant, usually have a longer time of DM evolution and poorer glycemic control, as shown by the characteristics of the populations included in the clinical trials analyzed. Therefore, this group of patients with DM2 will necessarily require the addition of other groups of drugs for the management of hyperglycemia. Frequently, DM2 is a progressive disease that requires the association of treatments that ideally act on different mechanisms of the pathophysiological process for adequate glycemic control. In the UKPDS study, which included recently diagnosed DM2 patients, 50% of them required the incorporation of a second agent before the third year of follow-up to maintain adequate glycemic control. (19)

Moreover, the early combination of drugs for the treatment of diabetes is associated with a greater durability of metabolic control, as evaluated in the VERIFY study using a sequential strategy based on metformin monotherapy vs. an initial dual combination of metformin plus vildagliptin. The incidence of treatment failure, defined by two consecutive A1c values $>7\%$, was 62.1% in metformin monotherapy with a mean time of 36 months vs. 43% with the dual combination strategy with a mean time of 61 months. (20) In addition, early and intensive glycemic control by combining drugs has been associated with a lower incidence of diabetes-related complications as long as this goal is safely achieved without increasing the risk of hypoglycemia. An observational study involving 34 737 patients during a mean follow-up of 13 years reported an increase in the incidence of microvascular and macrovascular complications (HR 1.20 [95% CI 1.06–1.36]) among those patients who did not achieve a glycemic control with A1c $<6.5\%$ during the first year after diagnosis. (21) Once again, it is difficult to think about achieving and maintaining these objectives by proposing the start of pharmacological treatments with a single agent.

Finally, we cannot fail to mention, in our reality, the cost of treatments used for the management of diabetes. From data collected at the time of writing this document, the monthly cost of using 2000 mg per day of metformin was around 1500 to \$2000, while the cost of SGLT2i could rise from \$ 5000 to \$10000 and for GLP-1ra from \$18000 to \$30000 per month. Certainly, the development of cost-effectiveness analyses in our country can help us to make decisions if we wish to choose a single first-line drug. However, this situation, as we have commented, is less likely to oc-

cur in the group of patients about which we are debating, because most patients at high cardiovascular risk will require two or more drugs as an initial strategy for adequate glycemic control.

In my opinion, this is not the time to ask ourselves whether we should displace metformin as the first-line hyperglycemic treatment for patients with DM2. It is time for us to consider the early association of metformin with drugs with proven cardiovascular impact, since adequate glycemic control continues to be a central strategy to reduce the high burden of morbidity and mortality in our patients.

Conflicts of interest

Dr. Hugo Sanabria has received fees as speaker and member of the advisory board from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Novo Nordisk, as speaker from Montpellier, Roemmers and Servier, and financial support for research from Bayer and Novo Nordisk.

REFERENCES

- Foretz M, Guigas B, Viollet B. Understanding the glucoregulatory mechanisms of metformin in type 2 diabetes mellitus. *Nat Rev Endocrinol* 2019;15:569-89. doi:10.1038/s41574-019-0242-2
- Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393-403. doi: 10.1056/NEJMoa012512.
- Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. *Lancet Diabetes Endocrinol* 2015;3:866-75. doi: 10.1016/S2213-8587(15)00291-0
- Dziubak A, Wojcicka G, Wojtak A and Beltowski J. Metabolic Effects of Metformin in the Failing Heart. *Int J Mol Sci* 2018;19:2869. doi: 10.3390/ijms19102869.
- Eurich DT, Weir DL, Majumdar SR, Tsuyuki RT, Johnson JA, Tjosvold L, Vanderloo SE, McAlister FA. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure systematic review of observational studies involving 34 000 patients. *Circ Heart Fail* 2013;6:395-402. doi: 10.1161/CIRCHEARTFAILURE.112.000162
- Roussel R, Travert F, Pasquet B, Wilson PWF, Smith SC, Goto S, Ravaud P, Marre M, Porath A, Bhatt DL and Steg PG. Metformin use and mortality among patients with diabetes and atherosclerosis. *Arch Intern Med* 2010;170:1892-9. doi: 10.1001/archinternmed.2010.409
- UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive bloodglucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854-65. doi: 10.1016/S0140-6736(98)07037-8
- Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577-89. doi: 10.1056/NEJMoa0806470
- Palmer SC, Mavridis D, Nicolucci A, Johnson DW, Tonelli M, Craig JC, et al. Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes: A Meta-analysis. *JAMA* 2016;316:313-24. doi: 10.1001/jama.2015.14654
- Griffin SJ, Leaver JK, Irving GJ. Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes. *Diabetologia* 2017;60:1620-9. doi: 10.1007/s00125-017-4337-9.
- Hernandez AF, Green JB, Janmohamed S, D'Agostino RB, Granger CB, Jones NP, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet*.

2018;392:1519-29. doi: 10.1016/S0140-6736(18)32261-X

12. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2016;375:311-22. doi: 10.1056/NEJMoa1603827

13. Marso SP, Bain SC, Consoli A, Elashewitz FG, Jódar E, Leiter LA, et al; SUSTAIN-6 Investigators. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2016;375:1834-44. doi: 10.1056/NEJMoa1607141

14. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*. 2019;394:121-30. doi: 10.1016/S0140-6736(19)31149-3.

15. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015;373:2117-28. doi: 10.1056/NEJMoa1504720

16. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 2017;377:644-57. doi: 10.1056/NEJMoa1611925

17. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al.

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2019; 380:347-57. doi: 10.1056/NEJMoa1812389

18. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charrytan DM, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med* 2019;380:2295-306. doi: 10.1056/NEJMoa1811744

19. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA*. 1999;281:2005-12. doi: 10.1001/jama.281.21.2005

20. Matthews DR, Paldanius PM, Proot P, Chiang Y, Stumvoll M, Del Prato S; VERIFY study group. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. *Lancet* 2019;394:1519-29. doi: 10.1016/S0140-6736(19)32131-2.

21. Laiteerapong N, Ham SA, Gao Y, Moffet HH, Liu JY, Huang ES, et al. The Legacy Effect in Type 2 Diabetes: Impact of Early Glycemic Control on Future Complications (The Diabetes & Aging Study). *Diabetes Care* 2019;42:416-26. doi: 10.2337/dc17-1144

ANTAGONIST

AUGUSTO LAVALLE COBO¹

For a long time, metformin has been the first-choice drug in the therapeutic scheme of most type II diabetes (DM2) patients. In the last years, cardiovascular (CV) safety studies of drugs belonging to GLP-1 receptor agonists (GLP-1ra) and sodium-glucose co-transporter-2 inhibitors (SGLT2i) have evidenced a decrease of cardiovascular events, such as major adverse cardiovascular events (MACE), hospitalizations for heart failure (HF) and mortality, even in patients with established cardiovascular disease. These results have to consider whether metformin should still be the first-choice drug in patients with DM2, especially those at high CV risk.

This question would be easily answered if comparative studies existed between metformin and these new drugs. However, there are currently no studies providing these data, so I will try to answer the question by analyzing, first, the evidence by which metformin has the privilege of being foremost in the podium and second, the information available on the use of GLP-1ra and SGLT2i.

The ideal treatment of DM2 patients should satisfy the following premises: 1) HBA1c reduction; 2) absence of weight gain (ideally, reduction); 3) low risk of hypoglycemia; 4) reduction of microvascular complications; 5) reduction of macrovascular complications; 6) reduction of CV and/or total mortality. Does metformin fulfill all these points? There is evidence about the benefit in terms of metabolic control, weight loss, good tolerance and low risk of hypoglycemia. (1) It is also known that a good metabolic control is associated with reduction of microvascular complications. Therefore, metformin treatment meets the first four pre-

ises postulated above. However, does it reduce macrovascular complications? Does it have an impact on mortality? So many years of presence and experience with this drug make one think that there is information from methodological high quality clinical trials and a large number of patients assessed to answer this question. However, when we evaluate this evidence, as we will see next, we find that the answer does not fulfill the points mentioned above.

The most cited study is the macrovascular impact of metformin reported in the United Kingdom Prospective Diabetes Study (UKPDS). (2) The study showed after 10 years of follow-up, 39% risk reduction of acute myocardial infarction (AMI), 41% risk reduction of vascular stroke and 36% of total mortality in the group assigned to intensive metformin treatment compared with a group that received intensive sulfonylurea (SU) or insulin treatment. These attractive numbers would allow to declare that metformin meets requirements 5 and 6 to be considered as an ideal drug for the treatment of DM2. However, I would like to make some comments about this study. In the first place, its primary objective was not to compare metformin treatment with other therapeutic strategies, but designed to assess if the intensive treatment or a strict glycemic control (with SU or insulin) improved the outcome of patients with DM2 compared with those who received conventional treatment (at that time diet and exercise). (3) A second branch of the study evaluating the subgroup of 1704 patients with overweight/obesity (52% of the UKPDS population) compared intensive treatment with metformin (342 patients) versus intensive treatment with SU

¹ Coordinator of the Cardiology Department, Sanatorio Finocchio - Former Head of SAC Cardiovascular Epidemiology and Prevention Council - E-mail: augustolavalle@gmail.com

or insulin (951 patients) and the reduction of events cited above derives from this analysis. Secondly, in addition to including a very small number of patients compared with CV safety studies of the different antidiabetic drugs, the number of events described in the study was also low (39 AMI, 12 stroke and 50 deaths in the metformin group). At the time of study performance patients were not receiving statins, assuming from the evidence available now, that had they been used, the number of events would possibly have been less. If a study of these characteristics about a X drug were currently published, is there a possibility that from these results drug X would come to occupy the first place in the therapeutic algorithm of most clinical practice guidelines in the world? My answer is No.

Even if the UKPDS is the most cited study about the CV impact of this drug, it is not the only one. A meta-analysis including 12 randomized clinical trials comparing metformin versus placebo or another intervention in DM2 patients with CV events, did not show the same results as the UKPDS study. (4) The total number of patients in the study was 2079 (again a low n), and 416 AMI, 111 strokes 347 CV deaths and 593 all-cause deaths were reported. Although there was evidence of reduced CV mortality, all-cause mortality and AMI in patients receiving metformin, none of them attained statistical significance. Moreover, the risk for stroke was not reduced.

According to what has been expressed up to here, it is shown that the quality of the evidence that considers metformin as a first-line therapeutic option in DM2 patients at high CV risk, is low. Similarly, to have a vision more in line with reality, it is important to analyze with what intervention it is compared. It is in this line related to treatment of DM2 patients where no studies of better methodological quality appeared throughout time with evidence discrediting metformin, but new antidiabetic agents emerged. Ten years after the publication of the UKPDS study, the main regulatory agencies started to demand CV safety stud-

ies from the pharmaceutical industry to approve new antidiabetic drugs. It was the results of the SGLT2i and GLP-1ra CV safety studies that led to reconsider the place of metformin in the therapeutic algorithm.

The first study of the new oral antidiabetic agents demonstrating reduced CV events was the EMPA-REG-OUTCOME trial. (5) In a population of 7020 DM2 patients at high CV risk (including patients with established CV disease) receiving recommended antidiabetic treatment, use of empagliflozin compared with placebo showed a significant 14% reduction of MACE, 38% CV death, 32% all-cause death and 35% hospitalizations for HF. Continuing with SGLT2i, canagliflozin reduced the risk of MACE by 15% and of hospitalization for HR by 33% in a population at high CV risk but with a lower number of patients than the previous study. (6) Finally, in a population of more than 17 000 DM2 patients and lower CV risk, dapagliflozin reduced by 17% the composite endpoint of CV mortality and hospitalization for HF. (7)

GLP-1ra also showed reduction of CV events in their studies, except for hospitalizations for HF, where the results were not lower than the control group. In the LEADER study, evaluating the use of liraglutide in a population of DM2 patients, mostly with established CV disease (81%), a significant 13% reduction of MACE, 22% CV mortality and 15% all-cause death was observed. (8) In a similar population with respect to the presence of CV disease, semaglutide significantly reduced MACE by 26% and the incidence of non-fatal stroke by 39%. (9) Same as with SGLT2i agents, the use of these drugs was also evaluated in a population including mainly DM2 patients in primary prevention. In this case, dalaglutide was superior to placebo with a significant 12% reduction of MACE and 24% of non-fatal stroke. (10)

In addition to the CV benefit mentioned, these pharmacological groups, specially SGLT2i, showed an additional renal effect. This is not a minor finding, since kidney injury is an important comorbidity

STUDY	Total N	With Metformin		Without Metformin	
		n	%	n	%
EMPA-REG-OUTCOME (Empagliflozin)	7020	5193	74	1827	26
CANVAS PROGRAM (Canagliflozin)	10 142	7825	77.2	2317	22.8
DECLARE (Dapagliflozin)	17 160	14 068	82	3092	18
Sigt-2i (Total)	34 322	27 086	79	7236	21
LEADER (Liraglutide)	9340	7144	76.5	2196	23.5
SUSTAIN-6 (Semaglutide)	3297	2414	73.2	883	26.8
REWIND (Dulaglutide)	9901	8037	81.1	1864	18.8
Glp-1ra (Total)	22 538	17 595	78	4934	22

Table 1.

in DM2 patients associated with increased mortality and incidence of CV events.

Both pharmacological groups demonstrated to be superior to conventional treatment in terms of reducing CV events when compared in all the CV risk spectrum (primary and secondary prevention), providing greater benefit that even attained significant reduction of CV and all-cause mortality in higher risk populations.

The number of patients enrolled only in the treatment arm of these studies was 34 322 patients for SGLT2i and 22 538 for GLP-1ra, well above the 364 patients included in the UKPDS study and the 2079 patients of the metformin meta-analysis cited.

Despite what was earlier mentioned, one of the mainstays used to justify the indication of metformin as first-line treatment is that the studies evaluating these new molecules (SGLT2i and GLP-1ra) were made on the basis of treatment that included metformin. Although this is true, it is a half-truth, as 7236 (21%) patients enrolled in SGLT2i studies and 4934 (22%) included in GLP-1ra trials were not receiving metformin at the time of entering the study (Table 1). In the already mentioned EMPA-REG-OUTCOME study, primary outcome results from patients with or without metformin as basic treatment reported MACE reduction of 8% (HR 0.92, 95% CI 0.77-1.10) and 28% (HR 0.72 95% CI 0.56-0.94), respectively. The number of events in the empagliflozin arm was 282, more than twice those observed in the UKPDS study. In the HARMONY study, assessing albiglutide, a GLP-1ra agent, in a population of DM2 patients with CV disease, MACE reduction occurred in 23% of patients with metformin and 21% of those without metformin. (11) These data correspond to subgroups, and hence they should be considered in this context, which means that we cannot assert that empagliflozin is more effective than metformin, but we can assume that the effect of these drugs is independent of the concomitant use of metformin. Moreover, the assessment of metformin in the UKPDS study is a subgroup analysis, so I ask myself if we should not have the same consideration when analyzing these data.

Finally, an argument that could support the use of metformin as a first-line therapeutic option lies on the pathophysiological complexity of DM2 and the involvement of different organs and systems [the so-called “ominous octet” postulated by DeFronzo (12)]. This contention is based on the beneficial impact this drug might have on some of the “octet” components. With the emergence of GLP-1ra agents, this argument seems to have become obsolete, as incretins would impact on more “octet” constituents, a hypothesis postulated by DeFronzo himself. (13)

As a result of these considerations, it can be understood why clinical practice guidelines on DM2 patient management started to position SGLT2i and DLP-1ra agents at the same level or even above metformin in the different therapeutic algorithms. (14, 15)

Based on this analysis, I consider that metformin

should not be the first-line therapeutic option in DM2 patients at high CV risk, at least as monotherapy. In case it is decided to initiate the treatment of this group of patients with metformin, this choice should not delay the use of drugs with proven cardiovascular benefit.

Conflicts of interest

None declared. (See authors' conflicts of interest forms on the website/Supplementary material).

REFERENCES

1. Sanchez-Rangel E, Inzucchi S. Metformin: clinical use in type 2 diabetes. *Diabetologia* 2017;60:1586-93. doi: 10.1007/s00125-017-4336-x.
2. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854-65. doi: 10.1016/S0140-6736(98)07037-8
3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53. doi: 10.1016/S0140-6736(98)07019-6
4. Griffin SJ, Leaver JK, Irving GJ. Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes. *Diabetologia* 2017;60:1620-9 doi: 10.1007/s00125-017-4337-9
5. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015;373:2117-28. doi: 10.1056/NEJMoa1504720.
6. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Eng J Med* 2017;377:644-57. doi: 10.1056/NEJMoa1611925.
7. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2019;380:347-57. doi: 10.1056/NEJMoa1812389
8. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2016;375:311-22. doi: 10.1056/NEJMoa1603827.
9. Marso SP, Bain SC, Consoli A, Elascowitz FG, Jódar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2016;375:1834-44. doi: 10.1056/NEJMoa1607141
10. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*. 2019;394:121-30. doi: 10.1016/S0140-6736(19)31149-3
11. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB, Granger CB, Jones NP, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet* 2018;392:1519-29. doi: 10.1016/S0140-6736(18)32261-X
12. DeFronzo RA. From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. *Diabetes* 2009;58:773-95. doi: 10.2337/db09-9028
13. Abdul-Ghani M, DeFronzo RA. Is It Time to Change the Type 2 Diabetes Treatment Paradigm? Yes! GLP-1 RAs Should Replace Metformin in the Type 2 Diabetes Algorithm. *Diabetes Care* 2017;40:1121-7. doi: 10.2337/dc16-2368
14. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020;255-323. doi: 10.1093/eurheartj/ehz486.
15. Consenso de Enfermedad Cardiovascular y Diabetes SAC-SAD 2019, <https://www.sac.org.ar/wp-content/uploads/2019/11/consenso-diabetes-2019.pdf>

AGONIST REPLY

Although we have learnt about the importance of the comprehensive management of risk factors to reduce complications related with diabetes, we must not neglect the role of adequate glycemic control as one of the central axes to achieve these objectives. In this context, the treatment of hyperglycemia in DM2 patients undoubtedly represents a great challenge. It is enough to observe the more than 8 pharmacological groups with more than 30 drugs currently available for the management of glycemic control.

The characteristics of the ideal normoglycemic drug have been considered and metformin complies with many of them, in addition to acting on the most relevant pathophysiological DM2 mechanism, as insulin resistance. It is effective, with a favorable profile on other cardiovascular risk factors, without risk of hypoglycemia or other adverse events, although, as considered, the impact on diabetes-related complications remains a controversial issue. It should be noted that this discussion persists, basically, due to the lack of clinical trials with adequate designs to evaluate the cardiovascular impact of metformin, and not because of studies demonstrating its inefficacy.

If we consider an initial treatment exclusively based on monotherapy, I would add another key point in the analysis of the ideal normoglycemic agent that was not considered in the discussion arguments against the use of metformin, which is the cost of treatment. SGLT-2i are at least 5 times and GLP-1ra 10-15 times more expensive than metformin treatment. Surely there will be subgroups of patients in whom the relationship between cost and benefit is favorable to the use of new groups, such as SGLT-2i in DM2 patients with heart failure or kidney failure, but will this equation be maintained in all the clinical scenarios of DM2 patients that require only one drug for glycemic control? Will it be for both SGLT-2i and GLP-1ra agents? An exhaustive cost-effectiveness analysis in our setting is essential to find answers to these questions.

However, this discussion may be sterile because most of our patients with diabetes and high cardiovascular risk frequently present glycemic controls far from the objectives and prolonged disease evolution requiring at least two drugs for adequate metabolic control, and the combination of SGLT-2i or GLP-1ra with metformin becomes the ideal combination in these patients.

Due to the aforementioned considerations, in my opinion, metformin will continue to be a first-line treatment drug for hyperglycemia, but of course this should not mean a delay in the association with new pharmacological groups that have shown a reduction in cardiovascular and renal events.

Dr Hugo Sanabria

ANTAGONIST REPLY

The agonist mentions as metformin strong points its effective glycemic control, insulin-sensitizing action, pleiotropic effects, safety and low cost. For these and other attributes it is called "Saint Metformin". I agree about its favorable pathophysiologic profile. I also concur about the low methodological quality and the discrepancy of results in studies evaluating its cardiovascular impact, a fact that does not occur in SGLT-2i and GLP-1ra cardiovascular safety studies. Regarding the analysis of these trials, the observations of the agonist are correct, but I wish to stress that the controversy revolves around which should be the first therapeutic option and not about which drug is best as monotherapy. On this last point I emphasize what is mentioned in the VERIFY registry, where 6 out of 10 patients who received monotherapy with metformin did not achieve the HbA1c <7% goal, and I add that in the DISCOVER registry sub-analysis of the population included in Argentina, in patients with 6.4 years of mean diabetes evolution, mean HbA1c was 8.8% (similar to the value observed with the poor metabolic control that the agonist mentions in SGLT-2i and GLP-1ra clinical trials), and, above all, an important data....84% were receiving metformin monotherapy. (1)

The agonist refers to the monthly cost of each treatment and points out that this is lower with metformin treatment. Nevertheless, I wonder, what is the cost of treating a cardiovascular or renal event and its consequences). What I can easily reply is that an event that does not take place has zero cost. It is true that we need local cost-effectiveness studies, but these should not be focused in assessing metformin vs. new drugs, but metformin + new drugs vs. metformin + other antidiabetic agents, since, as previously mentioned, a high proportion of patients will require combined therapy. It is in this point that I underscore my position of abandoning a glucocentric approach and start with a drug with proven cardiovascular benefit before using metformin, as the beneficial effect of these agents is observed in the absence of metformin, (2) and, in the case of needing a second drug, metformin is an excellent option.

Dr. Augusto Lavalle Cobo

REFERENCES

1. Walter D, Frechtel G, Gorbán de Lapertosa S, Commendatore V, Cherkoff A, Villarino A, et al. Estudio Discover en la Población Argentina. *Revista de la Sociedad Argentina de Diabetes* 2020;54:31-8
2. Masson W, Lavalle Cobo A, Lobo M, Masson G, Molinero G. Novel antidiabetic drugs and risk of cardiovascular events in patients without baseline metformin use: a meta-analysis. *Eur J Prev Cardiol* 2020 Sep 30:zwaa074. doi: 10.1093/eurjpc/zwaa074. Epub ahead of print.