Invited editorial

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Diabetes mellitus and chronic kidney disease: A neglected and dangerous liaison

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Non-insulin antidiabetic pharmacotherapy has been completely revolutionized in the recent decade[1] and the European Society of Cardiology (ESC) has joined forces with the European Association for the Study of Diabetes (EASD) to publish new guidelines acknowledging the need to update the management of diabetes mellitus.[2]

The main revolution regards the target of the pharmacotherapy itself. The traditional target of lowering glycosylate haemoglobin (HbA1c) levels remains mandatory only in order to reduce microvascular complications,[2] although the focus of pharmacotherapy has progressively included the cardiovascular safety of antidiabetic drugs (e.g. thiazolidinediones are contraindicated in patients with heart failure) and the reduction of cardiovascular risk.[2] This aspect is crucial because regulatory laws have been modified accordingly: for marketing authorization, the European Medicine Agency requires the demonstration of safety of an antidiabetic drug, while the reduction of cardiovascular events is optional, although hoped for.[3]

The meta-analysis of Pulipati et al.[4] published in this issue is timely because it is focused on cardiovascular outcomes and analyses a subgroup of patients with very high cardiovascular risk, namely those with diabetes mellitus and chronic kidney disease (CKD). Pulipati et al.[4] analysed the cardiovascular benefit of glucagon-like peptide-1 receptor agonists (GLP1RAs) versus placebo, combining the results of seven trials, and found a significant reduction in all-cause mortality (odds ratio (OR) 0.88), cardiovascular mortality (OR 0.88), primary composite endpoint (OR 0.86) and non-fatal stroke (OR 0.86), although there was no statistical difference in non-fatal myocardial infarction. The main strengths of this meta-analysis are: (a) the large number of patients involved ($n = 56{,}004$); (b) the use of a per patient-year analysis to add robustness, accounting for different durations of follow-up between the studies; and (c) the focus on CKD.[4] Indeed, the Pulipati et al.[4] specifically categorized the severity of CKD, analysing two subgroups of patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 ($n = 9366$; five trials) and eGFR <30 mL/min/1.73 m^2 ($n = 345$; three trials), finding no significant difference in the primary composite endpoint.

According to the new ESC/EASD guidelines, GLP1RAs, as well as sodium–glucose co-transporter two inhibitors (SGLT2i), are the drugs of choice with or without metformin in patients with diabetes mellitus at high or very high risk for or established atherosclerotic cardiovascular disease, thanks to their ability to reduce cardiovascular events.[2] Although liraglutide and semaglutide show nephroprotection,[5,6] to date no specific trial regarding GLP1RAs has been conducted in diabetic patients with CKD and only liraglutide was demonstrated to reduce the combined cardiovascular endpoint in the subgroup analysis of the LEADER trial,[5] while the other molecules were found to be neutral.

The meta-analysis was nominally also positive in this context, showing a trend towards a reduction in the combined cardiovascular endpoint, but, as a result of large confidence intervals, statistical significance was not reached. This might be due to the significant heterogeneity in the included trials, along with putative unfavourable pharmacological characteristics.[4] Indeed, renal function does not negatively influence the response to GLP1RA.

Similarly, all SGLT2i showed nephroprotection.[7–9] Although previously contraindicated for eGFR <60 mL/min/1.73 m^2, a specifically designed trial (CREDENCE) was recently prematurely stopped

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after the enrolment of 4401 patients with CKD with an eGFR 30–90 mL/min/1.73 m^2 and 2.6 years of follow-up as a result of the superiority of canagliflozin 100 mg/day versus placebo in reducing the composite outcome of end-stage renal disease by 30%, a doubling of serum creatinine levels, or renal or cardiovascular death, with significant benefits in cardiovascular secondary outcomes.[10] Two other specific trials with dapagliflozin (DAPA-CKD, NCT03036150) and empagliflozin (EMPA-Kidney) are ongoing.[11]

The meta-analysis of Pulipati et al.[4] is pivotal because it encourages the scientific community to reason and focus on specific subgroups of patients to maximize the efficacy with respect to cardiovascular outcomes. Given the paucity of data about GLP1RAs in patients with diabetes mellitus and CKD, the authors highlighted the need of trials in this field. Phenotyping patients with diabetes mellitus is an unmet need and it is key to major achievements in improving their prognosis.

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References

1. Niessner A, Tamargo J, Koller L, et al. Non-insulin anti-diabetic pharmacotherapy in patients with established cardiovascular disease: A position paper of the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy. *Eur Heart J* 2018; 39: 2274–2281.
2. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020; 41: 255–323.
3. European Medicines Agency. CPMP/EWP/1080/00 Rev. 1. Committee for Medicinal Products for Human Use (CHMP). www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-prevention-diabetes-mellitus-revision_en.pdf (accessed 25 February 2020).
4. Pulipati VP, Ravi V and Pulipati P. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes mellitus: A systematic review and meta-analysis. *Eur J Prev Cardiol* 2020; 27: 1922–1930.
5. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016; 375: 311–322.
6. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016; 375: 1834–1844.
7. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016; 375: 323–334.
8. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; 377: 644–657.
9. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019; 380: 347–357.
10. Jardine MJ, Mahaffey KW, Neal B, et al. The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study rationale, design, and baseline characteristics. *Am J Nephrol* 2017; 46: 462–472.
11. Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009; 374: 1677–1686.

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