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Treating chronic kidney disease to reduce cardiovascular risk

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Chronic kidney disease (CKD) is a complex syndrome and a relevant problem of public health due to its large incidence and prevalence and to the high costs for its management. The hallmark of CKD, the progressive reduction in the glomerular filtration rate (eGFR), is strongly associated with an increase in cardiovascular events, such as fatal and non-fatal heart attack, stroke and heart failure, and mortality. Therefore, clinicians should pay any effort for preventing or slowing down the decline of renal function in order to reduce not only the occurrence of critical renal events (the need for dialysis or renal transplantation, among the most dreadful) but also the incidence of cardiovascular events. Accordingly, an early diagnosis and a targeted treatment in patients with kidney disease are crucial to reduce the evolution towards more advanced stages of the disease and the occurrence of complications. For a long time, the therapeutic approach to the majority of CKD patients was based on the strict control of risk factors, such as the diabetic disease and hypertension, together with the use of renin–angiotensin–aldosterone system inhibitors, particularly in the presence of albuminuria. Over time, this strategy proved to be only partially effective, since most CKD patients showed a progressive worsening of renal function. Gliflozins and incretins are novel anti-diabetic drugs that have been demonstrated to slow down the slope of eGFR reduction in patients with CKD, irrespective of diabetic status. Concurrently, these drugs showed to significantly impact cardiovascular prognosis reducing the incidence of clinical events. For their ability to act on a wide spectrum of disease, gliflozins and incretins are also called 'cardio–nephro–metabolic' drugs.

Chronic kidney disease (CKD) is a complex syndrome that represents a relevant problem of public health due to its continuously increasing incidence and prevalence.[1] It is estimated that more than 730 million individuals in the world suffer from CKD and that in 2017 this disease was the cause of more than 1 million and half deaths.[2] In Italy, it is estimated that around 6 million people (10% of the population) is affected by CKD. Among these, roughly 42 000 were treated with extracorporeal dialysis, 45 000 with peritoneal dialysis, and more than 27 000 underwent to kidney transplantation in the period 2008–12 according to the Italian Registry of Dialysis and Kidney transplantations. Definition and staging of CKD are represented in *Figure 1*.

Even if everyone's attention is understandably focused on that estimated glomerular filtration rate (eGFR) 'cut-off' of 60/mL/m below which, by convention, we can officially speak of kidney disease, it is of fundamental importance to remember that the utmost attention must be aimed at those individuals, not yet patients, who, despite the absence of renal structural alterations, present only micro-albuminuria defined as a urinary excretion of albumin between 30 and 300 mg/day or as an albuminuria/creatinuria ratio on spot urine between 30 and 300 mg/g (UACR). This finding, far from being a simple indicator of renal damage as long believed, has proved to be a formidable marker of endothelial dysfunction and systemic organ damage, capable of impacting the cardiovascular prognosis even more than on the progression of CKD, regardless of the extent of filtrate decline, even in the general population.[3] All this to confirm, if ever

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Stage of CKD	eGFR result	What it means
Stage 1	90 or higher	– Mild kidney damage – Kidneys work as well as normal
Stage 2	60-89	– Mild kidney damage – Kidneys still work well
Stage 3a	45-59	– Mild to moderate kidney damage – Kidneys don't work as well as they should
Stage 3b	30-44	– Moderate to severe damage – Kidneys don't work as well as they should
Stage 4	15-29	– Severe kidney damage – Kidneys are close to not working at all
Stage 5	less than 15	– Most severe kidney damage – Kidneys are very close to not working or have stopped working (failed)

Figure 1 Definition and stages of chronic kidney disease.

there was still a need, of how much CKD is able to increase cardiovascular risk (fatal or non-fatal heart attack, stroke, disability-related, heart failure).

Since most uremic patients die of cardiovascular causes even before going on dialysis, it will not be enough to treat these patients, but it will be necessary to 'take care of them' by preventing and/or slowing down the progression of CKD in order to also reduce the incidence of new cardiovascular events.

Making a correct and early assessment of renal dysfunction is the first step to impact on the prognosis. It is useful to remember that a precise evaluation of chronic renal function can be obtained by evaluating its clearance with exogenous markers such as inulin or other less used substances such as Cr-EDTA or iothalamate. These substances have in common the ability to be filtered by the glomeruli but not reabsorbed or secreted by the tubules, thus giving an exact measure of the filtrate. However, these are long and expensive investigations, and above all they do not respond to the clinical need for repeated checks and rapid responses. All of this has favoured the use of creatininaemia for a long time (less frequently of cystatinaemia). It retains a certain value especially in the context of screening tests of populations but does not express the real value of the filtrate due to its prolonged half-life (about 7–9 h) and to have an exponentially inverse relationship with the filtrate. Nephrological research then provided us with the 'equations derived from creatininaemia' whose acronyms (Cockcroft-Gault, MDRD Study Equation, CKD-EPI just to mention the most used) quickly entered into common use.[4-9] However, it is useful to remember that the aforementioned formulas are not the exact measurements but estimates of the filtrate!

Clearly making an etiological diagnosis of CKD where possible will allow a case-specific therapy which, in particular cases, also makes use of immunosuppressive therapy.

In general, the attempt to slow down the decline of renal function for a long time could only take advantage of the control of hypertension and diabetes, on the inhibition of the renin-angiotensin-aldosterone system (RAAS), on changes in diet and lifestyle and, as the disease progressed, on the correction of the metabolic acidosis and on the strict control of the calcium-phosphorus balance. Careful monitoring was added of all those nephrotoxic substances (classic example non-steroidal anti-inflammatory drugs or anti-neoplastic drugs) that one might eventually be forced to take. Given the complexity and vastness of the topic, it will be advisable to concentrate, albeit in a synthetic way, on those conditions that the clinician most frequently encounters in his daily work.

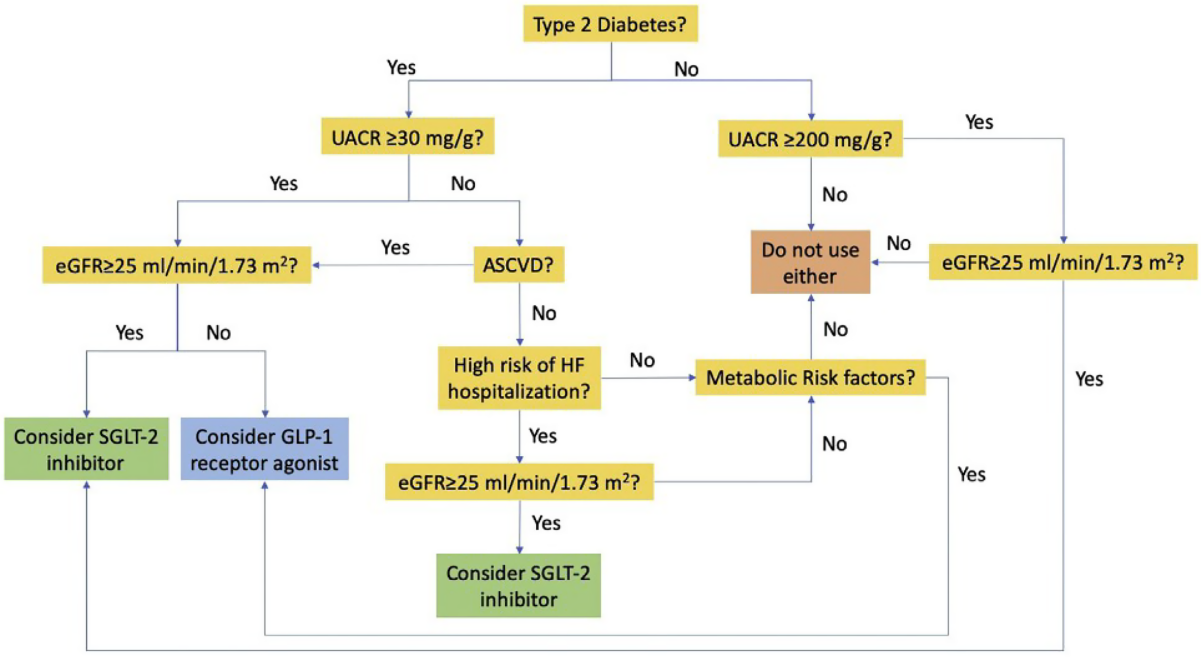
Inhibition of the renin-angiotensin-aldosterone system

Multiple trials have shown that therapy with ACE inhibitors (ACEI) or sartans (ARBs) is able to slow down the decline in renal function especially in the presence of albuminuria.

In the REIN trial, CKD patients randomized to ramipril vs. placebo showed a highly significantly reduced decline in renal function in the ACEI arm, especially if proteinuria >3 g/dL was present.[9]

In the RENAAL study, type 2 diabetic CKD patients randomized to losartan had a 16% risk reduction of significant renal endpoints such as doubling of creatinine, need for dialysis, or death when compared with placebo.[10] And as far as sartans are concerned, similar results were obtained, for example, in the IDNT trial where irbesartan was compared with amlodipine. Finally, in the AASK trial, ramipril use was independently associated with a −22% and −38% composite risk (filtrate decline >50% from baseline, need for dialysis, or death) when compared with metoprolol and amlodipine.[7]

The combined use of an ACE inhibitor with a sartan, although still widely used in the nephrological field due to their synergistic action on proteinuria, is not supported by the current literature in diabetics with CKD. The NEPHRON-D study, which enrolled type 2 diabetic patients



Proposed algorithm for SGLT2 inhibitor and GLP-1 receptor agonist use in chronic kidney disease.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; HF, heart failure; SGLT2, sodium/glucose cotransporter 2; UACR, urinary albumin-creatinine ratio.
Li et al Clin J Am Soc Nephro 2020

Figure 2 Proposed algorithm for SGLT2 inhibitor and GLP1 receptor agonist use in chronic kidney disease. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP1, glucagon-like peptide 1; HF, heart failure; SGLT2, sodium-glucose co-transporter 2; UACR, urinary albumin-creatinine ratio. Li *et al*. Clin J Am Soc Nephro 2020.

with CKD randomized to losartan + lisinopril or losartan alone, was terminated due to an excess of adverse events (hyperkalaemia and episodes of acute renal failure) in the arm treated with the comparative combination with the monotherapy group.[10,11] The importance of reducing the daily sodium intake in the diet is also reaffirmed because this amplifies the nephroprotective effect of the RAAS antagonist drugs. An important meta-analysis (11 randomized controlled trials) shows that a low-sodium diet *per se* reduces urinary albumin excretion by 32%. The reduction of albuminuria becomes even more significant if it is accompanied by an anti-RAAS therapy (−41% vs. −17%, respectively), suggesting a synergistic effect between a low-sodium diet and ACEI or ARB therapy.[12] Therefore all patients taking RAAS inhibitors for the treatment of albuminuria should be encouraged to follow a diet with reduced sodium intake (−3 g/day).

Finally, the use of anti-aldosterone drugs (MRA) in patients intolerant to ACEI and ARB can be considered. This is because a recent meta-analysis of 31 randomized controlled trials, aimed at evaluating the efficacy and tolerability of different MRAs (spironolactone, eplerenone, canrenone, and finerenone) in reducing albuminuria compared with placebo or active drug confirmed the efficacy of these drugs in reducing the albuminuria vs. placebo but showed no superior effect when compared with ACEI or ARB in the face of highly significant risk of hyperkalemia.[13] More recently, much discussion has been generated by the data from the FIDELIO-DKD study. Although the reduction of albuminuria is not universally accepted as a surrogate endpoint of the 'need for dialysis', finerenone has been shown to reduce the composite risk of renal events by 18% in CKD type 2 diabetic patients receiving ACEI or ARB therapy, such as filtrate decline, need for dialysis, and CKD-related deaths when compared with placebo.[14]

Ultimately MRAs reduce albuminuria and slow down the progression of CKD but involve an increased risk of hyperkalaemia which requires careful control in daily practice.

Glycaemic control

The 2020K-DIGO guidelines recommended to individualize the glycaemic control on the basis of the severity of the renal disease, the comorbidities, and the individual risk of hypoglycaemia.[15] This recommendation was largely based on the increased risk of hypoglycaemia with the drugs in use at that time—namely, insulin, sulfonylureas, and glinides—as eGFR slow down. The availability of new anti-diabetic drugs (gliflozins and incretins) characterized by a high safety profile with a very low incidence of hypoglycaemia had basically changed the therapeutic algorithm of diabetes (*Figure 2*) in CKD patients.[16] Most randomized trials suggest that a

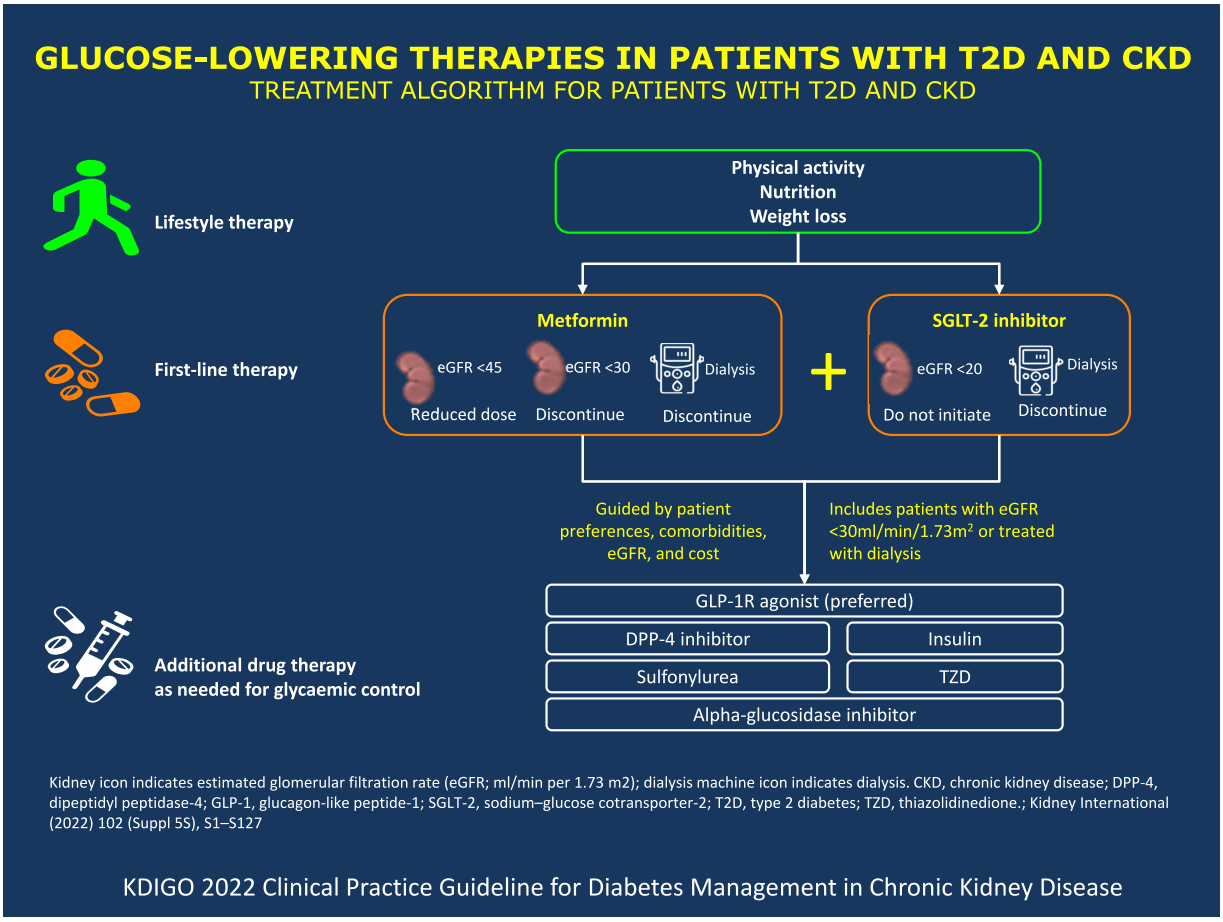


Figure 3 Proposed algorithm for SGLT2 inhibitor and GLP-1 receptor agonist use in CKD.

more intensive glycaemic control significantly slows down the decline in eGFR and albuminuria. Indeed, a large meta-analysis including data from the ADVANCE, ACCORD, UKPDS, and VADT trials demonstrated that intensive glycaemic control was associated with a 20% reduction in the risk of the renal endpoint (composite of worsening of renal function, change in UACR, and need for dialysis), essentially driven by a reduction in the risk of albuminuria. This reduction was proportional to the degree of UACR and independent of its baseline values.[17] Therapeutic management of diabetes in CKD has been radically changed from the introduction of new drugs such as gliflozins and incretins, since they have been demonstrated to be safe, effective, and with less needs for dose adjustments. The 2022 American Diabetes Association (ADA) guidelines provided specific recommendation about the use of gliflozins and incretins in diabetic patients with CKD and/or cardiovascular disease, suggesting the use of the former in patients with heart failure and proteinuria and the latter if ischemic cardiomyopathy or stroke co-exists.[18]

Gliflozins

Sodium-glucose co-transporter type 2 inhibitors (SGLT2i), also called gliflozins, have demonstrated to slow down the progression of CKD, in particular in patients with type 2 diabetes and albuminuria. Accordingly, the most recent ADA and European Association for the Study of Diabetes (EASD) guidelines recommend SGLT2i as drugs of first choice in all patients with type 2 diabetes and risk of CKD progression, regardless of the presence of cardiovascular disease.

A recent meta-analysis by Neuen *et al.* including 38 723 patients from the CREDENCE, CANVAS, EMPA-REG OUTCOME, and DECLARE-TIMI trials 58, showed that SGLT2i reduced the risk of the composite renal outcome (end-stage chronic kidney disease or CKD-related death) by −33% compared with placebo, regardless of baseline eGFR.[19]

The DAPA-CKD trial (4304 patients with an eGFR of 25 to 75 mL/min/1.73 m2 and UACR 200-5000 randomized to dapagliflozin or placebo) demonstrated that the SGLT2i dapagliflozin reduced the risk of all-cause mortality by 31% on top of optimal medical therapy, irrespective of diabetic status. Moreover, dapagliflozin reduced the composite renal outcome of worsening renal function, end-stage renal disease, or CKD-related death by 39%. The drug was well tolerated and easy to manage, and there was no significant difference in adverse events between the two study arms.[20]

More recently, the EMPA-KIDNEY trial, the largest nephroprotection study ever conducted to date (6609 patients with eGFR 20-45 mL/min/1.73 m^2 or eGFR 45-90 mL/min/1.73 m2 with UACR ≥200. randomized to empagliflozin or placebo) showed that the SGLT2i empagliflozin reduced the composite outcome of CKD progression and cardiovascular mortality by 28%. The study was terminated earlier than expected due to evidence of demonstrated benefits on renal endpoints and CKD-related mortality, even though it did not

reach the statistical significance for the reduction of all-cause mortality.[21]

These data pairs with the previously demonstrated effect of SGLT2i on preserving renal function in patients with heart failure, although with inconsistent effect on renal outcomes.[22] Nevertheless, the large beneficial impact of these drugs on renal function, the high safety profile, and their broad eligibility in the real-world population[23,24] made SGLT2i a pillar of the modern CKD treatment.

Incretins

GLP1 receptor agonists, an acronym that stands for 'glucagon-like peptide 1' commonly referred to as incretins, are the other class of anti-diabetic drugs that have recently been shown to be able to slow the decline of CKD and improve its renal outcomes. In the meta-analysis by Kristensen *et al.*[23] comprising five trials (ELIXA, LEADER, SUSTAIN-6, EXSCEL, and REWIND), GLP1a showed a −17% reduction in the renal composite endpoint (new-onset UACR > 300 mg/g, doubling of serum creatinine, need for dialysis, and CKD-related death) with a HR of 0.83 (95% CI 0.78–0.89).

However, it was noted that when only the more restrictive and specific worsening of renal function data, such as doubling of serum creatinine and need for dialysis, were taken into account, the significance was not maintained (HR 0.87, 95% CI 0.73–1.03). Although there are currently no trials directly comparing SGLT2i and GLP1a on renal outcomes, the Zelniker meta-analysis (including eight trials on renal and cardiovascular endpoints) shows a −38% (HR 0.62, 95% CI 0.58–0.67) reduction in the risk of worsening of renal function of SGLT2i vs. −18% (HR 0.82, 95% CI 0.75–0.89) evidenced by GLP1a.[24] In light of these data, SGLT2i appear more effective than GLP1a in reducing the progression of CKD and should be preferred in the suggested therapeutic algorithm (*Figure 3*).

Finally, the data that are beginning to appear on the benefits of the combined use of these two classes of drugs in diabetic patients with atherosclerotic disease and heart failure are very promising. When GLP1ra was added to SGLT2i, a reduction in the risk of atherosclerotic events (all-cause mortality, heart attack, stroke) was demonstrated, but no effect on the risk of heart failure.[25-27]

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Data availability

No new data were generated or analysed in support of this research.

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