Hypertension in chronic kidney disease and future heart failure

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Purpose of review
Hypertension and chronic kidney diseases (CKDs) are known risk factors for the development or worsening of heart failure. In last years, several new therapeutic approaches for the management of people with diabetic and nondiabetic CKD and hypertension have been investigated. In this brief review, the most recent findings regarding the ability of SGLT-2 inhibitors and nonsteroidal mineralocorticoid receptor antagonists (nsMRA) and GLP-1 receptor agonists to prevent heart failure in patients with hypertension and CKD will be discussed.

Recent findings
In the last 3 years, several large clinical trials involving very large numbers of CKD patients have been published showing that these new therapeutic approaches significantly reduce the risk of heart failure events and hospitalizations in patients with diabetic and nondiabetic nephropathies and hypertension as well as in patients with heart failure without nephropathy. Moreover, these drugs retard the progression of CKD towards end-stage kidney disease.

Summary
These observations already have a major impact on the management of people with hypertension and CKD. SGLT-2 inhibitors are now recommended as first-line therapy in people with diabetes, CKD and heart failure. The use of nsMRA is increasing and could replace spironolactone over time in heart failure as well as in early CKD stages.

Keywords
diabetes, estimated glomerular filtration rate, glucagon-like peptide-1 receptor agonists, nonsteroidal mineralocorticoid receptor antagonist, SGLT-2 inhibitors

INTRODUCTION

Hypertension, chronic kidney disease (CKD) and heart failure are three frequent clinical entities that are tightly linked in terms of pathophysiology, association with comorbidities (diabetes, obesity, and so on), therapeutic approaches and risk of cardiovascular death. As illustrated in Fig. 1, the links between these clinical conditions are often bidirectional. Thus, hypertension can be a cause or a consequence of CKD and the same is true for the relation between CKD and heart failure. Hypertension is the leading cardiovascular risk factor with a worldwide age-standardized prevalence of 32% in adult women aged 30–79 years and 34% (32–37) in men [1]. In patients with CKD, these figures may reach more than 75% [2▪]. Regarding CKD, its global prevalence was 9.1% (8.5–9.8) in 2017 with a marked increase since 1990 (+29%) [3]. Cardiovascular complications including heart failure are common among CKD patients [4]. They represent the first cause of death in CKD patients with an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m^2 and the second cause of death, behind cancer, in people with an eGFR more than 60 ml/min/1.73 m^2 [5]. In CKD stages 4 and 5, more than 40% of patients die from a cardiovascular event, for example more CKD patients die from a cardiovascular event than from their kidney disease [5]. Heart failure is also frequent in the CKD population and its prevalence increases as eGFR decreases [6▪]. Thus, the incidence of new-onset heart failure in individuals with CKD ranges between 17 and 21% and its prevalence can reach approximately 45% in patients undergoing chronic dialysis. In general, heart failure has a poor

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KEY POINTS

- Heart failure is a common complication of hypertension and chronic kidney disease (CKD).
- In last years, several large randomized clinical trials have investigated the ability of these new drug classes to provide cardio-renal protection in diabetes, in CKD and in heart failure patients.
- These studies have demonstrated that SGLT-2 inhibitors, GLP-1 receptor antagonists as well as nonsteroidal mineralocorticoid antagonists prevent heart failure events and hospitalizations in CKD.
- These drugs also retard the progression of CKD and provide cardiovascular protection.

prognosis in advanced CKD (stages 4 and 5). Moreover, the risk of end-stage kidney disease is higher in people with an advanced CKD and heart failure with a reduced ejection fraction (HFrEF) when compared to patients with no heart failure [7].

CLASSICAL MANAGEMENT OF HEART FAILURE IN CHRONIC KIDNEY DISEASE PATIENTS WITH HYPERTENSION

The cardiovascular risk of CKD patients is so high that many clinicians question whether it can be lowered to the level of the general population using the traditional therapeutic approach [8]. Indeed, the residual risk remains high despite the implementation of hypertension [9,10] and heart failure guidelines [11,12▪], which recommend a strict control of risk factors such as blood pressure, dyslipidaemia and diabetes. Yet, a recent analysis of 20 254 patients with CKD and 35 236 matched controls from a large prospective cohort of more than 100 000 adults, Geng *et al.* [13] have shown that a strict control of blood pressure (<130 mmHg), lipids (low-density lipoprotein cholesterol: <2.6 mmol/l) and glucose (fasting blood glucose: <6.1 mmol/l) is associated with no excess risk of death, myocardial infarction or stroke when compared to the general population. Yet, the benefits were observed only when all three parameters were well controlled. Kidney disease progression was also retarded. Unfortunately, no data on heart failure was available in this analysis. These observations suggest that the residual risk of CKD patients is due in part to an imperfect management of cardiovascular risk factors probably caused by some form of therapeutic inertia.

However, one must acknowledge that the management of hypertension and heart failure in CKD patients is not always easy even though similar drug classes are used to lower blood pressure in hypertension, to prevent CKD progression and to prevent and treat heart failure [14]. As kidney function is declining, clinicians are confronted with several pharmacological issues, such as the renal excretion of drugs or the increased risk of hyperkalaemia or volume depletion, which can potentially aggravate the clinical situation. In addition, other factors contributing to the high cardiovascular risk of CKD patients develop in advanced CKD such as anaemia, hyperparathyroidism or a poor nutritional status.

NEW OPPORTUNITIES IN THE MANAGEMENT OF HEART FAILURE IN PATIENTS WITH HYPERTENSION AND CHRONIC KIDNEY DISEASE

In the last decade, several new drug classes have become available to manage CKD and heart failure patients. Initially, the development programme of

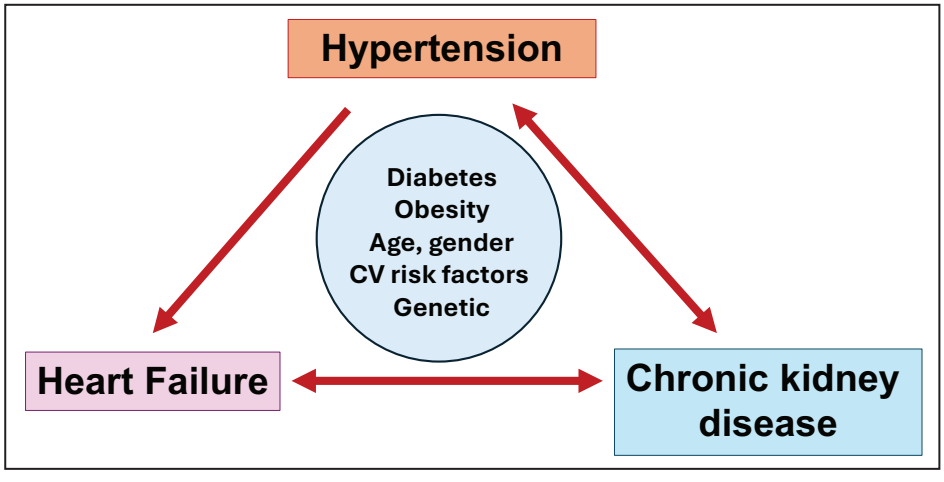

FIGURE 1. Schematic representation of the links between hypertension, chronic kidney disease and heart failure with the common risk factors.

these drugs was focused on patients with diabetic nephropathy. This was the case of nonsteroidal mineralocorticoid receptor antagonists (nsMRA), SGLT-2 inhibitors and GLP-1 receptor agonists. Thereafter, some of these compounds, mainly SGLT-2 inhibitors and nsMRA, were investigated in patients with nondiabetic nephropathies and in heart failure. One important characteristic of the randomized controlled trials (RCTs) conducted to demonstrate the efficacy and safety of these compounds was the concomitant assessment of cardiac and kidney endpoints in addition to mortality. Thereby, thousands of people with CKD were enrolled in these trials providing a unique opportunity to assess the cardiorenal benefits of these drugs in this patient population [15,16▪▪,17,18▪▪,19,20▪,21].

SGLT-2 inhibitors

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors have been developed to treat diabetes. They lower blood glucose by reducing the renal reabsorption of glucose in the proximal tubule which leads to a reduction in glycated haemoglobin (Hb1Ac). In addition, urinary sodium and water excretions are increased. This results in a reduction of systolic blood pressure by about 4–5 mmHg and a reduction of serum uric acid and body weight. One important renal effect of SGLT-2 inhibitors is the decrease in intraglomerular pressure which contributes to the reduction of glomerular hyperfiltration, a classical feature of several nephropathies. The consequence is a functional decrease in eGFR and a reduction of albuminuria. SGLT-2 inhibitors have also pleiotropic effects, which are beneficial for the heart as shown in Fig. 2 [2▪]. The cardiovascular and renal benefits of SGLT-2 inhibitors have been demonstrated in multiple large RCTs involving various patient groups including people with type 2 diabetes with and without diabetic nephropathy, patients with CKD and more recently individuals with heart failure and a reduced or preserved ejection fraction [15,16▪▪,17,18▪▪,22–26]. In last years, several systematic reviews and meta-analyses have been performed in these clinical indications [19,27,28,29▪,30–33]. The main conclusions for CKD patients are the following: SGLT-2 inhibitors reduce the risk of disease progression by 37% in diabetic patients and by 23% in advanced CKD when compared to placebo [27], the benefits on kidney disease progression are observed in patients with and without diabetes, the renal benefits are independent of the baseline eGFR, SGLT-2 inhibitors also reduce the risk of hospitalization for heart failure by approximately 30% and the risk reduction is larger among CKD patients than in patients without CKD, SGLT-2 inhibitors decrease the risk of cardiovascular death but do not modify the risk of noncardiovascular death and the use of SGLT-2 inhibitors is associated with an increased risk for urinary tract and genital infections.

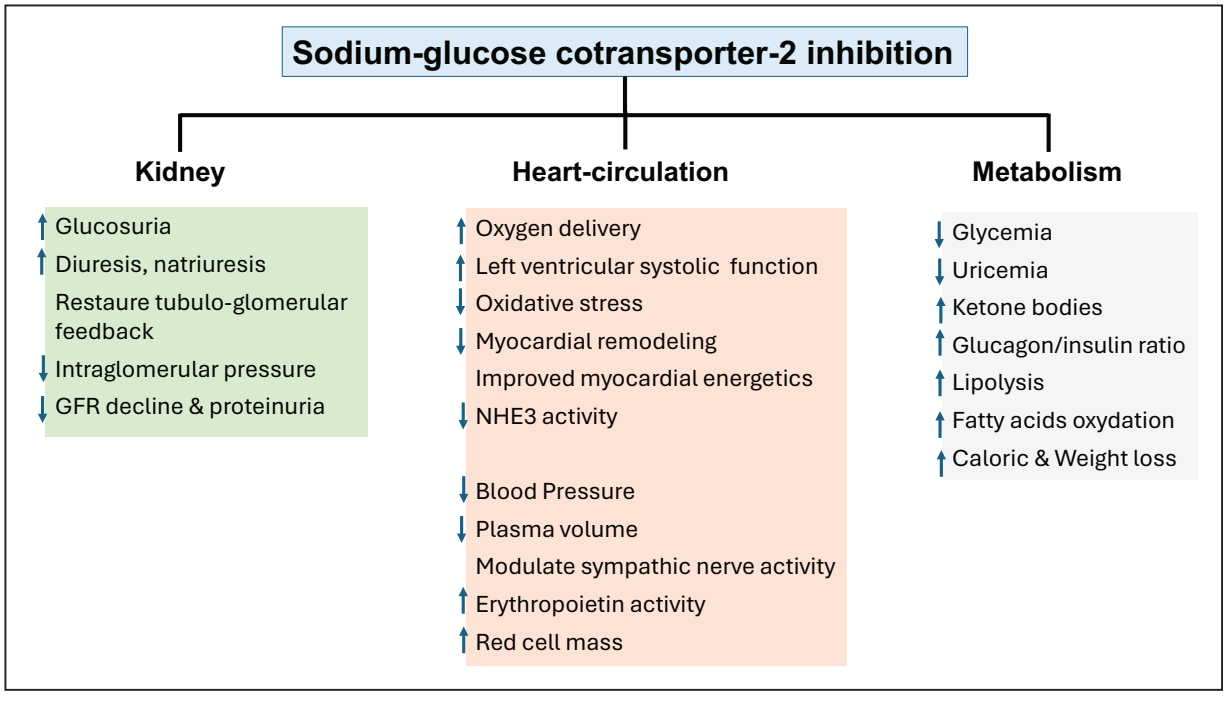

FIGURE 2. Description of the pleiotropic effects of SGLT-2 inhibitors on the kidney, the heart and circulation and on the metabolism.

In people with heart failure and a preserved ejection fraction (HFpEF) [29▪], SGLT2 inhibitors reduce the risk of first heart failure hospitalization or cardiovascular death by 20% and heart failure hospitalization by 26%. However, SGLT-2 inhibitors do not modify the risk of all-cause mortality. In heart failure patients with a reduced ejection fraction (HFrEF), SGLT-2 inhibition is associated with a significant reduction in cardiovascular death and hospitalization for heart failure and in recurrent episodes of heart failure (-25%) [33].

Taken together, these data demonstrate that SGLT-2 inhibitors offer significant cardiorenal protection in patients with type 2 diabetes, CKD and heart failure. In addition, they are very effective in preventing heart failure hospitalizations both in CKD and in individuals with preexisting heart failure. SGLT-2 inhibitors are not recommended as first-line therapy in hypertension, but guidelines recognize their usefulness for cardiorenal protection in above-mentioned indications when associated with hypertension [9,10]. There is now a strong support in favour of using SGLT-2 inhibitors in nephrology, cardiology and diabetes. This is the reason why several scientific societies are now recommending them in their guidelines as first line therapy for specific indications [9–11,12▪,34,35]. As suggested in a recent Australian analysis, a wide use of SGLT-2 inhibitors may have a great potential to prevent large numbers of patients experiencing CKD progression or dying due to heart failure or cardiovascular diseases [36▪].

Non-steroidal mineralocorticoid receptor antagonists

Classical steroidal mineralocorticoid receptor antagonists (spironolactone and eplerenone) are used primarily in patients with hypertension due to an excess of mineralocorticoids, such as primary aldosteronism [37], and in heart failure where RCTs have demonstrated their usefulness [38]. Today, they are also recommended in the management of true resistant hypertension [9]. However, their use in CKD patients is often limited by the risk of hyperkalaemia particularly in CKD stages 4 and 5. Nevertheless, in patients with mild to moderate CKD, steroidal aldosterone antagonists have been shown to lower proteinuria, eGFR and SBP and hence to provide some renal protection when combined with blockers of the renin-angiotensin system (RAS) [39].

Finerenone, a newly developed nsMRA, has been investigated in diabetes and CKD stages 2 to 4 and a moderately elevated albuminuria and in patients with CKD stages 1 or 2 and a severely elevated albuminuria in two placebo-controlled RCTs involving more than 13 000 patients, for example the FIGARO and the FIDELIO trials [40,41]. In both trials, finerenone or placebo were administered on top of a maximum tolerated RAS inhibition. In one trial (FIGARO), the primary endpoint was cardiovascular (a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke or hospitalization for heart failure) and the secondary endpoint was renal (a composite of kidney failure, a sustained decrease in eGFR, or death from renal cause). In the other one (FIDELIO), the primary endpoint was renal and the secondary was cardiovascular. With this design, results could be pooled in a global analysis called FIDELITY [42]. The major findings of these two large RCTs were the following: compared to placebo, finerenone reduced the composite cardiovascular endpoint by 14% and the composite renal endpoint by 25%, the cardiovascular benefit of finerenone was driven primarily by a 29% reduction of the incidence of hospitalization for heart failure [41], the tolerability profile was good and the incidence of hyperkalaemia was low during the 3 years of follow-up (1.2% with finerenone and 0.4% with the placebo), in CKD stage 4, finerenone had no significant impact on renal endpoints and the incidence of hyperkalaemia was higher at 26 versus 13% in the placebo group but a low percentage of participants left the study because of hyperkalaemia.

More recently, finerenone was studied in people with heart failure and a mildly reduced or preserved ejection fraction in the FINEARTS-HF trial [43]. The study enrolled 6001 patients with symptomatic heart failure and a LVEF at least 40%. Among participants, 88% were hypertensive and about half of them had an eGFR less than 60 ml/min/1.73 m^2 [44]. The primary endpoint was a composite of worsening heart failure events (defined as a first or recurrent unplanned hospitalization or urgent visit for heart failure) and death from cardiovascular causes. In this trial, finerenone decreased significantly the risk of worsening heart failure by approximately 18% and reduced the number of deaths from cardiovascular causes, but this latter change was not significant. Of note, the finerenone-induced reduction of the risk of cardiovascular death and worsening heart failure occurred irrespectively of the level of ejection fraction [45▪▪].

The global cardiovascular and renal benefits of finerenone in type 2 diabetes and CKD and heart failure have been summarized in a recent meta-analysis [45▪▪]. Data available strongly support the use of a nsMRA in CKD patients to prevent heart failure episodes and HF hospitalizations. Whether these data will be additive to those observed with SGLT-2 inhibitors remains to be demonstrated.

Glucagon-like peptide-1 receptor agonists

GLP-1 receptor agonists represent another class of drugs developed to treat type 2 diabetes. Several controlled RCTs have shown that this drug class reduces atherosclerotic cardiovascular diseases in type 2 diabetes associated with a high cardiovascular risk, or with an established cardiovascular disease [46]. Regarding kidney function, GLP-1 receptor agonists lower albuminuria but the impact on CKD progression remains to be demonstrated. Preliminary data on eGFR trajectory are encouraging, but not yet conclusive and clinical studies are still ongoing [47].

There are more data regarding the ability of GLP-1 receptor agonists to prevent heart failure hospitalizations in type 2 diabetes and CKD. In the FLOW trial, investigators have examined the impact of semaglutide or placebo on a composite of heart failure events (new onset or worsening of heart failure leading to hospitalization or to an urgent visit) or cardiovascular death [48▪▪]. More than 3500 participants were randomized in this study and followed for an average of 3.4 years. The time to first heart failure event was significantly prolonged with semaglutide and the number of heart failure events was lowered by 27%. Cardiovascular death was also reduced by 29%. This cardiovascular benefit was obtained regardless of the history of heart failure. These results suggest that GLP-1 receptor agonists may also be good candidates for the prevention of heart failure in diabetes and CKD, but more data are expected to support the recommendation.

CONCLUSION

The detection and the prevention of heart failure in patients with hypertension and CKD has always been a challenge for clinicians. With the classic treatment approach combining blockers of the renin-angiotensin system, beta-blockers, diuretics and MRAs the impact of heart failure events was relatively low mainly because these drugs were causing aggravations of kidney function, hyperkalaemia and uncomfortable side effects. The situation has changed considerably with the availability of SGLT-2 inhibitors and nsMRA. First, several large RCTs have demonstrated the cardiorenal benefits of these new drugs, enabling to provide evidence-based recommendations in CKD, diabetes and heart failure. Second, the tolerability profile of these drug classes is markedly improved. Today, these new approaches are increasingly used in clinical practice. However, there is still more to come with the ongoing development of GLP-1 receptor agonists and aldosterone synthase inhibitors. In the future, it is obvious that the management of heart failure in hypertension and CKD will change drastically. Paradoxically, the next difficulty that clinicians will face is the rational and cost-effective use of the multiple drugs available to manage heart failure.

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Conflicts of interest

The author has no conflict of interest to declare for this manuscript.

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