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Seven suggestions for successful SGLT2i use in glomerular disease – A standalone CKD therapy?

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Abstract

Purpose of review: Recent advances in the world of glomerular diseases have largely focussed on remission induction with immune modulating therapy. It is well recognised that even with the best available treatments, patients with glomerular diseases may have an increased risk of progressive renal and cardiovascular disease.

Recent findings: The arrival of large trials looking at the benefits of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in patients with chronic kidney disease (CKD) and diabetes or not has shifted the entire focus of current management and the shift needs to go further. This review summarises the background to these landmark trials and provides practical guidance for implementation of the results in a general nephrology clinic. In sub-group analyses of the DAPA-CKD clinical trial, SGLT2i improved renal outcomes in patients with IgA nephropathy highlighting the potential for this drug class in glomerular disease. We also discuss where the gaps in evidence are and where future trials in glomerular diseases, be they primary or secondary, should be focussed.

Summary: The renal community has never before had evidence of this strength upon which to base recommendations for patients with CKD and we should be grasping it with both hands.

Keywords: chronic kidney disease, glomerulonephritis, sodium glucose transporter 2, diabetes

Introduction

Glomerular disease management is historically focused on renoprotection through blood pressure reduction(1), renin-angiotensin system (RAS) inhibition (1–3) and, where appropriate, immunomodulation(4). The incremental increase in mortality risk associated with both chronic kidney disease and nephrotic syndrome has been clearly described (5,6)but remains poorly mitigated. Clinical trial design has been hampered by the opinion that hard endpoints such as end stage kidney disease or 40% decline in eGFR or death were unachievable in a clinical trial timeframe, and alternatives were sought (7). The recent publication of landmark trials of sodium-glucose cotransporter 2 inhibitors (SGLT2i) has completely changed the landscape of future trials in the management of glomerular disease – both primary and secondary. This review focuses on the mechanisms of action of these medicines, their current role, how to safely adopt them in clinic and where the gaps in evidence now lie.

Background

In early trials of management strategies in type 2 diabetes, intensive glycaemic control was found to reduce incident microvascular complications, with less convincing benefit on macrovascular complications including cardiovascular mortality(8). Furthermore, the cardiovascular profile of some oral hypoglycaemic agents was somewhat uncertain. In this context, a meta-analysis on the peroxisome proliferator activated receptor gamma agonist rosiglitazone was published showing that across 42 trials, cardiovascular mortality was increased 64% in the treatment arm(9) - prompting an advisory label on the product and apprehension of its use in patients with pre-existing cardiovascular background.

Subsequently, the Food and Drug Administration (FDA) issued recommendations in 2008, that approval of new anti-diabetic drugs required the demonstration of satisfactory cardiovascular safety, generally via a primary endpoint comprising a composite of cardiovascular mortality, myocardial infarction, and stroke. Large scale randomised cardiovascular outcome trials (CVOTS) followed of dipeptidyl peptidase 4 (DPP4) inhibitors, glucagon linked peptide-1 agonists, and SGLT2i.

Although these CVOTs focused on cardiovascular endpoints, a range of secondary outcomes examined effect on kidney outcomes. The first of these was the EMPA-REG(10) trial, where empagliflozin reduced incipient nephropathy and worsening kidney function. Then in the CANVAS trial, canagliflozin reduced progression of albuminuria, slowed the reduction in estimated glomerular filtration rate (eGFR) and need for kidney failure requiring replacement therapy (KFRT) by 40%(11). Finally, in DECLARE-TIMI58, dapagliflozin reduced progression of a renal composite outcome by 24% (12).

Renal outcome trials

The CREDENCE trial of canagliflozin 100mg daily versus placebo in 4401 patients with diabetes was the first the published CVOT to pre-declare a renal primary endpoint: a composite of doubling of serum creatinine, end stage kidney disease, or death from renal or cardiovascular causes (13). The trial participants had mean eGFR 56ml/min (18) and required proteinuria for inclusion (uACR 300-5000mg/g). The trial was terminated early after 2.4 years, at which point canagliflozin reduced the primary end point by 30%. The DAPA-CKD trial(14) evaluated the effect of dapagliflozin 10mg daily versus placebo on a similar combined renal end point, and for the first time, recruited patients without diabetes, who comprised a third of the study population. 4304 patients were included, with mean eGFR 43 (12) ml/min and again, inclusion

required significant proteinuria (uACR 200-5000mg/g). Dapagliflozin reduced the primary end point by 39%, with similar benefit seen in patients both with and without diabetes. These trials are the first studies to demonstrate a reduction in mortality with an intervention in patients with chronic kidney disease (CKD)(15). There is no evidence as yet for benefit in patients with CKD without proteinuria at this stage, but EMPA-KIDNEY (NCT03594110) is including these patients.

A recent meta-analysis has concluded that for every 1000 patients with CKD without diabetes treated with SGLT2i for a year, 19 first kidney disease events (decline in eGFR >40%) were avoided (16).

These clinical trial outcomes have been borne out in real world settings (17) and therefore it is the responsibility of the renal community to interpret and implement the findings of these landmark trials and overcome any barriers, perceived or actual.

Proposed Mechanisms of action of SGLT2i

In a reversal of the typical drug development timeline, translational research is playing catch up to explain the overwhelming clinical benefit of SGLT2i in CVOTs, and indeed much of the pleiotropic effects remain poorly explained (18).

SGLT2 is a glucose transporter that is localised in the proximal convoluted tubule of the kidney and resorbs the majority of glucose filtered at the glomerulus. SGLT2 are upregulated in diabetes which can result in a maladaptive response which exacerbates hyperglycaemia.

The SGLT2i act in the proximal tubule to inhibit sodium and glucose reabsorption via SGLT2, increasing distal delivery of sodium, chloride and water to the macula densa. This results in tubuloglomerular feedback with glomerular afferent arteriolar vasodilatation, reduction in intraglomerular perfusion pressure and reduction in filtration (19). The osmotic effects of increased sodium and glucose delivery continue

in the distal nephron, despite likely upregulation of distal sodium reabsorption, and an osmotic diuresis is seen (20). Familial renal glycosuria is an inherited absence of SGLT2. In this condition, there can rarely be resultant hypotension or hypoglycaemia, but the condition is otherwise relatively benign, with no association with CKD (21).

Clinical effects

Several clinical effects of these drugs are predictable. On average, weight loss of around 2Kg is expected. The initial volume loss appears to then be maintained by loss of abdominal girth and an increase in lipolysis, maintaining the initial weight loss. Glycaemic control is improved in diabetes, with an average reduction in HbA1c of around 0.6%, although this benefit is lost with reductions in eGFR. Systolic blood pressure is mildly reduced by around 3mmHg. (22,23)

Reduction in proteinuria is seen with SGLT2i, presumably as a consequence of the reduction in intraglomerular perfusion pressure. An average reduction of 30% in uACR is seen by 26 weeks(24). Beneficial effects on kidney outcomes in clinical trials are independent of reduction in proteinuria. What is known now is the greater the proportional reduction in proteinuria, the greater the reduction in risk of cardiovascular or renal end points (25).

Some clinical effects are unexpected and as yet unexplained, such as the reduction in non-osmotically active sodium stores(26). The effect on interstitial versus intravascular sodium is one of ways in which SGLT2i differ from conventional diuretics.

Implementation of the evidence

The early focus of trials was on diabetic kidney disease (13)(10), but subgroup analysis from DAPA-CKD suggests that the next opportunity for nephrology is using SGLT2i in the setting of non-diabetic proteinuric CKD(27,28). The following seven

suggestions will hopefully allow the impressive results of these large randomised controlled trials to be implemented with improved outcomes for patients (figure 1). We additionally highlight some ongoing controversies and how these agents might be used in glomerular disease.

1. Should these medicines be used as monotherapy? At present, there is no evidence for use of SGLT2i in patients with CKD as monotherapy. In CREDENCE and DAPA-CKD patients were required to be prescribed maximally tolerated ACE/ARB for inclusion. In both these trials >98% of participants were treated with these agents at baseline. Therefore we would not recommend instituting SGLT2i without ACE/ARB for renoprotection.
2. Should I check eGFR and potassium shortly after starting an SGLT2i? The effects of these medicines on glomerular haemodynamics mean that an initial reduction in eGFR of 20-30% is to be expected, much like can be seen with ACEi(28). In fact, data has shown that an early drop in eGFR is associated with better outcomes in patients prescribed SGLT2i (29) therefore, checking for a drop in renal function is not necessary but could be considered for individual prognostication. No effect on potassium was seen in trials with these medicines, despite patients being prescribed ACE/ARB.
3. Will all patients with primary glomerulonephritis benefit from SGLT2i? In DAPD-CKD, patients with primary glomerulonephritis were included. 6.3% (270) had a diagnosis of IgA nephropathy (IgAN)(30). This means that more patients were trialled with SGLT2i in DAPA-CKD than with methylprednisolone in TESTING (31)(n=262) or immunosuppression in STOP-IgA(32) (n=162), large multicentre IgAN trials. Other primary GNs including FSGS were also included in DAPA-

CKD. Patients receiving active immunosuppression were not included and similarly, patients with lupus nephritis and ANCA-associated vasculitis were excluded. Therefore, there are some important exclusion criteria at present for these drugs. Patients with CKD without proteinuria were also not studied but EMPA-KIDNEY will hopefully provide further information on this cohort(22).

4. Where do these drugs fit in the spectrum of therapy for patients with glomerular diseases where immunosuppression is contemplated? For patients with an immune-mediated primary glomerulonephritis and a healthy cardiometabolic phenotype, such as a young person with primary focal segmental glomerulosclerosis, we believe that management should continue as before with prompt and aggressive immunosuppression with the primary aim of prompt remission induction in keeping with existing KDIGO guidelines(4). For patients in whom prompt remission is less likely, for example a patient with primary membranous nephropathy who does not fit the criteria for immunosuppression but is likely to remain proteinuric for some time, then the role for SGLT2i in this setting should be established (figure 2). At present, for patients with IgA nephropathy, management is largely around blood pressure control and maximising RAS inhibition, with steroid therapy considered for a minority with heavier proteinuria despite these measures. Given the results of DAPA-CKD, we believe any clinical trial in IgA nephropathy should include SGLT2i and maximised ACE/ARB as standard of care(33).
5. Do I need to reduce the patient's diuretic dose when I start these medicines? Initial intravascular volume reduction is seen with SGLT2i, although longer term the effects are seen less on the intravascular volume and more on the interstitium(26). Data from DAPA-HF suggests diuretic doses may not need to

be adjusted(34) but in a real world setting, close observation is recommended and individualised management decisions instituted.

6. Is there a level of eGFR below which the benefits are not seen? The licence for level of eGFR to start these medicines varies between countries, but in the clinical trials, these medicines were continued until the patient reached end stage kidney disease, assuming they were tolerated and benefits were seen regardless of level of eGFR at initiation into the trial (30,35).
7. What are the sick day rules for these medicines? The risk of euglycaemic ketoacidosis with these medicines is well described, although no instances have been observed in trials of patients without diabetes(16). However, it is recommended to advise patients to discontinue their medicines if they are fasting or unable to eat, undergoing a major operation or following a low carbohydrate diet. They should recommence once they are reliably eating. There is also a 3-fold increased risk of fungal genital infections with SGLT2i.

Future directions

There are likely to be further trials of these medications in different clinical situations. It would be helpful to know if the benefits of these medicines are additive or synergistic to RAS inhibition and whether SGLT2i as standalone treatment is of benefit. Secondly, whether they can be used in the setting of acute volume overload, as an additional transporter not currently targeted by conventional diuretics. We note pilot trials have been performed in patients with acute decompensated heart failure and suggest these agents are likely to be safe and efficacious in this setting, although larger trials are required(36). Interestingly, this class of drugs has been associated with a reduced incidence of acute kidney injury, another as yet unexplained finding (37) which may lead to an expansion in indication, for example, in prevention of acute kidney injury

(AKI) in high risk settings. Furthermore, it remains uncertain at what stage of CKD SGLT2i should be started in patients with or without diabetes, with absolute benefit likely to be less with well-preserved renal function. It also remains uncertain whether patients should follow a reduced sodium diet to gain further benefit.

What is clear is that any future studies in glomerular disease will require to incorporate SGLT2i as existing standard of care. There is now a clear basis that in emerging trials of novel immunotherapies for glomerular disease, patients should be well established on SGLT2i in addition to RAS inhibition, before being randomised.

Conclusion

In conclusion, SGLT2i have proven benefits for patients with chronic kidney disease and proteinuria, the like of which has not been seen before. It is the duty of clinicians to target the initiation of these medicines promptly and appropriately as above, in order that patients can accrue the benefits, which have been sorely lacking up until this point. It is expected that the remit for these drugs will widen in the near future and as clinicians become familiar with their usage, they should become cornerstones of standard nephrology care.

Key Points:

1. Evidence for prescribing SGLT2i in patients with CKD and proteinuria, with or without diabetes, is incontrovertible.
2. Simple steps can be followed to implement this safely.

3. Studies of SGLT2i in patients with glomerular diseases are urgently required, particularly in IgA nephropathy where steroid therapy is the only recommended immunomodulatory therapy but has a significant side-effect profile.
4. Future studies of glomerular diseases without the inclusion of SGLT2i would be obsolete.

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Conflicts of Interest

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Legend

Figure 1: Seven steps to successful SGLT2i use. Abbreviations: ACEi -angiotensin converting enzyme inhibitor, ARB- angiotensin receptor blocker, SGLT2i – sodium-glucose cotransporter 2 inhibitors, eGFR- estimated glomerular filtration rate, K-potassium, APKD- adult polycystic kidney disease, GN- glomerulonephritis, KFRT- kidney failure requiring replacement therapy.

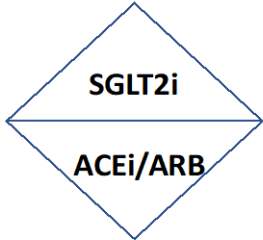
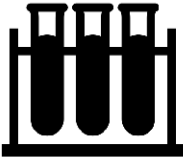

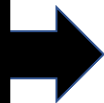
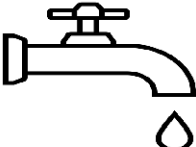
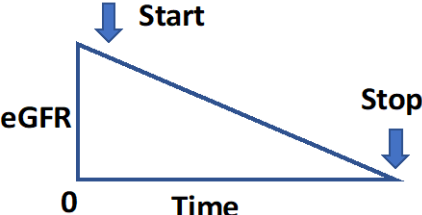

	<p><u>Step 1:</u> Co-prescribe SGLT2i with ACEi/ARB</p>
	<p><u>Step 2:</u> eGFR / K check not required</p>
<p>Vasculitis Lupus nephritis APKD Active immunosuppression</p> 	<p><u>Step 3:</u> These conditions excluded from trials</p>
<p>GN not immuno-suppressed</p>  <p>Start SGLT2i</p>	<p><u>Step 4:</u> Use in non-immunosuppressed GN</p>
	<p><u>Step 5:</u> Diuretic dose will probably not need adjusted</p>
	<p><u>Step 6:</u> Continue SGLT2i until KFRT</p>
	<p><u>Step 7:</u> Advise of sick day rules</p>

Figure 2: Role of SGLT2i in management of glomerular diseases. Abbreviations – FSGS- focal segmental glomerulosclerosis, DMN- diabetes mellitus nephropathy, RASi- renin angiotensin system inhibition, SGLT2i – sodium-glucose cotransporter 2 inhibitors

