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Finally, Some Reason for Hope in Proteinuric Kidney Disease

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Abstract

Background: After years of predictable outcomes with limited tools to combat the ravages of proteinuric chronic kidney disease (CKD) associated with or without diabetes, exciting new options are available to slow the progression of CKD. **Purpose:** Focusing on sodium-glucose co-transporter 2 inhibitors (SGLT2), angiotensin receptor blockers (ARB), angiotensin converting enzyme inhibitors (ACE I), and new mineralocorticoid antagonists (MRA), this review examines how these agents compliment the standard of care in an attempt to educate and stimulate broader use of these agents. **Methods:** Using the search terms "mineralocorticoid antagonist, sodium glucose co-transporter 2 inhibitors, proteinuria, albuminuria, and diabetic kidney disease," five randomized controlled clinical trials were identified and then analyzed in the context of the results found from the Irbesartan Diabetic Nephropathy Trial (IDNT). Two trials using SGLT2 and 2 using MRA were reviewed. **Results:** In the 2 SGLT2 trials renal outcomes were reduced by 30% - 39% among patients with estimated GFR ranging from roughly 25 - 90 mL/min. In the 2 MRA trials, renal outcomes fell by 13% - 18% among patients with estimated GFR ranging from 25 - 90 mL/min. In the IDNT, renal outcomes fell by 19%. Trial duration ranged from 28 - 41 months, and in all trials, the IDNT, Ace inhibitors (ACE I) and ARBs use was uniform. There is small overlap in the 5 trials in which both MRA and SGLT2 agents were used. **Conclusions:** Over a wide range of renal function, both MRA and SGLT2 inhibitors demonstrate outstanding efficacy in diabetic and non-diabetic (SGLT2) proteinuric kidney disease. Compared to the prior standard of care, these agents dramatically improve outcomes.

Keywords

Chronic Kidney Disease, Sodium-Glucose Co-Transporter 2 Inhibitors, Mineralocorticoid Agonists, Angiotensin Receptor Blockers, Angiotensin

Converting Enzyme Inhibitors

1. Introduction

In 1990-2018, the prevalence of End Stage Renal Disease (ESRD) in the US rose in a linear gradient from 866 cases per million to 2242 cases per million. In 2009-2018, all-cause mortality in ESRD fell by nearly 17% but remains quite high. Among those starting dialysis in 2013, 50% of those were dead at 4 years in the hemodialysis (HD) cohort and at 56 months in a peritoneal dialysis (PD) cohort. These numbers aren't appreciably different than in 2008 (43 months in HD, 53 in PD). In 1990, the number of incident patients with ESRD was nearly 51,000, in 2018, this number rose to nearly 132,000 in a linear fashion [1]. According to the Kidney Project, a University of California at San Francisco research outfit, 1% of Medicare enrollees have kidney failure, but account for 7% of expenditures/total budget [2]. Nephrology as a field has had very disappointing outcomes, high incidence/prevalence of ESRD, high mortality rates, and an extremely high cost of care. Multiple efforts have been made to address these with marginal responses [3].

Plagued by high morbidity, mortality and cost, ideally prevention of progression to ESRD would be preferable [4]. In 2001, Lewis *et al.* published the Irbesartan in Diabetic Nephropathy Trial (IDNT), evaluating a population of diabetic and hypertensive patients with proteinuric kidney disease. Subjects were randomized to a target blood pressure of 135/85 or less, and received an antihypertensive regimen with a backbone of Irbesartan, Amlodipine, or placebo. The aim was to determine, independent of blood pressure control, whether an angiotensin receptor blocker (ARB) or calcium channel blocker (CCB) would provide kidney protection against progression of nephropathy in the setting of type 2 diabetes (T2DM). Pertinent renal outcomes fell by 20% and ARBs became the agent of choice for diabetic kidney disease [3] [5]. Later, other trials showed how ACE I reduced renal outcomes in non-diabetic proteinuric kidney disease.

For the next 15 - 20 years, the standard of care in proteinuric kidney disease (diabetic or otherwise) was etched in stone: treat with some form of ARB or ACE I to reduce proteinuria to slow the progression of kidney disease. Other adjunctive therapies such as antihyperlipidemics, mineralocorticoid antagonists, non-dihydropyridine calcium channel blockers or certain forms of beta blockers were also employed [3]. But as above, the prevalence of ESRD rose. How effective was this novel therapy if more and more patients were on dialysis? [6] [7].

2. Results

2.1. Implications of the IDNT

In the IDNT (**Table 1**), 1715 patients were randomly assigned to therapy and followed up for 2.5 years. The primary composite endpoint included doubling of

Table 1. Clinical trials of SGLT2 inhibitors and novel MRA in proteinuric kidney disease.

Trial	FIGARO-DKD (N = 7437)	FIDELIO (N = 5734)	CREEDENCE (N = 4401)	DAPA-CKD (N = 4304)	IDNT (N = 1715)	P VALUE
Year Published	2021	2020	2019	2020	2001	
DM%	100	100	100	67	100	<0.00001
Mean eGFR (ml/min) or Cr (mg/dL)	68	44	56	43	1.67	0.009
GFR range (mL/min)	25 - 90	25 - 60	30 - 90	25 - 75	N/A	
Proteinuria (g/d)	0.31	0.83	0.92	0.95	2.9	0.028
HbA1c	7.7	7.7	8.3	N/A	8.1	
Age	64	65	63	62	59	<0.00001
M/F	69/31	69/31	66/34	67/33	67/33	
W/B/A	72/3.5/20	63/5/25	67/5/20	52/5/35	76/11/4	
ACE/ARB	100	100	100	100	50	
SGLT2 USE (%)	8	4.6	100	100	0	
Renal Outcome RR (%)	13	18	30	39	20	<0.0001
Trial length (mos)	41	30	30	28	30	<0.00001

baseline serum creatinine, the development of ESRD, or death from any cause. Versus Amlodipine, Irbesartan reduced the risk of composite outcome by 23%, and 20% versus placebo [8].

Maqsood *et al.*, reviewed 6 trials of non-diabetic proteinuric kidney disease concluding that reducing the absolute amount of proteinuria with an ACE I or ARB slowed the overall progression of kidney disease and often contributed to better cardiovascular outcomes as well [7].

Efforts to uncover novel pathways to slow the progression of kidney disease were unsuccessful [3] [10]. Combining ACE I and ARB was not felt to be effective and was associated with concerning lab abnormalities. When the focus shifted to management of T2DM, new pathways were discovered offering promising results [7] [8].

2.2. SGLT2 Inhibitors

Healthy kidneys can reabsorb up to 180 g/d of glucose but above this level, glucosuria ensues, a teleological safety valve of sorts [9] [10]. Sodium Glucose Co-transporter 2 Inhibitors have existed for over 100 years. A compound known as phlorizin, which comes from apple tree bark, had been studied for over 150 years. As early as 1933, it was tested in a small cohort, and was found to increase glucose in the urine, lower blood glucose levels, and prevent reabsorption of glucose. Because its effects were not limited to the kidney, inhibiting glucose absorption in the intestine, it could lead to hypoglycemia, and was not felt to be safe for clinical use. Little progress occurred in this field for many years thereafter [11].

SGLT2 cotransporters are responsible for reabsorbing roughly 90% of renally filtered glucose. Pharmacological inhibition of SGLT2 co-transporters reduces hyperglycemia by decreasing renal glucose threshold, thus increasing urinary glucose excretion [12]. Canagliflozin was the first SGLT2 inhibitor to be FDA-approved in 2013 followed by Dapagliflozin, (marketed as Farxiga®) in January 2014 and empagliflozin (marketed as Jardiance®) in August 2014 [4].

The CREEDENCE trial (**Table 1**), published in 2019, enrolled 4401 subjects with T2DM, a mean estimated glomerular filtration rate (eGFR) of 56 ml/min, with roughly 900 mg/d of albuminuria, mean hemoglobin A1c of 8.3%, 100% received some form of ACEI or ARB, and randomized participants to Canagliflozin or placebo and found a 30% reduction in renal outcomes over the course of 30 months [13]. The DAPA-CKD trial (**Table 1**), published in 2020, randomized 4304 subjects among whom 67% were diabetic, but all proteinuric (950 mg/d), mean eGFR of 43 ml/min, all taking an ACE I or ARB, and found renal outcomes fell by 39% over 28 months [14].

In each trial, the standard of care, first established nearly 20 years earlier, in the IDNT, was applied such that all patients were treated with ACE I or ARB as the backbone of antiproteinuric therapy. These agents led to a 30% - nearly 40% reduction in renal outcomes including progression to end stage renal disease, deaths from renal causes, and sustained decline in eGFR by 50% [15]. While this was novel and a quantum leap in the treatment of type 2 diabetes associated with chronic kidney disease, that it was also effective in nondiabetic proteinuric kidney disease opened the door to much broader application of these agents [8] [15] [16] [17].

With such disappointing trends and rising numbers of patients with ESRD, the capacity to slow the progression of kidney disease above and beyond the protection afforded by ARB/ACE I use, is the most important advance made in the care of patients with chronic kidney disease since the IDNT [3]. Broader application of these agents will hopefully lead to a reduction in the number of patients starting any form of dialysis, potentially provide more time to facilitate renal transplantation, and reduce death rates in this population.

2.3. ACEI/ARB

Somewhat concurrently with the advent of SGLT2 inhibitor therapy was the introduction of selective mineralocorticoid antagonism. The use of ACEI/ARB to slow the progression of kidney disease has been well established but other agents have the capacity to reduce proteinuria which is associated with progressive kidney disease. Two trials stand out in terms of diabetic kidney disease, Sun *et al.* and Fidelio [18] [19].

Sun *et al.* performed a meta-analysis of 18 trials evaluating the potential benefits and adverse effects of adding a mineralocorticoid receptor antagonist (MRA) to angiotensin-converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB), as standard treatment in patients with diabetic nephropathy.

Among 1786 subjects studied, they found co-administration of MRA and ACEI/ARB significantly reduced urinary albumin excretion and the urinary albumin-creatinine ratio, lowered blood pressure but did not improve the eGFR. Hyperkalemia was more common in the treated groups. Of these 18 studies, only 1 included the use of Finerenone and the remainder studied Spironolactone or Eplerenone [19].

Finerenone is a selective MRA. Preclinical data shows kidney and cardiovascular benefits of finerenone were associated with potent anti-inflammatory and antifibrotic effects through inhibition of overactivation of the mineralocorticoid receptor. The delayed response seen in the Fidelio Trial (see below), may support the hypothesis that finerenone slows CKD progression by influencing tissue remodeling [18].

Fidelio (**Table 1**) was published in 2020 and enrolled 5734 patients with T2DM, hypertension and with a mean eGFR 44 ml/min, ~830 mg/d of proteinuria, all treated with ACEI/ARB, and found an 18% risk reduction in renal outcomes (kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes) vs placebo at 30 months [18].

FIGARO-DKD (**Table 1**) was published in 2021 and enrolled 7437 patients with T2DM, hypertension and with a mean eGFR 44 ml/min, ~830 mg/d of proteinuria, all treated with ACEI/ARB, and found an 18% risk reduction in renal outcomes (kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes) vs placebo at 41 months. This finding failed to reach statistical significance as the hazard ratio confidence interval was 0.76 - 1.01, but clearly showed a strong trend toward encouraging renal outcomes while demonstrating a 13% risk reduction in primary cardiovascular outcomes (composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) [5] [20].

3. Discussion

End Stage Renal Disease research has stagnated over the last 2 decades until the introduction of SGLT2 inhibitors and selective MRAs [7] [18]. Each agent, when combined with an ACEI or ARB has been shown to be effective in either diabetic kidney disease with proteinuria or kidney disease with proteinuria but without diabetes. Each also has shown strong cardiovascular data [7].

In all of these trials the prerequisite therapy had to include ACEI or ARB, but very few subjects took both SGLT2 inhibitors and MRAs. While ACEIs prevent the production of Angiotensin II, ARBs reduce the action of Angiotensin II [19]. MRAs act later in the Renin-Angiotensin-Aldosterone pathway [18], inhibiting the effects of Aldosterone. SGLT2 inhibitors reduce renal glucose reabsorption and in turn may also reduce blood pressure [21]. Because these newer agents act through different pathways, it's conceivable combining them would have salutary effects on renal outcomes [8] [15] [16] [17]. Determining this will be the next important frontier in treating diabetic kidney disease associated with proteinu-

ria, but less likely to be considered among non-diabetic patients in whom only the SGLT2 inhibitors have demonstrated efficacy.

There are some tedious side effects associated with these agents, particularly urinary tract infectious disease, mycotic infections, and diabetic ketoacidosis associated with SGLT2 inhibitors, and hyperkalemia with MRAs [11] [18]. On some level this has reduced broader application of these agents. The medical field unpredictably tolerates various side effects in its pharmacological armamentarium. Transaminitis is associated with statin use [22], and radiocontrast nephropathy is associated with intravenous contrast dyes [23]. Severe, chronic interstitial nephritis may result from lithium use in bipolar disorder [24], yet all of these agents are used commonly in medical practice. The side effect profile associated with these novel agents is comparatively benign [18].

4. Conclusions

Their efficacy, particularly of the SGLT2 inhibitors in non-diabetic and diabetic kidney disease associated with proteinuria, dwarfs the standard of care. We believe these agents, and to the lesser extent, the MRAs, should be significantly more widely used among patients with these medical problems.

In doing so, slowing the progression of chronic kidney disease by novel means, could reduce the incidence of ESRD, provide more time to identify kidney transplant donors, reduce morbidity and mortality associated with kidney failure, and reduce skyrocketing costs of care in this population.

Conflicts of Interest

The authors declare no conflicts of interest.

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