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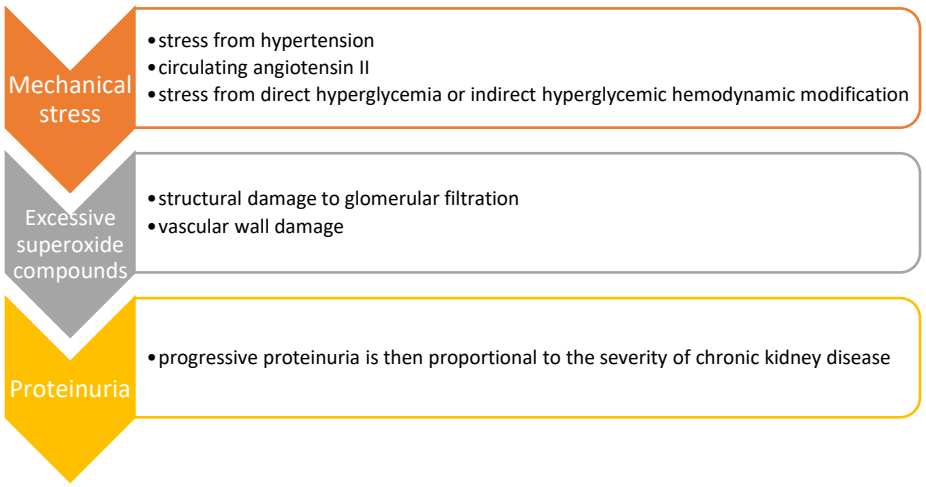
Prevention and Delayed Progression of Diabetic Nephropathy

Russell Scott
Southern Illinois University School of Medicine, Doctor of Medical Science, russell.scott@siu.edu

INTRODUCTION/EPIDEMIOLOGY

Morbidity and mortality associated with diabetes mellitus remain a national and global challenge. Diabetes mellitus, both types 1 and 2, are diseases defined by multiple microvascular and macrovascular comorbid complications. For the purpose of this research, the author will focus on diabetes mellitus comorbidity and specifically, diabetic nephropathy (DN). Proteinuria, specifically albuminuria, is a marker for diabetic renal damage. For reference purposes, severe (macroalbuminuria) DN is defined by urine albumin excretion greater than or equal to 300mg/day as measured by urine albumin-to-creatinine ratio (UACR). The pathogenesis caused by DN includes mechanical stress and elevated levels of angiotensin II.[1] Mechanical stress is mainly caused by systolic hypertension.[1]

Figure 1. Pathogenesis of Diabetic Nephropathy[1]

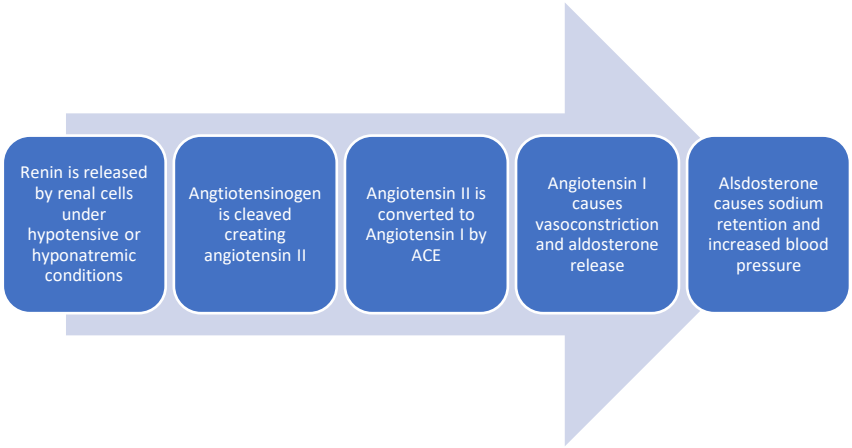


Both mechanical stress and angiotensin II cause excessive generation of superoxide compounds.[1] These compounds in turn lead to structural damage to the glomerular filtration system and cause damage to the vascular wall.[1] Diabetic nephropathy is the major cause of end-stage renal disease (ESRD).[2] With normal renal function, protein is not filtrated into the urine and is reabsorbed back into circulation. Initially DN is characterized by hyperfiltration and protein, specifically

albuminuria in the early phases of disease, which is then followed by progressive renal function decline.[2] Diabetic nephropathy prevalence can vary among type 2 diabetes mellitus patients and can be confounded by other concomitant glomerular or tubular pathologies, or peripheral vascular disease (PVD).[2] All-cause mortality in patients with DN is approximately 30 times higher than in diabetes patients without nephropathy.[2] Interestingly, the overwhelming majority of patients with DN will die from cardiovascular disease (CVD) before reaching ESRD.[2] Diabetic Nephropathy accounts for 30 to 50 percent of cases of ESRD in the United States.[3] Thirty to forty percent of diabetes patients develop DN.[3] As end-stage complications of DN such as ESRD are irreversible, management of DN is focused on prevention and delayed progression. At its core, management or prevention of DN can be divided into four categories: CVD risk reduction, glycemic control (hemoglobin A1c [HbA1c] less than seven percent), blood pressure control (targeting less than 125/80), and inhibition of the renin-angiotensin system (RAS).[3,20]

Looking at the renin-angiotensin system at a glance, renin is released by renal cells when the kidneys sense hypotension or hyponatremia. Renin's substrate angiotensinogen is then cleaved, creating the inactive peptide angiotensin II. Angiotensin II is converted to angiotensin I

Figure 2. Renin-Angiotensin System[4]



Abbreviation: ACE, angiotensin-converting enzyme.

by angiotensin-converting enzyme (ACE) in endothelial cells in the lungs. Angiotensin II causes vasoconstriction as well as aldosterone release from the adrenal gland, resulting in sodium retention and increased blood pressure. Current guidelines with the highest graded evidence-based recommendations for prevention and delayed progression of DN is treatment with a RAS-blocking agent.[3]

Clinicians are faced with numerous challenges regarding DN management. A major challenge includes patients that have true allergies or intolerances to RAS blocking agents, specifically ACE inhibitors and angiotensin receptor blockers (ARB). The research contained will explore these challenges to see if there are existing alternative therapies that prevent or delay the progression of DN and thus would be suitable RAS blockade replacement.

METHODS

The reader will notice that some of the literature presented in this exercise appears to be dated at face value. We must be reminded that evidence supporting the efficacy of RAS blocking agents has been well documented over time and that inhibition of this pathway has been the cornerstone of management of DN for decades. As part of epidemiologic research, at times it is imperative to provide data extending throughout the entirety of the experimentation process, from its inception until the current state of the research.

Numerous types of research studies were examined including multiple randomized controlled trials and various observational studies. The evidence in these trials has subsequently resulted in highly graded expert and guideline-based recommendations. This clinical guidance grading system consists of two components: recommendation strength (one or two) and quality of evidence (A,B, and C).[5] Grade one carries a strong recommendation, grade two is weaker. Grade A contains high-quality evidence, grade C contains lower-quality evidence. The majority of evidence supporting RAS blockade for prevention or delayed progression of DN carries a 1B recommendation which equates to a strong recommendation with moderate evidence quality including randomized controlled trials (RCT).[6] As we know in scientific research, evidence obtained from RCTs is the benchmark or “gold standard” regarding strength of evidence. It is also widely accepted that other forms of research can be used with confidence based on appropriate peer review. This non-RCT research can have very strong evidence as determined by peer review including assessment and validation of study design and strength of evidence based

on other determinants such as volume of study participants. Observational studies and meta-analyses, such as some of those contained within
this research exercise, can be examples of these types of research that contain acceptable data as determined by peer review.

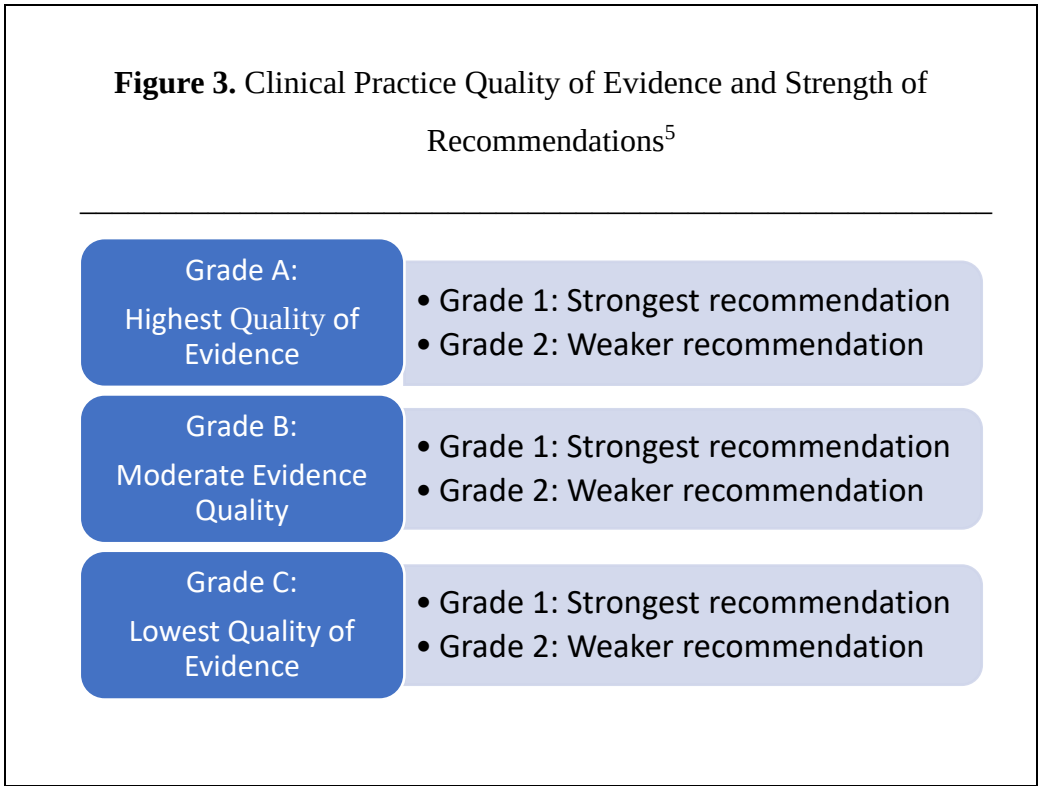


Figure 3. Clinical Practice Quality of Evidence and Strength of Recommendations[5]

RESULTS and DISCUSSION

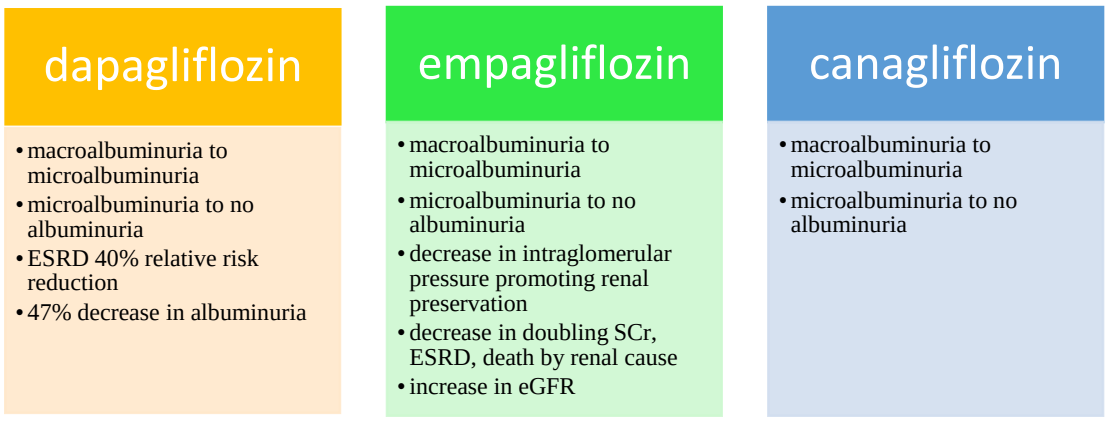
Exploration of the literature pertaining to alternative DN management therapeutics compared to RAS blockade reveals potentially promising data. In a meta-analysis that included the review of 12 RCTs with a total of 947 patients, there was no statistically significant difference between ACEi and CCBs pertaining to progression from microalbuminuria (urine albumin excretion 30-299mg/day) to macroalbuminuria (urine albumin excretion greater than or equal to 300mg/day), making them equally effective at reducing the progression of DN in both type 1 and type 2 diabetes.[7] This similarity was noted in non-dihydropyridine CCBs such as verapamil and diltiazem and not in dihydropyridines such as amlodipine.[8] Six of the RCTs totaling 609 patients

with long-term comparison of ACEi and CCBs with early DN revealed progression to normoalbuminuria in both cohorts.[7] Long-term treatment or comparisons were defined as observational periods occurring greater than 1 year.[7] According to Bakris GL, both ACE inhibitors (lisinopril) and CCBs (diltiazem) reduced albuminuria to a similar degree in type 2 diabetes patients with severe albuminuria or macroalbuminuria.[7] Although it is documented in another section of this article, it is worth mentioning in this section that additional studies are needed to assess the antiproteinuric effect of combining non-dihydropyridine CCBs with MRAs.

Sodium-glucose co-transporter 2 inhibitors have benefits beyond glucose lowering effects including cardiovascular (CV) benefits and potential renoprotective effects.[9] Clinical evidence indicates that SGLT2 inhibitors can reduce the risk of onset or progression of albuminuria and can provide additional synergistic effects through a range of mechanisms.[9] Some of the mechanisms include blood pressure lowering, reduction of intraglomerular pressure and hyperfiltration, modification of inflammatory processes, and reduction of ischemia-related renal injury.[9] Several cardiovascular outcome trials have included positive renal endpoints adding to the growing evidence and enthusiasm that these agents offer renoprotective effects in type 2 diabetes patients.[9] The CV outcome trials referenced in the article by Davidson JA are two RCTs. In several trials comparing SGLT2 inhibitors to placebo investigating CV and renal endpoints including the EMPA-REG OUTCOME trial and CANVAS Program, comparisons in type 2 diabetes patients with chronic kidney disease (CKD) up to stage III revealed that empagliflozin, dapagliflozin, and canagliflozin reduced baseline macroalbuminuria to microalbuminuria and microalbuminuria at baseline to no albuminuria.[9] When empagliflozin was stopped during the EMPA-REG OUTCOME trial, rises in estimated glomerular filtration rate (eGFR) declined to pretreatment levels.[9] Researchers have postulated that the hemodynamic effect of empagliflozin associated with the reduction of intraglomerular pressure may promote long-term kidney function preservation.[9] Aside from the albuminuria improvement with canagliflozin in the CANVAS Program, the composite outcome of sustained doubling of serum creatinine (SCr), ESRD, and death from renal causes was less frequently observed in the empagliflozin arm compared to the placebo arm.[9] A long-term dapagliflozin study in patients with renal insufficiency revealed that dapagliflozin reduced albuminuria over two years in type 2 diabetes patients and CKD stage III without increasing the rate of adverse events.[9]

Blood pressure-lowering effects of SGLT2 inhibitors are maintained in patients with CKD and could contribute to reduced renal burden along with providing adjunct blood pressure support in combination with other antihypertensive therapeutics.[9] Furthermore, SGLT2 inhibitor use in type 2 diabetes patients can reduce kidney endpoints including ESRD.[10,11] The evidence supported in articles by Palmer et al. and Salah et al. is obtained from meta-analyses of numerous RCTs. Palmer et al. conducted a very large meta-analysis of 33 trials including approximately 100,000 type 2 diabetes patients with eGFR below 15 ml/min per 1.73 ^{m2} or ESRD requiring transplant and broadly concluded that SGLT2 inhibitors reduced kidney failure.[10] Although guidance exists that recommends against the use of SGLT2 inhibitors in patients with eGFR less than 25 mL/min/1.73 m^2, there is evidence that use of these agents under these circumstances can be continued safely.[12] In a meta-analysis of 11 phase three RCTs with patient inclusion criteria of type 2 diabetes and stages IIIb – IV CKD, dapagliflozin reduced albuminuria by 47 percent observed over 102 weeks.[12] Additionally, pleiotropic benefits of the SGLT2 inhibitor dapagliflozin were also

Figure 4. Summary or SGLT2 inhibitor renal outcomes[9,10,11,12]



Abbreviations: SGLT2, sodium-glucose co-transporter 2; ESRD, end-stage renal disease; SCr, serum creatinine; eGFR, estimated glomerular filtration rate.

Definitions: microalbuminuria, 30-299mg/day of urine albumin excretion; macroalbuminuria, >300mg/day of urine albumin excretion

observed in this meta-analysis including sustained observed improvements in blood pressure and decreased body weight.[12] It is notable that in the observed diabetes patients with CKD stages III-IV, HbA1c reduction was not appreciated compared to placebo indicating that SGLT2 inhibitor effects on albuminuria, blood pressure, and weight loss are dissociated from their glucose-lowering effects and possibly attributed to natriuretic and diuretic mechanisms.[12] The lack of HbA1c reduction observed in CKD stages III – IV in the article by Dekkers et al. is likely explained by the concept that as the glucose-lowering effect of SGLT2 inhibitors is dependent on glomerular filtration, glucose excretion through urination declines with increasing severity of renal impairment.[9,12] According to Dekkers et al., the anti-proteinuric effect of dapagliflozin is considered clinically significant based on large epidemiological studies, possibly translating to a relative risk reduction of 40 percent for end-stage kidney disease.[12] This determination, as defined by Dekkers et al., is supported by evidence obtained in a meta-analysis of several phase three RCTs.

There is emerging evidence that SGLT2 inhibitors improve glycemic control and reduce blood pressure in type 1 diabetes, suggesting a potential for type 1 renoprotective effects.[13] These renoprotective benefits may also be possible by the reduction of hyperfiltration, which is a risk factor for DN and vascular dysfunction.[13] Thus, SGLT2 inhibitors may be a safe therapeutic option in type 1 diabetes patients that concomitantly reduce hyperglycemia, hyperfiltration, and blood pressure leading to renoprotective benefits.[13] There are several ongoing dedicated trials providing optimism for researchers that SGLT2 inhibitors will continue to provide evidence and guidance regarding their ability to slow the development and progression of DN in both type 1 and type 2 diabetes.[9,13]

Promising renoprotective evidence also exists for GLP1 receptor agonists. In a large trial of type 2 diabetes patients, the GLP1 receptor agonist liraglutide decreased the incidence of multiple kidney endpoints including new onset macroalbuminuria, doubling of serum creatinine, and ESRD when combined with usual care, however components of usual care are not specified and may or may not include RAS blockade.[14] The LEADER trial cited in the article by Mann et al. is a placebo-controlled RCT that included over 9,000 participants with type 2 diabetes and cardiovascular disease comparing liraglutide to placebo for CVD endpoints. This RCT noted approximately 5.7 percent of patients in the liraglutide arm developed renal outcomes compared

to 7.2 percent in the placebo arm, translating to a reduction of new or worsening nephropathy (proteinuria, increasing serum creatinine, reduction in eGFR) by 22 percent over a 3.8 year follow up interval, including a 26 percent reduction in macroalbuminuria.[14,17] In study participants, the liraglutide verses placebo comparison yielded a 17 percent reduction in the UACR in the liraglutide arm.[14] Also noted in additional trials (AWARD-7 and REWIND),

Table 1: Summary of Renal Endpoint Trial Data for Glucagon-like Peptide 1 Receptor Agonists[13,14,15,16,17]

RCT	GLP1 Receptor Agonist	Number of Participants	Follow-up Interval	Renal Outcome
LEADER	liraglutide	> 9,000	3.8 years	26% reduction in macroalbuminuria
AWARD-7	dulaglutide	577	1 year	29% reduction in UACR
REWIND	dulaglutide	> 9,000	5.4 years	30% reduction in eGFR decline
SUSTAIN-6	semaglutide	> 3,000	1.8 years	46% reduction in macroalbuminuria
AMPLITUDE-O	efpeglenatide	> 4,000	1.8 years	32% reduction in renal outcomes[a]

Abbreviations: RCT, randomized-control trial; UACR, urine albumin-creatinine ratio; eGFR, estimated glomerular filtration rate; GLP1, glucagon-like peptide 1.

[a] decrease in kidney function or macroalbuminuria.

the GLP1 receptor agonist dulaglutide slowed the rate of eGFR decline and prevented the worsening of albuminuria in patients with type 2 diabetes with and without CKD.[15,16] The

AWARD-7 trial cited in the article by Tuttle et al. is a multicenter open-label RCT with 577 participants from 99 sites in nine different countries. The antiproteinuric effects of dulaglutide noted that the 1.5 milligrams (mg) arm revealed approximately a 29 percent reduction in UACR compared to the insulin arm.[14] The REWIND trial cited in the article by Gerstein et al. is a multicenter, randomized, double-blind, placebo-controlled trial at 371 sites in 24 countries with over 9,000 participants and the renal endpoint included an approximate 30 percent reduction in eGFR decline compared to the placebo arm.[15] The SUSTAIN-6 RCT contains over 3,000 participants structured similarly to LEADER, though comparing semaglutide instead of liraglutide, and the SUSTAIN-6 trial revealed a 46 percent reduction in macroalbuminuria.[16] The GLP1 receptor agonist efpeglenatide is compared to placebo in the AMPLITUDE-O RCT that includes over 4,000 type 2 diabetes participants with CVD or CKD, assessing for CV and renal outcomes (decrease in kidney function or macroalbuminuria).[17] Efpeglenatide was shown to reduce the risk of renal outcomes by 32 percent over mean follow-up of 1.8 years.[17]

In addition to the prevention of worsening albuminuria in diabetes patients, the renoprotective benefit of prevention of macroalbuminuria onset has been attributed to GLP1 receptor agonists.[16] Glucagon-like peptide 1 receptor agonists induce their renoprotection through multiple pathways. These pathways include glucose and blood pressure lowering effects in addition to weight loss, among other potential benefits.[16] In addition to SGLT2 inhibitors, the anti-hyperglycemic therapeutics with the strongest evidence of cardiovascular and kidney outcomes in patients with pre-existing cardiovascular or kidney disease are GLP1 receptor agonists.[9] In type 2 diabetes patients with DN, GLP1 receptor agonists can improve glycemic control and provide additional renoprotective benefits.[17,18,19]

Mineralocorticoid receptor antagonists have been included in the hypertension and heart failure treatment paradigm for decades. There are numerous RCTs that show benefit of albuminuria reduction in diabetes patients when MRAs are added to RAS blocking agents. It is well documented that the majority of patients with hypertension are treated with multiple antihypertensive agents to achieve blood pressure goal compared to a lone agent. Mineralocorticoid receptor antagonists have pleiotropic benefits apart from diuresis including anti-fibrotic, anti-hypertensive, and antiproteinuric effects.[20] Plausibility for renoprotection in diabetes patients exists regarding these pleiotropic benefits including antiproteinuric effects,

regarding combined MRAs with other potential antiproteinuric effects of non-ACE inhibitor and non-ARB agents such as non-dihydropyridine CCBs. Additional studies need to be conducted to assess this plausibility. Regarding lone MRA therapy for reduction or delayed DN progression when there is the inability to utilize RAS blocking agents, preclinical evidence reveals that MRAs reduce proteinuria in type 2 diabetes patients with DN and improve cardiovascular outcomes in chronic kidney disease patients.[21] Based on these findings, further investigation for validation with additional clinical trials is necessitated.

CONCLUSION

As DN is a leading contributor to diabetes morbidity and mortality and is the leading cause of end-stage renal disease, prevention and delayed progression of DN is a critically important aspect of comprehensive diabetes management, both in type I and type II diabetes. Renin-angiotensin system blockade is the current industry standard therapeutic for DN prevention and delayed progression in both type I and type II diabetes based on decades of literature comprising the highest-quality evidence from randomized-controlled trials (RCT). When patients have allergies, intolerances, or contraindications to RAS blockade therapeutics, clinicians are faced with the need to find comparable or suitable alternatives for the management of DN. Based on available research, promising data are emerging supporting renoprotective benefits of CCBs, SGLT2 inhibitors, and GLP1 receptor agonists in type II diabetes patients, along with CCBs and SGLT2 inhibitors in type I diabetes patients. In limited circumstances, these benefits may be comparable to RAS blockade and suitable alternatives that are worth implementing in other circumstances, with the potential for promising data still to come. The medical community is in need of more research on both adjunct MRA therapy or MRA monotherapy for the prevention and delayed progression of DN in both type 1 and type 2 diabetes patients, though current evidence is promising.

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