A Systematic Literature Review of Treatment Patterns, Safety Profiles, and Long-term Disease Progression in Patients With Chronic Kidney Disease and Type 2 Diabetes Mellitus

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BACKGROUND AND OBJECTIVES

- Diabetes is one of the leading causes of chronic kidney disease (CKD) worldwide, with CKD affecting 36% to 40% of patients with diabetes, or ~11 to 12 million patients in the United States (US) (Nelson 2019[1]; Wu 2016[2]; CDC 2020[3]).
- As new therapies are developed to slow the progression of CKD in patients with comorbid type 2 diabetes mellitus (T2D), it is important to understand the real-world treatment patterns, safety profiles of current treatments, and residual risk for long-term disease progression among patients with CKD and T2D.
- This systematic literature review (SLR) was conducted to evaluate these research questions using published data for patients in the US.

METHODS

- Search terms included key words for disease, outcomes, and study designs of interest to identify real-world studies of patients with CKD and T2D receiving finerenone, steroidal mineralocorticoid receptor antagonists (sMRAs) (eg, spironolactone and eplerenone), angiotensin-converting enzyme inhibitors/ angiotensin-II receptor blockers (ACEIs/ARBs), glucagon-like peptide-1 receptor agonists (GLP-1s), or sodium-glucose cotransporter-2 inhibitors (SGLT-2is).
- Following Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and the National Institute for Health and Care Excellence (NICE) guidance for SLRs, inclusion/exclusion criteria were applied by 2 independent reviewers, and quality assessments were conducted on included studies. All data extracted from the studies and included in the SLR were fully validated by a second researcher.

RESULTS

- A total of 17 studies were included; of which, 14 reported treatment patterns, 6 reported safety, and 9 reported disease progression. Most of the studies were retrospective analyses (n=14), and the remaining 3 were cross-sectional.

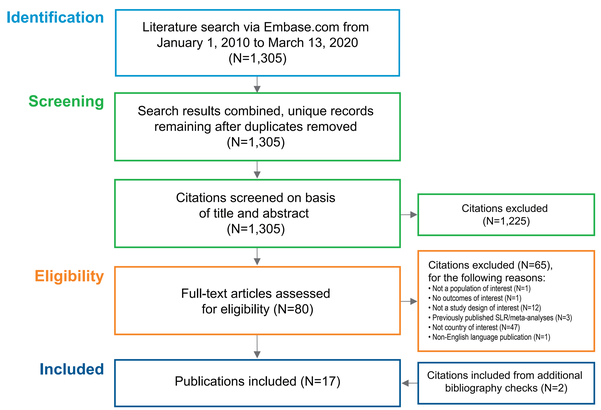
Treatment patterns

- The proportion of patients receiving each class of treatment varied widely; however, ACEIs and ARBs were used most frequently (**Figure 2**).
- The usage of ACEIs and ARBs reported in the literature appears to be in line with current guidelines, though the use of SGLT2 inhibitors (SGLT2is) appears low in this patient population.
  - Current therapeutic adoption of SGLT2is may be underreported in the literature as there has not been adequate time to gather data since the introduction of SGLT-2is as a treatment option for CKD associated with T2D.
- sMRA usage, CKD stage, and albuminuria severity may contribute to the variations in ACEI and ARB use (**Figure 3**), with concomitant sMRA treatment, earlier stage CKD, and macroalbuminuria associated with higher proportions of patients receiving ACEI or ARB.

Safety and disease progression

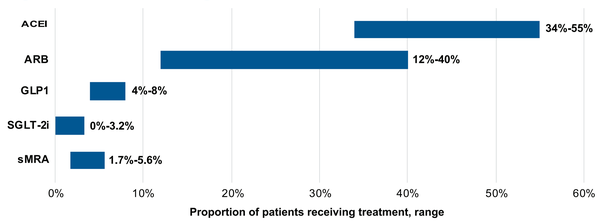
- The incidence of serious hyperkalemia was infrequently reported, but among patients with stage CKD 3 or 4, rates varied by treatment and comorbid heart failure (HF) (**Figure 4**).

Figure 1. PRISMA diagram showing flow of literature



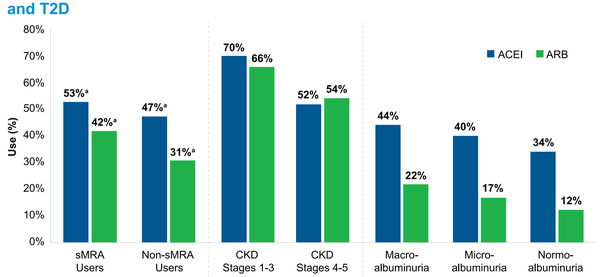
Key: PRISMA[4] – Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR – systematic literature review.

Figure 2. Patients receiving each class of treatment



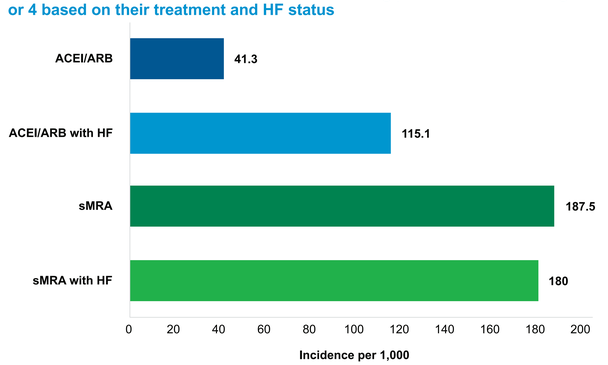
Key: ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin-II receptor blocker; GLP-1 – glucagon-like peptide-1 receptor agonist; sMRA – steroidal mineralocorticoid receptor antagonist; SGLT-2i – sodium-glucose cotransporter-2 inhibitor.

Figure 3. Factors potentially affecting ACEI and ARB use in patients with CKD and T2D



[a]Each percentage reported is the average of 2 studies.
Normoalbuminuria: urinary albumin excretion <30 mg/24 hrs or ACR <30 µg/mg; microalbuminuria: urinary albumin excretion 30–300 mg/24 hrs or ACR 30–300 µg/mg; macroalbuminuria: urinary albumin excretion >300 mg/24 hrs or ACR >300 µg/mg.
Key: ACEI – angiotensin-converting enzyme inhibitor; ACR – albumin-to-creatinine ratio; ARB – angiotensin-II receptor blocker; CKD – chronic kidney disease; hrs – hours; sMRA – steroidal mineralocorticoid receptor antagonist; T2D – type 2 diabetes.

Figure 4. Incidence of serious hyperkalemia among patients with CKD stage 3 or 4 based on their treatment and HF status



Key: ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin-II receptor blocker; HF – heart failure; sMRA – steroidal mineralocorticoid receptor antagonist.

- Potassium monitoring was protective of hyperkalemia in all patients treated with an ACEI or ARB (risk ratio [RR]: 0.19, 95% CI: 0.11, 0.36), as well as patients with HF who were treated with an ACEI or ARB (RR: 0.46, 95% CI: 0.16, 1.36), and patients treated with an sMRA (RR: 0.26, 95% CI: 0.01, 4.79).
- sMRA users, compared to matched non-users, experienced higher frequencies of acute kidney injury (AKI), renal decline, diabetic retinopathy, stroke, hyperkalemia, acute coronary syndrome, peripheral artery disease, and HF. Progression to end-stage renal disease (ESRD) was similar among sMRA users and matched non-users.
  - The highest rates of safety events were seen among sMRA users of <6 months compared with users of ≥6 months and non-users.
  - When patients with HF were considered separately, safety event rates were similarly highest for sMRA users of <6 months.
- ACEI, ARB, and sMRA users had residual disease progression.
  - As these drug classes are recommended for use in patients with risk factors for disease progression, this association may be due to the patient population assessed rather than due to the treatment received.

LIMITATIONS

- There were limited data addressing treatment switches and sequences, as well as rates of cardiovascular mortality.
- The studies identified by this review were based in the US; therefore, the results of this literature review may not represent real-world trends in other geographical regions.

CONCLUSIONS

- ARBs or ACEIs were used more frequently than GLP-1s or SGLT-2is.
- sMRA use was correlated with a greater likelihood of receiving ARB or ACEI treatment, rates of adverse events, and renal decline.
- ARB or ACEI administration was associated with an increased risk of CKD disease development and progression to ESRD.
- Limited usage and availability of GLP-1s or SGLT-2is during the time period covered by identified studies is a potential explanation for the lack of overall reported outcomes data for these treatments.
- Additional research is needed on patients with CKD and T2D to address current gaps in the literature, including treatment switching and sequences, impact of the introduction of SGLT2is on treatment patterns, development of HF, and cardiovascular mortality.

Studies Included in the SLR

- Ajiboye O, Segal JB. National trends in the treatment of diabetic nephropathy in the United States. *J Clin Pharm Ther.* 2017 Jun;42(3):311-317.
- Arnold SV, McGuire DK, Inzucchi SE, Tang F, Mehta SN, Lam CSP, Goyal A, Sperling LS, Wong ND, Hammar N, Fenici P, Kosiborod M. Assessing use of patient-focused pharmacotherapy in glycemic management through the Diabetes Collaborative Registry (DCR). *J Diabetes Complications.* 2018 Nov;32(11):1035-1039.
- Blankenburg M, Fett AK, Eisenring S, Haas G, Gay A. Patient characteristics and initiation of mineralocorticoid receptor antagonists in patients with chronic kidney disease in routine clinical practice in the US: A retrospective cohort study. *BMC Nephrol.* 2019 May 16;20(1):171.
- Blankenburg M, Kovesdy CP, Eisenring S, Fett A, Schokker EW, Korn J, Gay A. Treatment patterns in type 2 diabetes patients with chronic kidney disease-a cohort study. *Diabetes.* 2018;67(Suppl 1):A142.
- Blankenburg M, Kovesdy CP, Fett AK, Griner RG, Gay A. Disease characteristics and outcomes in patients with chronic kidney disease and type 2 diabetes: A matched cohort study of spironolactone users and non-users. *BMC Nephrol.* 2020 Feb 26;21(1):61.
- Boye K, Mody R, Wu J, Lage MJ, Botros FT, Woodward B. Effects of dulaglutide and insulin glargine on estimated glomerular filtration rate in a real-world setting. *Diabetes.* 2018;67(Suppl 1):A416-A417.
- Campbell HM, Khan N, Raisch DW, Borrego ME, Sather MR, Murata GH. Angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers for end-stage renal disease/mortality in type 2 diabetes. *Diabetes Res Clin Pract.* 2013 Dec;102(3):233-241.
- Dawwas GK, Smith SM. Risk of inflammatory bowel disease with sodium glucose co-transporter-2 inhibitors compared to dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes. *Pharmacoepidemiol and Drug Saf.* 2019;28(Suppl 2):38.
- Iyer N, Li Q, Dang-Tan T, Gamble C, Bakris G. Use of glucose-lowering treatments among patients with diabetic kidney disease in the United States. *J Manag Care Spec Pharm.* 2019;25(Suppl 10-A):S41-S42.
- Leehey DJ, Kramer HJ, Daoud TM, Chatha MP, Isreb MA. Progression of kidney disease in type 2 diabetes - beyond blood pressure control: an observational study. *BMC Nephrol.* 2005;6:8.
- Morales-Alvarez MC, Garcia-Dolagaray G, Millan-Fierro A, Rosas SE. Renal function decline in Latinos with type 2 diabetes. *Kidney Int Rep.* 2019 May 22;4(9):1230-1234.
- Patorno E, Gopalakrishnan C, Bartels DB, Brodovicz KG, Liu J, Schneeweiss S. Preferential prescribing and utilization trends of diabetes medications among patients with renal impairment: Emerging role of linagliptin and other dipeptidyl peptidase 4 inhibitors. *Endocrinol Diabetes Metab.* 2018.1:e00005
- Pope E, Castro R, Preblick R, Zhou FL. Patient profile and burden of illness: chronic kidney disease (CKD) in a population with type 2 diabetes (T2D). *Endocr Pract.* 2019;25(1):38A.
- Raebel MA, Ross C, Xu S, Roblin DW, Cheetham C, Blanchette CM, Saylor G, Smith DH. Diabetes and drug-associated hyperkalemia: effect of potassium monitoring. *J Gen Intern Med.* 2010;25(4):326-333.
- Wu B, Bell K, Stanford A, Kern DM, Tunceli O, Vupputuri S, Kalsekar I, Willey V. Understanding CKD among patients with T2DM: prevalence, temporal trends, and treatment patterns – NHANES 2007–2012. *BMJ Open Diabetes Res Care.* 2016 Apr 11;4(1):e000154.
- Zhang Q, Rajagopalan S, Mavros P, Engel SS, Davies MJ, Yin D, Radican L. Differences in baseline characteristics between patients prescribed sitagliptin versus exenatide based on a US electronic medical record database. *Adv Ther.* 2010 Apr;27(4):223-232.
- Zhou Z, Chaudhari P, Yang H, Fang A, Zhao J, Law E, Wu E, Jian R, Seifeldin R. Healthcare resource use, costs, and disease progression associated with diabetic nephropathy in adults with type 2 diabetes: a retrospective observational study. *Diabetes Ther.* 2017 Jun;8(3):555-571.

Poster references

1. Nelson RG, Grams ME, Ballew SH, et al. Development of risk prediction equations for incident chronic kidney disease. *JAMA.* 2019;322(21):2104-2114.
2. Wu B, Bell K, Stanford A, et al. Understanding CKD among patients with T2D: prevalence, temporal trends, and treatment patterns-NHANES 2007-2012. *BMJ Open Diabetes Res Care.* 2016;4(1):e000154.
3. Centers for Disease Control and Prevention (CDC). National Diabetes Statistics Report, 2020. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2020a. Accessed September 13, 2021. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf
4. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021 Mar 29;372:n71.
5. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group: de Boer I, Caramori L, Chan J, et al. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int.* 2020;98(45):S1-S115.

Presented at: Kidney Week 2021; virtual.

Disclosure: Funding for this study was provided by Bayer US.