

# Findings

## SGLT2 Inhibitors Prevent Kidney Failure in Type 2 Diabetes: Meta-Analysis

Sodium-glucose cotransporter-2 (SGLT2) inhibitors lower the risk of dialysis and other clinically important kidney outcomes in patients with type 2 diabetes, concludes a systematic review and meta-analysis in *The Lancet Diabetes & Endocrinology*.

The review identified four randomized controlled trials of SGLT2 inhibitors that reported data on major kidney outcomes in patients with type 2 diabetes. The EMPAREG OUTCOME trial evaluated empagliflozin in 7020 patients; the CANVAS Program and CREDENCE trial evaluated canagliflozin in 10,142 and 4401 patients, respectively; and the DECLARE-TIMI 58 trial evaluated dapagliflozin in 17,160 patients. The CREDENCE study was designed as an event-driven kidney outcome trial; the other three studies were cardiovascular outcome trials.

Meta-analysis included data on 38,723 patients, mean age 63.0 to 63.9 years and 65% male. Percentage of patients with chronic kidney disease (estimated glomerular filtration rate [eGFR] less than 60 mL/min/1.73 m<sup>2</sup>) ranged from 7.4% in the DECLARE-TIMI 58 trial to 59.9% in CREDENCE. The primary outcome of dialysis, transplantation, or death due to kidney disease occurred in 252 patients. Incident kidney failure occurred in 335 patients and acute kidney injury (AKI) in 943.

Treatment with an SGLT2 inhibitor was associated with a one-third reduction in the risk of the primary outcome: relative risk (RR) 0.67, compared to placebo. Patients receiving SGLT2 inhibitors were also at lower risk of kidney failure, RR 0.65; and AKI, RR 0.75. All of these effects were consistent across studies.

Some data suggested that the benefit of SGLT2 inhibitors might be reduced at lower levels of eGFR. However, there was significant benefit in all eGFR subgroups; for patients with a baseline eGFR of 30 to 45 mL/min/1.73 m<sup>2</sup>, the RR was 0.70.

The reduction in adverse kidney outcomes with SGLT2 inhibitors was similar for subgroups defined by baseline albuminuria and use of renin-angiotensin system inhibitors. Effects on long-term eGFR slope varied, with the greatest placebo-subtracted difference observed in the CREDENCE trial: 2.74 mL/min/1.73 m<sup>2</sup> per year.

Cardiovascular outcome trials have reported promising effects of SGLT2 inhibitors on kidney outcomes. However, there are limited data on their effects in patients at high risk of patient-level kidney outcomes.

This meta-analysis of more than 38,000 patients with type 2 diabetes finds significant reductions in dialysis, transplantation, or death due to kidney disease with SGLT2 inhibitor therapy [Neuen BL, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2019; DOI: 10.1016/S2213-8587(19)30256-6]. ■

## Racial/Ethnic Minority Groups Have Higher Risk of Diabetes at Lower BMIs

Compared to white Americans, racial/ethnic minority groups have a higher prevalence of diabetes and prediabetes at a lower body mass index (BMI), reports a study in *Diabetes Care*.

The study included approximately 4.9 million adults aged 20 years or older in 2012–2013. Data were drawn from a consortium of three US integrated healthcare systems (Kaiser Permanente, HealthPartners Minnesota, and Denver Health). Race/

ethnicity was classified as white in 50% of individuals, Hispanic in 21.6%, Asian in 12.7%, black in 9.5%, Hawaiian/Pacific Islander in 1.4%, and American Indian/Alaska Native in 0.5%.

Cases of diabetes and prediabetes were ascertained by diagnosis, laboratory results, and use of antihyperglycemic medications. Racial/ethnic disparities in prevalence were assessed across BMI levels. The analysis included adjustment for socioeconomic and/

or environmental disparities.

Standardized for age, estimated prevalence was 15.9% for diabetes and 33.4% for prediabetes. Prevalence of diabetes increased along with BMI in all racial/ethnic groups, although prediabetes prevalence did not. Diabetes prevalence was 27.7% in Hawaiians/Pacific Islanders, 22.2% in Hispanics, 21.4% in blacks, 19.6% in American Indians/Alaska Natives, and 19.3% in Asians, compared to 12.2% in whites.



**References:** 1. Noone D, Licht C. An update on the pathomechanisms and future therapies of Alport syndrome. *Pediatr Nephrol*. 2013;28(7):1025-1036. 2. Watson S, Bush JS. Alport Syndrome. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2019. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK470419>. 3. National Organization for Rare Disorders (NORD). Alport Syndrome. NORD website. <https://rarediseases.org/rare-diseases/alport-syndrome>. Accessed September 13, 2019. 4. Savige J. Alport syndrome: its effects on the glomerular filtration barrier and implications for future treatment. *J Physiol*. 2014;592(4):4013-4023. 5. Meng XM, Nikolic-Paterson DJ, Lan HY. Inflammatory processes in renal fibrosis. *Nat Rev Nephrol*. 2014;10(9):493-503. 6. Tecklenborg J, Clayton D, Siebert S, Coley SM. The role of the immune system in kidney disease. *Clin Exp Immunol*. 2018;192(2):142-150. 7. Kashtan CE, Ding J, Garosi G, et al. Alport syndrome: a unified classification of genetic disorders of collagen IV  $\alpha345$ : a position paper of the Alport Syndrome Classification Working Group. *Kidney Int*. 2018;93(5):1045-1051. 8. Savige J, Gregory M, Gross O, Kashtan C, Ding J, Flinter F. Expert guidelines for the management of Alport syndrome and thin basement membrane nephropathy. *J Am Soc Nephrol*. 2013;24(3):364-375. 9. Liapis H, Jain S. The interface of genetics with pathology in Alport nephritis. *J Am Soc Nephrol*. 2013;24(12):1925-1927. 10. Savige J, Colville D, Rheault M, et al. Alport syndrome in women and girls. *Clin J Am Soc Nephrol*. 2016;11(9):1713-1720. 11. Jais JP, Knebelmann B, Giatras I, et al. X-linked Alport syndrome: natural history and genotype phenotype correlations in girls and women belonging to 195 families: a "European Community Alport Syndrome Concerted Action" study. *J Am Soc Nephrol*. 2003;14(10):2603-2610. 12. Gross O, Kashtan CE, Rheault MN. Advances and unmet needs in genetic, basic and clinical science in Alport syndrome: report from the 2015 International Workshop on Alport Syndrome. *Nephrol Dial Transplant*. 2017;32(6):916-924. 13. Groopman E, Goldstein D, Gharavi A. Diagnostic utility of exome sequencing for kidney disease. Reply. *N Engl J Med*. 2019;380(21):2080-2081. 14. Nestor JG, Groopman EE, Gharavi AG. Towards precision nephrology: the opportunities and challenges of genomic medicine. *J Nephrol*. 2018;31(1):47-60.

For prediabetes, prevalence was 37.1% in Asians, 36.7% in Hawaiian/Pacific Islanders, 35.3% in Hispanics, 32.0% in blacks, 31.1% in American Indians/Alaska Natives, and 31.0% in whites.

Compared to whites, all racial/ethnic minority groups had a higher diabetes prevalence at a given BMI, with the differences being most marked at lower BMI levels. In the normal weight range, 5% of whites had diabetes, compared to about 10% of Asians and American Indians/Alaska Natives and 13% to 14% of Hispanics, blacks, and Hawaiian/

Pacific Islanders. On adjusted analysis, the association between BMI and diabetes was strongest in whites and lowest in blacks.

Obesity and race/ethnicity are major risk factors for diabetes, but racial/ethnic disparities in diabetes do not correspond to differences in obesity. This study in a very large insured population finds that Americans of racial/ethnic minority groups have a higher prevalence of diabetes and prediabetes at lower BMI levels.

The findings suggest that factors other than obesity contribute to the disproportio-

nately high burden of diabetes/prediabetes in racial/ethnic minorities, who are at increased risk even at relatively low BMI levels. The findings “highlight the importance of tailored screening, prevention, and intervention strategies to mitigate the risk of diabetes and prediabetes,” the researchers write [Zhu Y, et al. Racial/ethnic disparities in the prevalence of diabetes and prediabetes by BMI: Patient Outcomes Research To Advance Learning (PORTAL) multisite cohort of adults in the U.S. *Diabetes Care* 2019; DOI: 10.2337/dc19-0532]. ■

## iBox Score Predicts Allograft Loss After Kidney Transplantation



A new integrative box risk prediction (iBox) score performs well in predicting long-term kidney allograft failure across countries and clinical settings, reports a study in the *British Medical Journal*.

The score was developed using data from a prospectively enrolled derivation cohort of 4000 consecutive adult kidney transplant recipients (from living or deceased donors) at three French hospitals between 2005 and 2014. Allograft loss, defined as definitive return to dialysis or preemptive transplantation, was assessed using follow-up data to 2018. Independent predictors on multivariable analysis—including demographic factors, measures of allograft function and histology, and the recipient’s immunologic profile—were incorporated into the iBox score. The score was validated in cohorts of 2129 recipients from European centers and 1428 from North American centers, with additional validation using data from three randomized trials.

The combined cohorts comprised 1775 transplant recipients; at a median follow-up of 7.12 years, the allograft failure rate was 14.1%. The iBox score had accurate calibration and discrimination, with a C index of 0.81 in both the derivation and validation cohorts. Its discriminative capability was confirmed using 3-, 5-, and 7-year follow-up data. The iBox score also performed well in data from randomized trials evaluating therapeutic interventions.

The new risk prediction score was validated in clinical scenarios involving immunosuppressive regimens and response to rejection therapy. In a systematic review, the iBox score provided additional value over previously reported risk scores, as well as scores based on measures of allograft function.

The iBox score meets the need for an integrated tool for predicting the long-term risk of allograft failure after kidney transplantation. Combining demographic, functional, histologic, and immunologic variables, it can be readily implemented for risk prediction in clinical practice. An online interface for calculating allograft survival estimates for individual patients is available at [www.paristransplantgroup.org](http://www.paristransplantgroup.org) [Loupy A, et al. Prediction system for risk of allograft loss in patients receiving kidney transplants: international derivation and validation study. *BMJ* 2019; 366:l4923]. ■

## It's time for kidney talk

When you see unexplained signs of kidney disease, think **Alport syndrome**. It can filter through a family.

### Incurable disease

- Alport syndrome (AS) is a **permanent, hereditary condition** responsible for a genetically defective glomerular basement membrane, causing chronic kidney inflammation, tissue fibrosis, and kidney failure<sup>1-6</sup>
- Across the entire range of AS genotypes, **patients are at risk of progressing towards end-stage kidney disease (ESKD)**<sup>3,7,8</sup>

### Hidden signs

- **Patients often go undiagnosed**, as the clinical presentation of AS is highly variable and family history may be unavailable<sup>3,9-11</sup>
- **Persistent, microscopic hematuria is the cardinal sign of AS** and should prompt immediate diagnostic investigation—particularly when combined with any family history of chronic kidney disease<sup>8,11,12</sup>

### Early action

- Expert guidelines published in the *Journal of the American Society of Nephrology* now **recommend genetic testing as the gold standard for diagnosing Alport syndrome**<sup>8</sup>
- Early AS detection via genetic diagnosis, and its ability to guide a patient’s treatment decisions, demonstrates the **powerful impact of precision medicine in nephrology**<sup>12-14</sup>

Reata and Invitae have collaborated to offer no-charge genetic testing for rare chronic kidney disease diagnosis and greater clinical insights. For more information regarding the KIDNEYCODE program or to order a test, please visit [www.invitae.com/chronic-kidney-disease](http://www.invitae.com/chronic-kidney-disease) or contact Invitae client services at [clientservices@invitae.com](mailto:clientservices@invitae.com) or 800-436-3037.

**Abnormal kidney function can have a strong family connection—  
Alport syndrome**

Learn more about Alport syndrome at  
[ReataPharma.com](http://ReataPharma.com).



© 2019 Reata Pharmaceuticals, Inc. All Rights Reserved. US-NON-190003110/19