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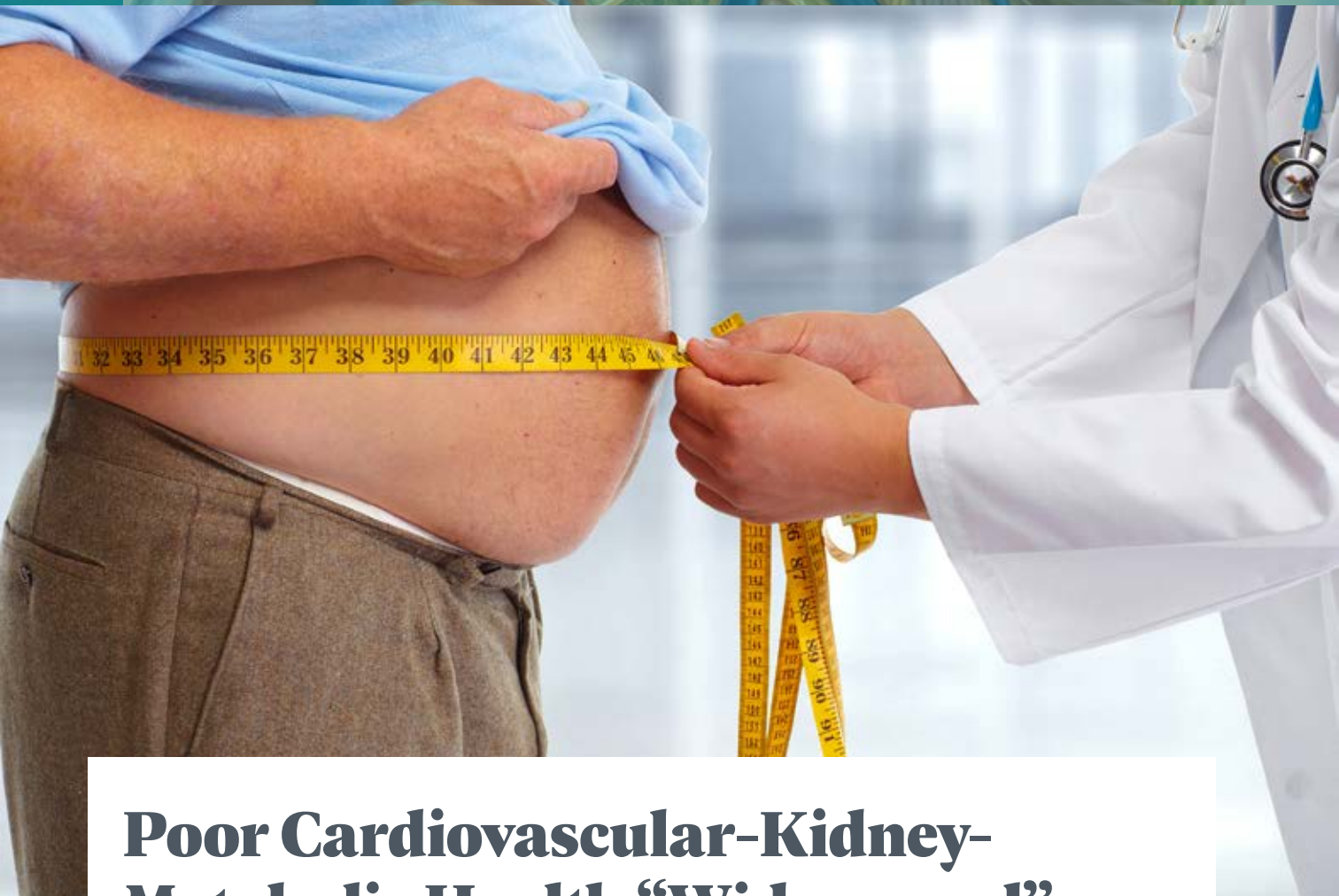


Inside

Poor Cardiovascular-Kidney-Metabolic Health “Widespread” Among US Adults, According to Findings from New Study

Lanifibranor Plus Empagliflozin Effective in T2D, MASH: Proof-of-Concept Phase 2 Findings

Advanced-Stage CKD Prevalence Rising Rapidly Worldwide: Multidimensional Modeling Study



Poor Cardiovascular-Kidney-Metabolic Health “Widespread” Among US Adults, According to Findings from New Study

By **Sydney Jennings** *Editor*

New research published online in *JAMA* highlights the widespread prevalence of cardiovascular-kidney-metabolic (CKM) syndrome among US adults. Findings also show that adults 65 years or older, men, and Black adults face an increased risk of advanced stages.

Between 2011 and 2020, almost 90% of US adults met the criteria for stage 1 or higher of CKM syndrome and 15% met the criteria for advanced stages (stages 3 or 4). However, there was no improvement in these prevalence rates over the study period.

“The lack of progress, in part, may reflect concomitant improvement and worsening of different risk factors over time,” researchers from Brigham and Women’s Hospital and Harvard Medical School in Boston, Massachusetts, wrote.

In recent years, there has been a shift in the medical and scientific communities’ appreciation for the connections among CKM diseases and for their combined impact on cardiovascular mortality. In 2023, the American Heart Association introduced the framework for CKM syndrome, which included staging and corresponding screening approaches. The stages are based on risk factors and established disease and range from 0 (no risk factors) to 4 (established cardiovascular disease [CVD]), according to the study.

Citing a lack of studies on the stages of CKM syndrome in the US population, investigators conducted a nationally representative study to examine “the prevalence and temporal evolution of CKM syndrome stages,” they wrote.

Investigators used the National Health and Nutrition Examination Survey (NHANES; 2011 to March 2020) to identify adults 20 years or older who underwent physical examination and fasting laboratory measurements.

A total of 10 762 adults (mean age, 47.3 years; 51.8% women) had their disease categorized into the following CKM syndrome stages:

- **STAGE 0:** No CKM risk factors (eg, hypertension)
- **STAGE 1:** Excess or dysfunctional adiposity
- **STAGE 2:** Additional metabolic risk factors or moderate- or high-risk chronic kidney disease (CKD)
- **STAGE 3:** Very high-risk CKD or high-predicted 10-year CVD risk
- **STAGE 4:** Established CVD (eg, coronary artery disease)

“Advanced CKM syndrome stages were defined as stages 3 or 4 because these identify individuals with or at high risk of CVD,” first author Rahul Aggarwal, MD, clinical fellow in medicine at Brigham and Women’s Hospital, and colleagues noted.

Temporal trends between 2011 and 2012 and between 2017 and March 2020 were assessed by CKM stage and for advanced stages using linear regression. Prevalence of advanced stages was compared among subgroups (age, sex, race, and ethnicity) using log-binomial regression.

Findings

Study participants identified with racial and ethnic groups as follows: White, 64.4%, Hispanic 15.3%, Black 11.5% Asian 5.6%, and other races and ethnicities, 3.3%.

Between 2011 and 2020, 10.6% of US adults met criteria for stage 0, 25.9% for stage 1, 49.0% for stage 2, 5.4% for stage 3, and 9.2% for stage 4. Aggarwal and colleagues added that the prevalence of each stage did not significantly change during

“Poor CKM health is widespread in the US population, especially among Black adults. Equitable health care approaches prioritizing CKM health are urgently needed.”



the study period (P for trend $> .05$ for each stage).

Advanced stages of CKM syndrome occurred in 14.6% of participants and did not significantly change over the study period, according to the study findings.

Prevalence varied by race, sex, and age. When investigators analyzed the prevalence of CKM syndrome among the subgroups, they observed that adults 65 years or older were more likely to have advanced stages than those aged 45 to 64 years (55.3% vs 10.7%; $P < .001$) and those aged 20 to 44 years (55.3% vs 2.1%; $P < .001$). Also, 18.2% of adults aged 20 to 44 years had stage 0 disease.

In addition, men were more likely than women to have advanced

stages of CKM syndrome (16.9% vs 12.4%; adjusted prevalence ratio [PR], 1.36; 95% CI, 1.24-1.49; $P < .001$). Black adults were significantly more likely to have advanced stages compared with White adults (18.9% vs 13.8%; adjusted PR, 1.38; 95% CI, 1.24-1.55; $P < .001$).

“Poor CKM health is widespread in the US population, especially among Black adults. Equitable health care approaches prioritizing CKM health are urgently needed,” Aggarwal et al said. ■

REFERENCE

Aggarwal R, Ostrominski JW, Vaduganathan M. Prevalence of cardiovascular-kidney-metabolic syndrome stages in US adults, 2011-2020. *JAMA*. Published online May 8, 2024. doi:10.1001/jama.2024.6892



Lanifibranor Plus Empagliflozin Effective in T2D, MASH: Proof-of-Concept Phase 2 Findings

By **Grace Halsey** Senior Editor

Data from an interim analysis of the phase 2 proof-of-concept LEGEND trial (NCT05232071) demonstrated that the investigational small molecule lanifibranor significantly lowered hemoglobin A_{1C} (HbA_{1C}) level when given alone and in combination with empagliflozin compared with placebo in adults with metabolic dysfunction-associated steatohepatitis (MASH) and poorly controlled type 2 diabetes (T2D).¹

Study results also showed statistically significant reductions in several markers of liver injury and glucose and lipid metabolism as well as improvement in hepatic

steatosis. The findings were announced in a press statement by Inventiva.¹

Lanifibranor is a peroxisome proliferator-activated receptor (PPAR) agonist designed to target the 3 PPAR isoforms. The orally available small molecule induces antifibrotic, anti-inflammatory, and beneficial vascular and metabolic changes. There are other PPAR agonists that target 1 or 2 PPAR isoforms for activation, according to Inventiva; however, lanifibranor is the only pan-PPAR agonist in clinical development for the treatment of MASH/nonalcoholic SH (NASH). The FDA granted lanifibranor both breakthrough therapy and fast-track designations for the treatment of MASH/NASH in 2020.^{1,2}

“These LEGEND results provide valuable insights on

the complementary mechanisms of action of an SGLT2 inhibitor and the pan-PPAR agonist, lanifibranor. MASH is a multifaceted disease that we believe will benefit from combination therapies in order to properly address the full cardiometabolic spectrum of the disease,” trial coprincipal investigator Michelle Lai, MD, associate professor of medicine at Harvard Medical School in Boston, Massachusetts, said in the announcement.¹

LEGEND trial

LEGEND is a multicenter, randomized, 24-week, placebo-controlled trial designed to assess the safety and efficacy of lanifibranor in combination with the SGLT2 inhibitor empagliflozin for the treatment of patients with noncirrhotic MASH/NASH and T2D. Investigators are using a double-blind design for the lanifibranor 800 mg daily vs placebo arm and an open-label format for the combination of lanifibranor 800 mg and empagliflozin 10 mg daily arm.¹

The interim analysis, planned per protocol, was performed once half the 63 randomly assigned patients with MASH completed the 24-week treatment period or prematurely discontinued treatment, according to the press release.¹

Findings¹

HbA_{1c}. The study’s primary efficacy end point was achieved, with an absolute reduction in HbA_{1c} level at week 24 among participants treated with lanifibranor alone or in combination with empagliflozin. Participants experienced decreases of 1.14% and 1.59%, respectively, vs a 0.26% increase in the placebo arm.

Hepatic steatosis. LEGEND researchers also reported statistically significant reductions in hepatic steatosis in participants treated with both lanifibranor and lanifibranor/empagliflozin (–47%

“These results are significant and strengthen confidence in the potential of lanifibranor to address the specific metabolic imbalance in patients with T2D while also addressing steatosis and fibrosis.”

and –38%, respectively) as measured by MRI proton density fat fraction compared with placebo (0%). Furthermore, 83% of participants who received lanifibranor alone and 67% treated with the SGLT2 inhibitor/pan-PPAR agonist combination reached a 30% or greater reduction in hepatic steatosis compared with 0% in the placebo arm.

Liver markers. Lai and colleagues also reported statistically significant effects for several secondary and exploratory end points, including alanine aminotransferase level, aspartate aminotransferase level, and insulin resistance. Importantly, the research team assessed markers of liver inflammation and fibrosis for the first time with lanifibranor and found significant effects with lanifibranor alone and in combination with empagliflozin.

Weight neutral. Although moderate, metabolically healthy weight gain has been observed in individuals treated with lanifibranor monotherapy, study participants treated with lanifibranor in combination with empagliflozin maintained a stable weight throughout the 24-week study. In addition, the visceral and subcutaneous adipose tissue ratio

was significantly reduced in both the lanifibranor alone (–5%) and combination with empagliflozin (–17%) groups whereas an increase in the ratio of 11% was reported in participants assigned to placebo.

“The study was designed as a proof of concept, and these results are significant and strengthen confidence in the potential of lanifibranor to address the specific metabolic imbalance in patients with T2D while also addressing steatosis and fibrosis, a hepatic consequence of insulin resistance,” Onno Holleboom, MD, PhD, associate professor at Amsterdam University Medical Center in the Netherlands and coprincipal investigator of the trial, concluded.¹ ■

REFERENCES

1. Inventiva announces positive results from the phase II, LEGEND, proof-of-concept study combining lanifibranor with empagliflozin in patients with MASH/NASH and T2D. News release. Inventiva. March 18, 2024. Accessed March 20, 2024. <https://inventivapharma.com/wp-content/uploads/2024/03/Inventiva-PR-Results-LEGEND-EN-03-18-2024.pdf>
2. Inventiva receives FDA breakthrough therapy designation for lead drug candidate lanifibranor in NASH. News release. Inventiva. October 12, 2020. Accessed March 20, 2024. <https://inventivapharma.com/inventiva-receives-fda-breakthrough-therapy-designation-for-lead-drug-candidate-lanifibranor-in-nash/>



Advanced-Stage CKD Prevalence Rising Rapidly Worldwide: Multidimensional Modeling Study

By **Grace Halsey** Senior Editor

Chronic kidney disease (CKD) may affect up to 1 in 6 individuals across 8 major industrialized nations by 2032, ranging from 11.7% in Australia to 16.5% in the US, a new model predicts. The rise in advanced-stage disease (stages 3-5) will be the most dramatic over the 8-year period at nearly 60% (59.3%). In 4 countries, including China, the increase in prevalence of advanced-stage CKD will increase by at least 30% over this time.¹

The data come from a modeling analysis developed in collaboration with AstraZeneca (AZ) and presented at the International Society of Nephrology World Congress of Nephrology 2024 in Buenos Aires, Argentina. The IMPACT-CKD study is the first to forecast the multidimensional impact of CKD over a 10-year period, projecting trends in the US, Brazil, the United Kingdom,

Spain, Germany, the Netherlands, China, and Australia, according to an AZ press statement.¹

The analysis goes beyond estimating the burden of illness, the international group of authors wrote in the study abstract.² “By offering a comprehensive assessment of a CKD patient’s journey, our aim is to provide insights and recommendations to effectively reduce the clinical, economic, societal, and environmental burdens associated with CKD,” they said.

Estimates are that by 2040, CKD will be the fifth leading cause of death worldwide, with the demands of treatment straining health care systems and national economies, researchers stressed.² The national health care budget allocation for CKD is projected to reach an average of 7.3% by then, with some countries distributing more than a quarter (25.7%) of their health care resources to CKD management, they wrote. In its early stages, CKD is asymptomatic, which accounts for the findings that up to 90% of individuals are unaware of

it until the disease reaches an advanced stage.³ Greater awareness of CKD among potential patients and health care professionals alike would support early recognition and treatment that could prevent disease progression to stages that require tremendous health care and social resources.¹

For the study, researchers used patient-level simulation to create 1 million individual patients based on country population size, according to the study abstract. The model maps national and regional CKD treatment pathways, covering the full course of disease from primary care to end-of-life care.¹

Findings¹

The analysis projects that nearly 125 million people across the 8 countries will have stage 3 to 5 kidney disease by 2023, which is an increase of 25% since the model began in 2022, researchers stated. The increased number of patients who will require advanced treatment services will increase dialysis requirements by more than 75% across the 8 countries. When the resources required for dialysis and transplant are combined, the cost is estimated at US \$186 billion. Costs associated with other renal replacement therapies will escalate by 77% or more. In at least 7 countries, there will be a 23% rise in CKD-related emergency and inpatient hospital costs, according to the study findings.

The impact on economic productivity will be significant as well, with combined patient and caregiver absenteeism responsible for a total of more than 3 billion missed workdays across the cohort, a loss equivalent to US \$37 billion. Furthermore, the model projects an environmental impact associated with CKD management that will make a carbon footprint equivalent to annual water usage of approximately 2.7 million households,

power for approximately 149.7 million light bulbs, and carbon dioxide emissions equivalent to that of approximately 17.3 million cars.

“Our modeling emphasizes the enormous impact CKD could have on patients, economies, and the environment,” Ruud Dobber, PhD, president of the BioPharmaceuticals Business Unit at AZ, said in the announcement.²

“But this future is not inevitable,” Dobber added. “We are committed to working with global policy makers to reduce the worldwide impact of end-stage CKD and drive earlier diagnosis and treatment to slow or halt progression of the disease.”

AZ recently launched the Accelerate Change Together for CKD, encompassing a series of studies and initiatives designed to improve understanding and outcomes of CKD worldwide.²

Other elements of the program include the REVEAL-CKD study (NCT04847531), which looks at the extent of underdiagnosis and the clinical impact of an early diagnosis, and the Inside CKD analysis, modeling future prevalence, disease burden, health care use and costs, and the benefits of screening.² ■

REFERENCES

1. Moura AF, Wheeler D, Brotons-Munto F, et al. Multidimensional burden of chronic kidney disease in eight countries: insights from the IMPACT CKD study. Abstract presented at: International Society of Nephrology World Congress of Nephrology 2024; April 13-16, 2024; Buenos Aires, Argentina. Accessed April 15, 2024. [https://www.kireports.org/article/S2468-0249\(24\)00629-6/pdf](https://www.kireports.org/article/S2468-0249(24)00629-6/pdf)
2. New modelling reveals the escalating toll of chronic kidney disease on patients, planet and economies. News release. AstraZeneca. April 15, 2024. Accessed April 15, 2024. <https://www.astrazeneca.com/media-centre/press-releases/2024/new-modelling-reveals-the-escalating-toll-of-chronic-kidney-disease-on-patients-planet-and-economies.html>
3. Chronic kidney disease in the United States, 2023. CDC. Updated May 30, 2023. Accessed April 15, 2024. <https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html>

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