News and Views

Balcinrenone + Dapagliflozin: The Next Frontier in Therapy for HF and CKD Patients?

Adding balcinrenone to dapagliflozin did not significantly improve proteinuria in patients with heart failure (HF) and chronic kidney disease (CKD) compared to dapagliflozin alone, according to findings of the MIRACLE (MIneRAlocorticoid reCeptor moduLator and sodium-glucosE cotransporter 2 inhibitor in HF and CKD) published in the *European Journal of Heart Failure*[1].

Balcinrenone is a novel selective mineralocorticoid receptor (MR) modulator, which "separates organ protective effects from acute effects on urinary electrolyte excretion", as shown in preclinical models[2]. Dapagliflozin is an SGLT2 (sodium-glucose cotransporter-2) inhibitor.

This phase 2b trial examined the safety and effectiveness of combination of balcinrenone and dapagliflozin in patients with HF and CKD; 160 sites in Europe, Asia and North America participated in this study, which was conducted from January 2021 to October 2023.

The primary objective of the study was to assess the effect of balcinrenone in combination with dapagliflozin on urinary albumin-to-creatinine ratio (UACR) compared with dapagliflozin + placebo. The dose-response relationship of three doses of balcinrenone (15, 50, or 150 mg/day) + dapagliflozin 10 mg/day on UACR effects was the secondary objective of the study. The assessment of the safety and tolerability of the combination was the safety objective of the study.

The study enrolled 133 patients with symptomatic HF. Participants with an ejection fraction of <60%, an estimated glomerular filtration rate (eGFR) of between 30 and 60 mL/min/1.73 m^2 and UACR of between 30 and 3,000 mg/g were eligible for the study. They were randomized 1:1:1:1 to receive either balcinrenone 15, 50, or 150 mg/day + dapagliflozin 10 mg/day, or dapagliflozin 10 mg/day + placebo, for a duration of 12 weeks. The enrollment was stopped early because of slow recruitment. Safety analysis was done on 131 participants.

Balcinrenone + dapagliflozin groups compared to dapagliflozin + placebo did not vary much in terms of relative reductions in UACR from baseline to week 12. No clear dose-response relationship was observed for balcinrenone.

Possible dose-dependent increases in serum potassium levels, nonsignificant trends towards decreased N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels and decreased eGFR in the highest dose group were noted.

Hyperkalemia occurred in 3.1% of patients receiving the combination treatment and in 9.1% in the placebo. Two participants on balcinrenone + dapagliflozin discontinued due to hyperkalemia (>6.0 mmol/L), while none discontinued the treatment in the dapagliflozin + placebo group. No new safety concerns were observed.

This study indicates that adding balcinrenone to dapagliflozin was comparable to placebo in improving UACR in patients with symptomatic HF, which is a key marker for cardiovascular risk. Also, because of a lack of dose-response relationship, increasing doses of balcinrenone did not provide additional benefits in reducing UACR.

Discontinuation of treatment because of hyperkalemia, especially with higher doses, underscores the necessity for vigilance in monitoring of potassium levels when using balcinrenone, especially when administering higher doses of the drug. The benefits therefore must be carefully weighed against the risks with the use of balcinrenone. The authors, however, suggest further studies to better understand the actions of balcinrenone in patients with HF and CKD to minimize risks while maximizing therapeutic benefits. These findings therefore may be used as a guide to tailor treatment regimens.

References

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2. Bamberg K, et al. Preclinical pharmacology of AZD9977: A novel mineralocorticoid receptor modulator separating organ protection from effects on electrolyte excretion. PLoS One. 2018;13(2):e0193380.

Challenges in Adult Vaccination: Perceived Barriers

About 25% of older adults report fear of needles and costs as obstacles to vaccination, according to a study published in the journal *Aging and Health Research*[1]. Lack of a doctor's recommendation, transportation and uncertainty how to schedule vaccines were other

perceived barriers. The less educated, single people and those residing in rural areas were more likely to face barriers in the uptake of vaccines This study focused on identifying the barriers that prevent older adults from accepting vaccines that are recommended for their age group. In addition, the study also explored how demographic factors influence vaccine acceptance.

The study used a mail survey conducted between May and June 2022 to gather data on experiences, perceptions, and behaviors related to vaccination among older adults aged 65 and older in North Dakota, a state in the US. The survey targeted equal numbers of males and females from three distinct strata: urban/high vaccine coverage (1,000 individuals), rural/high vaccine coverage (1,000 individuals), and rural/low vaccine coverage (2,000 individuals). Out of the 4,000 individuals surveyed, 901 (23.4%) responses were received. Their mean age was 75 years. More than half of the respondents were women (53.1%). Majority (~72%) lived in rural areas; one-quarter lived alone and most (86.4%) rated their health as good or better. "Over 90% had received at least one COVID-19 vaccine, nearly 90% had taken at least one flu vaccine in the last 5 years, 70.7% received a pneumococcal vaccine, and 67.8% received a shingles vaccine."

The survey included questions related to barriers to vaccination (such as needle phobia, cost, lacking doctor recommendation, transportation issues, and scheduling uncertainty), vaccine acceptance and various demographic characteristics including age, gender, socioeconomic status, education status, self-rated health, whether living alone. The study also specifically assessed the uptake of four different vaccines among the study population namely Influenza, COVID-19, Shingles, and Pneumococcal vaccines.

Analysis of data revealed cost (27.2%) to be the most common barrier to vaccination followed by needle anxiety (24.1%). Older persons who were single, living in rural areas, with lower levels of education, and who were not white were more likely to encounter obstacles such cost, lack of a doctor's referral, transportation and uncertainty how to schedule vaccines.

Cost was identified as the most prevalent barrier, affecting 27.2% of respondents. This barrier was particularly associated with the uptake of the shingles vaccine. Needle phobia was a significant concern for 24.1% of respondents. It was associated with the uptake of all vaccines except the COVID-19 vaccine. A lack of a doctor's recommendation was a barrier to the uptake of all vaccines except the shingles vaccine. Transportation barrier was particularly associated with the uptake of the pneumococcal vaccine. Participants residing in rural areas were more concerned about costs and also lacked recommendations from their doctor to receive vaccines. Similarly, those with lower educational status also mentioned lack of doctor referral as a hurdle. Transportation as a barrier was more common among those living alone, while the less educated respondents found it difficult to schedule the vaccination.

This study provides valuable insights into vaccination barriers among older persons highlighting how these barriers vary across demographic groups and their specific associations with acceptance of different vaccines. It further underscores the need for multifaceted strategies that address both demographic characteristics and vaccine-specific factors to improve immunization uptake among older adults. Understanding these variations helps tailor interventions and policies to address specific barriers faced by demographic groups. Education and support can enhance the overall vaccine acceptance rates.

Reference

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Assessing Risk of Endometrial Hyperplasia and Cancer in Recurrent Abnormal Uterine Bleeding

Older age, nulliparity, a history of endometrial polyps and a sampling interval of <12 months are significant predictors of endometrial hyperplasia and endometrial cancer in women with recurrent abnormal uterine bleeding (AUB) and previous benign endometrial findings, according to a study published August 1, 2024 in the journal *Obstetrics & Gynecology*[1].

In this retrospective study from Thailand, researchers set out to create predictive models for patients with recurrent AUB that would suggest the risk of subsequent development of endometrial hyperplasia and endometrial cancer. The selected participants had undergone endometrial sampling earlier between January 2013 and December 2021 that were benign. Using multivariate logistic regression, a model was built using the important variables linked to endometrial hyperplasia and endometrial cancer. Based on these risk factors, the patients were then further divided into risk categories.

Out of the total 456 patients included in the study, 8.3% developed endometrial hyperplasia and 2.2% developed endometrial cancer. The average interval between the

initial endometrial sampling and the second sampling was 25.1 months.

Patients older than 45 years were nearly 3 times more likely to develop endometrial hyperplasia and endometrial cancer with odds ratio (OR) of 2.86. The risk was increased 3.5 times in nulliparous women (OR 3.50), while a history of endometrial polyps was associated with a more than threefold increased risk of endometrial hyperplasia or cancer (OR 3.69). Among participants who underwent the second sampling in less than a year from the first sampling, the risk was more than doubled with OR of 2.36.

The study developed a scoring system based on the significant predictive factors for endometrial hyperplasia and endometrial cancer. This system allowed for categorization of patients into three distinct risk groups: 0-3 (low risk), 5-8 (intermediate risk), and 9-11 points (high risk), with corresponding probabilities of developing these conditions (4.7%, 15.5%, and 57.1%, respectively). "The area under the curve (AUC) was 73.1%, with a mean absolute error of 0.01."

This study has identified risk factors that indicate the risk of endometrial hyperplasia or endometrial cancer in patients with recurrent AUB and previous benign endometrial findings. Risk stratification also facilitates tailored clinical decision making, with more aggressive management strategies, including frequent follow-ups, investigations or intervention planned for the high-risk group. Counseling patients about their risk also helps them to make more informed decisions about their care.

Reference

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Glycemic Variability: A Harbinger of Diabetic Peripheral Neuropathy?

Diabetes patients with increased glycemic variability are at a substantially higher risk of developing diabetic peripheral neuropathy (DPN), as per a study recently published in the journal *Diabetes Research and Clinical Practice*[1].

A systematic review and meta-analysis was conducted to identify any relationship between glycemic variability, as measured by continuous glucose monitoring, and the risk of developing DPN in patients with type 1 and type 2 diabetes. Nine studies with a total of 3,649 patients were included in the meta-analysis.

Analysis revealed a significant association between increased glycemic variability and the incidence of DPN as indicated by various glycemic variability metrics. Patients with higher SD in blood glucose levels are over twice as likely to develop DPN compared to those with lower SD with OR of 2.58. Increased mean amplitude of glycemic excursions was associated with a 90% higher risk of developing DPN (OR 1.90). Higher mean of daily difference was also strongly associated with nearly a threefold increase in the risk of DPN (OR 2.88).

These findings underscore the potential of glycemic variability metrics as potential markers for the onset of DPN. Integrating these metrics into routine diabetes care could serve as an early warning system, allowing for more targeted interventions aimed at mitigating the risk of neuropathy.

Reference

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Chronic Obstructive Pulmonary Disease: A Potential Risk Factor for Herpes Zoster

Persons with chronic obstructive pulmonary disease (COPD) nearly 3 times more likely to develop herpes zoster (HZ) compared to those without COPD, according to a study published in the *Clinical Respiratory Journal*[1].

In this retrospective cohort study, the researchers compared the incidence rates of HZ between persons with and without COPD in the United States. Data for the study was obtained from an insurance database from January 2013 to December 2018.

A total of 161,970 participants with a diagnosis of COPD were categorized as COPD+, while 9,643,522 participants without COPD diagnosis were grouped as COPD−. Those with a history of HZ, prior HZ vaccination, postherpetic neuralgia (PHN), or herpes zoster ophthalmicus were excluded from the study. Participants with COPD tended to be older in age, have more comorbid conditions and also used steroids more frequently than those without COPD.

The incidence rate of HZ was significantly higher in the COPD+ cohort (13.0 per 1,000 person-years) compared to the COPD− cohort (2.3 per 1,000 person-years) with an adjusted incidence rate ratio (aIRR) of 2.77. COPD patients had a 5.7-fold higher incidence rate of HZ compared to those without COPD, even after adjustment. The unadjusted incidence rate of PHN was 1.7 times higher in the COPD+/HZ+ group

(64.8 per 1,000 person-years) compared to the COPD−/HZ+ cohort (37.1 per 1,000 person-years). However, after adjustment, this association was not statistically significant with aIRR of 1.07. The incidence rates of HZ and PHN increased with age across the cohorts. After adjusting for potential confounders, adults with COPD were found to have a 2.8-fold increased risk of developing HZ compared to those without COPD.

These findings underscore the need for greater awareness about the risk of HZ, which is a very painful condition, in COPD patients. They also establish the importance of proactive targeted prevention strategies, including Shingles vaccination for those at higher risk.

Reference

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Long-Term Lung Damage among COVID-19 Survivors

Over one-third of patients who had residual lung abnormalities at discharge after being hospitalized for COVID-19 continue to experience respiratory symptoms and lung abnormalities even 3 years after discharge, according to a study published in the *European Respiratory Journal*[1].

The study followed a group of 728 patients who had earlier been hospitalized with COVID-19 and had residual lung abnormalities at discharge from January to April 2020. It tracked the progression of residual lung abnormalities such as ground-glass opacities, reticulation and fibrotic-like changes, and pulmonary function over a period of 3 years. The participants were evaluated at multiple time points post-discharge: 6 months, 12 months, 2 years, and 3 years from the onset of symptoms. The tests undertaken included pulmonary function tests, 6-minute walk distance (6MWD), chest computed tomography (CT) scans including a self-reported questionnaire to assess the respiratory symptoms. A total of 792 persons who had tested negative for COVID-19 were also included in the study as the control group.

The proportion of patients with reduced diffusing capacity of the lung for carbon monoxide (D_{LCO}) (<80% of the predicted value) decreased from 49% at 6 months to 38% at 3 years (p = 0.001). The average 6MWD improved from 496 m in 6 months to 510 m in 3 years (p = 0.002). The prevalence of residual lung abnormalities decreased from 46% at 6 months to 36% at 3 years. These changes were evident regardless of the severity of disease.

Patients with residual lung abnormalities at 3 years were more likely to report respiratory symptoms (32%) compared to those with complete resolution (16%) (p < 0.001). They also had a lower average 6MWD (494 m) than those without abnormalities (510 m) (p = 0.003). A higher percentage of patients with residual lung abnormalities had abnormal D_{LCO} (57%) versus those with complete resolution (27%) (p < 0.001).

Regardless of the initial severity of the disease, COVID-19 survivors showed the highest prevalence of nonfibrotic changes 6 months after discharge, which progressively declined over the 3-year period. At 6 months, fibrotic changes were most common in patients with severity scores of 5 to 6, which remained for the 3 years of the study. Patients with fibrotic-like changes experienced more respiratory symptoms (44% vs. 25%) and had a lower D_{LCO} (57% vs. 50%) compared to those with nonfibrotic changes. A comparison of COVID survivors and controls revealed that around 38% of COVID-19 survivors had impaired D_{LCO} (<80% of predicted) compared to only 17% in the control group (p < 0.001). Also, 23% of COVID-19 survivors reported at least one respiratory symptom compared to just 2.2% of the control group (p < 0.001). The most common symptoms at 3 years were cough, dyspnea, and expectoration.

The study points out a clear distinction in the long-term pulmonary outcomes of COVID-19 survivors based on the initial severity of their illness. While many patients show improvement in radiological abnormalities and pulmonary function over time, those with severe initial disease remain at risk for persistent fibrotic lung changes that were associated with increased symptoms, lower 6MWD and abnormal pulmonary function, underscoring the importance of tailored post-recovery management.

Reference

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