News and Views

Combination Therapy in At-Risk Type 2 Diabetes Patients: The Way Forward?

New research published in the journal *Circulation* suggests that use of combination of sodium-glucose transporter-2 (SGLT2) inhibitor and glucagon-like peptide-1 receptor agonists (GLP-1RA), nonsteroidal mineralocorticoid receptor antagonist (MRA) drugs in patients with type 2 diabetes and kidney disease is beneficial in terms of reduced cardiovascular and renal events and mortality.[1]

This study utilized data from 12 trials (two of SGLT2 inhibitors [CANVAS and CREDENCE], 8 of GLP-1 rheumatoid arthritis trials (ELIXA, LEADER, SUSTAIN-6, EXSCEL, Harmony Outcomes, REWIND, PIONEER 6 and AMPLITUDE-O) and two of nonsteroidal MRA [FIDELIO-DKD and FIGARO-DKD]) with the aim to compare the effects of combination therapy versus conventional care on cardiovascular, renal and mortality outcomes in patients with type 2 diabetes and urinary albumin:creatinine ratio of ≥30 mg/g. The absolute reduction in risk was estimated by applying calculated combination treatment effects to patients receiving standard care in the CANVAS and CREDENCE trials.

Results showed that compared to patients receiving standard care, those treated with the SGLT2 inhibitors + GLP-1RA + nonsteroidal MRA combination were at a lower risk of experiencing a major adverse cardiovascular events (MACE) such as nonfatal myocardial infarction, nonfatal stroke or cardiovascular death, the primary study outcome. The hazard ratio (HR) for MACE was 0.65 in this patient group. The heart rate for hospitalization for heart failure was 0.42 in the combination therapy group; the HR was 0.64 for cardiovascular death and 0.67 for all-cause mortality. The absolute risk reduced significantly by 4.4% amounting to a number-needed-to-treat of 23. The absolute risk reduction for hospitalization due to heart failure was 3.4%, 4.4% for chronic kidney disease (CKD) progression, 2.4% for cardiovascular death and 3.1% for all-cause mortality. In 50-year-old patients, initiation of this combination treatment led to an estimated event-free survival of 21.1 years versus 17.9 years for conventional care representing a gain of 3.2 years with respect to MACE-free survival.

Improvement in survival with no hospitalization due to heart failure was also seen with a gain of 3.2 years. A gain of 5.5 years was noted for CKD progression, 2.2 years for cardiovascular-related mortality and 2.4 years for death due to any cause. Even when assuming only 50% additive effects of combination therapy, there were still clinically relevant gains in event-free survival. These gains were observed for MACE (2.4 years), CKD progression (4.5 years) and all-cause death (1.8 years).

SGLT2 inhibitors, GLP-1RAs and nonsteroidal MRAs like finerenone are viewed as breakthrough therapies for patients with type 2 diabetes. They are now increasingly being used to treat these patients, not only due to their antihyperglycemic effects but also because of their proven cardiorenal protective effects. The authors also note that several major international guidelines like the American Diabetes Association and the European Association for the Study of Diabetes (ADA-EASD), Kidney Disease: Improving Global Outcomes (KDIGO) and National Institute of Health and Care Excellence (NICE) recommend "a multi-medicine strategy, tailored to individuals' residual cardiorenal risk".

This study highlights the potential clinical benefits of combining these 3 classes of drugs in improving overall survival as well as cardiac and renal outcomes in patients with type 2 diabetes and at least moderately increased albuminuria. These findings support the combined use of SGLT2 inhibitor, GLP-1RA and nonsteroidal MRA in high-risk patients with type 2 diabetes to prevent cardiorenal events and premature mortality including the need for educating patients about the associated cardiorenal risk for "shared decision-making by patients and clinicians".

Reference

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PRISm: A COPD Risk Factor

New research suggests that persons with preserved ratio impaired spirometry (PRISm) and respiratory symptoms are at risk of progressing to chronic obstructive pulmonary disease (COPD).[1] A total of 9,789 participants were enrolled for the Nagahama study; they were followed-up after 5 years. All the study subjects underwent spirometry and were given questionnaires to gather information about respiratory symptoms such as prolonged cough,

sputum and dyspnea including comorbid conditions. The aim of the study was to examine PRISm in relation to respiratory symptoms through a large-scale, longitudinal general population investigation. The aim of the study was to examine PRISm in relation to respiratory symptoms through this large-scale, longitudinal general population investigation. The aim of the study was to examine PRISm in relation to respiratory symptoms through this large-scale, longitudinal investigation involving the general population.

Findings published in the *Annals of the American Thoracic Society* reveal that 438 of the 9,760 patients who were examined overall had PRISm, which was independently correlated with dyspnea. Around 53% of them reported respiratory symptoms. Seventy-three percent of the subjects with respiratory symptoms continued to have the symptoms, while 39% of the subjects with PRISm without symptoms at baseline, developed respiratory symptoms within 5 years. PRISm was also found to be a risk factor for the development of airflow limitation among the people with respiratory symptoms but without airflow limitation at baseline, even after controlling for smoking history and comorbidities.

PRISm is characterized by a forced expiratory volume in 1 second (FEV1) of <80% predicted and a FEV1/forced vital capacity (FVC) ratio of ≥0.70. While the condition is "transient" in most individuals, some are at risk of progressive impairment in pulmonary function.[2] This study shows that over half of the participants with PRISm had respiratory symptoms and dyspnea was a prominent feature of PRISm. Around three-fourth of them had persistent respiratory symptoms over the 5 years of this study. Given the finding that PRISm itself is an independent risk factor for the development of COPD among subjects with respiratory symptoms, the clinical course of individuals with symptomatic PRISm should be carefully monitored since PRISm has been described as a "precursor" of COPD.[2]

References

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Diagnosing Diabetes: Impact of Type of Anemia on HbA1c Levels

Persons with iron deficiency anemia (IDA) without a history of diabetes have high glycosylated hemoglobin (HbA1c) levels, according to a study published in the journal *BMC Endocrine Disorders*.[1] Furthermore, correcting the anemia results in normalized HbA1c levels.

This study retrospectively reviewed medical records of 324 patients, including a control group and those with either B12-related megaloblastic anemia, sickle cell anemia, IDA or beta-thalassemia trait with a mean age of 46.62 years. Majority of the participants with anemia were female. Adults in good health who had normal hemoglobin and HbA1c levels and had no known diabetes or anemia made up the control group. Individuals who self-reported diabetes/prediabetes or had raised fasting, random blood sugar or 2 hours postprandial blood glucose or anemia due to any other cause were not included in the study group. This study was conducted at a tertiary university hospital in Saudi Arabia with the objective to analyze the effect of the four anemia types on HbA1c levels from 2016 to 2022. Less than half (40.2%) were being treated for anemia.

Out of the 324 study participants, 103 had IDA, 67 had megaloblastic anemia, 33 had sickle cell anemia and 17 had the beta-thalassemia trait. The control group included 104 subjects.

Compared to the control group, which had a mean HbA1c value of 5.32%, patients with sickle cell anemia had a mean HbA1c of 5.83% and IDA patients with HbA1c of 5.75%. Patients with beta-thalassemia trait and megaloblastic anemia had lower mean HbA1c levels at 5.45% and 5.38% and were similar to that of the control group. Following treatment, HbA1c significantly dropped from 5.75% to 5.44% in IDA patients. In sickle cell anemia patients, those with lower hemoglobin levels had a significantly higher red-cell distribution width (RDW), which correlated with higher HbA1c levels.

The ADA in its 2023 Standards of Care in Diabetes recommends the use of HbA1c for diagnostic screening of diabetes and to monitor glycemic control. HbA1c value ≥6.5% is the cut-off for making a diagnosis of diabetes.[2]

This study highlights the influence of specific types of anemia on HbA1c levels. Patients with sickle cell disease and iron deficiency anemia without diabetes had significant high HbA1c levels, while there was no discernible change among patients with megaloblastic anemia and beta-thalassemia trait. The HbA1c level returned to normal in IDA patients after their anemia was treated. In sickle cell anemia patients, hemoglobin and HbA1c levels were inversely related, whereas high RDW was positively correlated with high HbA1c levels.

The falsely elevated HbA1c levels in both sickle cell anemia and IDA can result in misdiagnosis of diabetes

leading to unnecessary treatment and associated distress that can well be avoided. Clinicians should exercise great caution when relying on HbA1c alone to diagnose diabetes in patients with IDA and sickle cell disease. The authors therefore "recommend correcting the anemia in patients with IDA before using HbA1c for diagnostic purposes".

References

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Intrapartum Antibiotic Prophylaxis and Perinatal Infectious Morbidity

The risk of clinical chorioamnionitis and peripartum infectious morbidity is reduced by nearly half in women who were positive for Group B Streptococcus and received intrapartum antibiotic prophylaxis, according to a study published in the December 2023 issue of the *American Journal of Obstetrics and Gynecology*.[1]

This study was designed as an exploratory secondary analysis of a randomized trial. A total of 491 women undergoing induction at term at a tertiary care center were included in the study. Group B Streptococci Detection Method using a carrot broth-enriched subculture was used (Hardy Diagnostics, Santa Maria, CA). These women had been screened for Group B Streptococcus in the third trimester and were administered intrapartum antibiotic prophylaxis. The maternal (chorioamnionitis, peripartum infectious morbidity) and neonatal (admission to neonatal intensive care unit [NICU]) outcomes were noted between the Group B Streptococcus positive patients who received intrapartum antibiotic prophylaxis and Group B Streptococcus unknown prophylaxis-naïve patients. Peripartum infectious morbidity, postpartum endometritis and wound infection were among the secondary outcomes of the study.

Group B Streptococcus status was identified in 466 of the 491 women recruited for the study. Of these, 174 (37.3%) were Group B Streptococcus positive women who received intrapartum antibiotic prophylaxis and 292 (62.7%) were Group B Streptococcus negative women who did not receive intrapartum antibiotic prophylaxis.

Seventy-eight percent of the study subjects were non-Hispanic Black. Approximately 60% were nulliparous. Other demographic, clinical, induction and labor variables did not differ across the groups. Women who were Group B Streptococcus positive had a lower risk of peripartum infectious morbidity at 8.1% compared to the Group B Streptococcus negative women (15.8%). The odds ratio (OR) was 0.47. The clinical chorioamnionitis rate was also lower in the Group B Streptococcus positive women (8.1%) versus those who were Group B Streptococcus negative (14.7%) with OR of 0.51. Children born to women with Group B Streptococcus positive status were less likely to require intensive care in the NICU; 3.4% versus 15.1%, respectively.

Group B Streptococcus is a known risk factor for clinical chorioamnionitis. This study demonstrates the positive impact of intrapartum antibiotic prophylaxis for Group B Streptococcus positive patients undergoing labor induction at term in reducing the risk of intrapartum and peripartum infections as well as neonatal outcomes.

Reference

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Groundbreaking "First in Human" Gene-Editing Treatment of Hypercholesterolemia: Advent of a New Era in Therapeutic Medicine?

A single dose of a CRISPR-based gene-editing therapy resulted in substantial reductions in low-density lipoprotein cholesterol (LDL-C) and proprotein convertase subtilisin kexin-9 (PCSK9) levels in patients with heterozygous familial hypercholesterolemia (HeFH) and atherosclerotic cardiovascular disease (ASCVD), according to the results of the phase Ib HEART-1 trial, which were presented at the 2023 Scientific Sessions of the American Heart Association (AHA) held in Philadelphia, Pennsylvania from November 11-13, 2023.[1-3]

Ten patients, which included 8 men and 2 women, mean age 54 years, from the UK or New Zealand were included in this ongoing, first-in-human trial. All the 10 participants had HeFH with an average LDL-C of 201 mg/dL even though almost all were receiving maximum tolerated doses of statins at the time of their enrollment in the study. But none of the participants was taking PCSK9 inhibitors. Most of them had significant ASCVD and had already undergone a coronary revascularization procedure. Approximately 50% of the subjects reported having suffered a myocardial infarction at least once. Each patient was administered VERVE-101 as a single intravenous infusion; the first group of 3 patients received a low dose of 0.1 mg/kg,

while the other three groups received increasing dosages to a maximum of 0.6 mg/kg.

The 3 patients who received the 2 highest doses of VERVE-101 (0.45 mg/kg and 0.6 mg) had the greatest reductions in LDL-C and PCSK9 protein levels. Reductions in LDL-C of 39% and 48% were seen in the 2 patients receiving the 0.45 mg/kg dose, while the 1 patient receiving 0.6 mg/kg dose had a 55% decrease in LDL-C. The blood PCSK9 protein levels were reduced by 47% and 59% in the 2 patients in the 0.45 mg/kg dose group, and by 84% in the single patient in the 0.6 mg/kg group. At 6 months, LDL-C declined in the only patient administered 0.6 mg/kg dose, with follow-up continuing. The majority of the adverse events to date were minor and not linked to the medication. Serious adverse cardiovascular events in the form of a myocardial infarction, an arrhythmia and a cardiac arrest occurred in 2 patients with underlying advanced coronary artery disease. The change in LDL has been stable for up to 6 months thus far, with follow-up still ongoing, according to the authors. "All safety events were reviewed with the independent data safety monitoring board, who recommended continuation of trial enrollment with no protocol changes required", they noted.

VERVE-101 is an experimental therapy, which permanently inactivates the PCSK9 gene in the liver through the CRISPR-based gene-editing technology thereby reducing LDL-C. The PCSK9 gene plays a key role in regulating the LDL receptor and therefore cholesterol metabolism. Increased activity of the PCSK9 gene leads to higher levels of LDL- or the 'bad' cholesterol.

A year-long preclinical study published earlier this year first demonstrated the potential of VERVE-101 as a long-term treatment for raised LDL-C levels wherein a single dose of VERVE-101 resulted in 69% reduction in LDL-C and 83% decrease in PSCK9 levels. It was also well-tolerated. Significantly, these results persevered for 2.5 years after just one dose.[4]

The present study is the first human trial of VERVE-101, in patients with HeFH and ASCVD. These are interim data and are the "first reported results for any *in vivo* DNA base editing medicine administered to human trial participants". This was a small clinical trial with just 10 patients and since all received the investigational treatment, no direct comparison could be performed with another treatment, which according to the authors is a limitation of their study. Also, "the results were measured by reductions in LDL-C, not changes in the occurrence of heart attacks". The trial is ongoing and recruitment of patients for the highest two doses of VERVE-101 is still on. The US FDA mandates a long-term follow-up of participants for up to 15 years after administration of human gene therapy products. Participants of this trial would also be subjected to this long-term follow up after a year of observation.

These are certainly exciting results for mankind and have the potential to drastically alter the landscape of treatment. They come with lot of hope for patients with devastating genetic diseases. Recently, UK's Medicines and Healthcare products Regulatory Agency (MHRA) for the first time approved Casgevy, a therapy that utilizes the CRISPR gene editing tool for the treatment of beta-thalassemia and sickle cell disease.

In addition to the evident safety concern, which is of the utmost importance, gene editing also raises ethical concerns. Many questions come to mind. What will be its impact on the generations to come? Since this will obviously be an expensive therapy, will it be accessible to just the well-off, who can afford the high costs further adding to the existing disparities in access to health care. What will be the scope of its application? And so on. These are difficult to foresee. Such innovations not only call for stringent policies and regulations, but also immense self-regulation on the part of the scientific community. Are we ready?

Nevertheless, these results are promising and pave the way for a revolutionary novel treatment option, "a single-course therapy that may lead to deep LDL-C-lowering for decades" instead of large number of daily medications, which the patients are required to take and therefore may not comply with.

References

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