

News and Views

Should Combination Therapy be the First-line of Treatment in Type 2 Diabetes?

Combined therapy with sodium-glucose cotransporter-2 inhibitors (SGLT2i) or glucagon-like peptide-1 receptor agonists (GLP-1RA), compared to either drug alone, is associated with reduced risk of all-cause mortality and cardiovascular disease (CVD), according to a new study published in the journal *Diabetes, Obesity and Metabolism*.¹

This study retrospectively analyzed data of people with type 2 diabetes receiving insulin to examine the risk of all-cause mortality, hospitalization and cardiovascular outcomes at 5 years following monotherapy with either SGLT2i or GLP-1RA alone or their combination (SGLT2i + GLP-1RA). Out of the 2.2 million patients included, 143,600 received SGLT2i, 186,841 received GLP-1RA, while 108,504 were treated with the combination. The controls received neither SGLT2i nor GLP-1RA.

The risk of all-cause mortality was found to be decreased in all three intervention groups over a period of 5 years with hazard ratios (HR) of SGLT2i 0.49, GLP-1RA 0.47 and combination 0.25.

Similarly, the risks of hospitalization (HR 0.73, 0.69, 0.60) and myocardial infarction (HR 0.75, 0.70, 0.63) were also reduced in SGLT2i arm, GLP-1RA arm and the combination arm, respectively.

At 5 years, treatment with SGLT2i (vs. controls) reduced the risk of all-cause mortality with HR of 0.49. SGLT2i also reduce the risk of hospitalization (HR 0.73), myocardial infarction (HR 0.75), unstable angina (HR 0.79), heart failure (HR 0.73), atrial fibrillation (HR 0.74), stroke (HR 0.75), peripheral vascular disease or PVD (HR 0.79), lower limb amputation (HR 0.69) and chronic kidney disease or CKD (HR 0.79).

Similar trend was noted with GLP-1RA monotherapy (vs. controls) at 5 years with reduction in the risk of all-cause mortality (HR 0.47), hospitalization (HR 0.69), acute myocardial infarction (HR 0.70), unstable angina (HR 0.73), ischemic heart disease or IHD (HR 0.85), heart failure (HR 0.73), atrial fibrillation (HR 0.77), stroke (HR 0.77), PVD (HR 0.89), lower limb amputation (HR 0.66) and CKD (HR 0.90).

Treatment with combination therapy (SGLT2i + GLP-1RA) also reduced the risk of all-cause mortality

(HR 0.25), of hospitalization (HR 0.60), acute myocardial infarction (HR 0.63), unstable angina (HR 0.75), IHD (HR 0.84), heart failure (HR 0.60), atrial fibrillation (HR 0.65), stroke (HR 0.69), PVD (HR 0.84), lower limb amputation (HR 0.59) and CKD (HR 0.72) vs. controls.

This study demonstrates that the risk of all-cause mortality and CVD in patients with type 2 diabetes was reduced in all the three intervention arms when compared to the control group. However, the greatest reduction in risk for all-cause mortality was seen with combination therapy. Similarly, the probability of hospital admission was lowest with combination therapy, which also conferred greater cardiovascular protection. Optimal timely glycemic control prevents or delays the onset of diabetes-related macro- and microvascular complications. The antidiabetic drugs should address the “ominous octet” of factors implicated in pathophysiology of type 2 diabetes. They should also be cardioprotective and renoprotective and not just lower blood glucose. SGLT2i and GLP-1RAs are relatively newer antidiabetic drugs, which have also shown extra-glycemic benefits with improvements in cardiovascular and renal outcomes, besides effective glucose-lowering effects in patients with type 2 diabetes, with cardiovascular risk factors or underlying heart disease. Hence, they are game changers in diabetes care. Their combination might potentially provide superior control of blood glucose with low hypoglycemic risk along with cumulative cardiovascular and renal protection.

Reference

1. Riley DR, et al. All-cause mortality and cardiovascular outcomes with sodium-glucose co-transporter 2 inhibitors, glucagon-like peptide-1 receptor agonists and with combination therapy in people with type 2 diabetes. *Diabetes Obes Metab.* 2023;25(10):2897-909.

Simple Blood Test for Bipolar Disorder: Study

Researchers at the University of Cambridge created a straightforward blood test to improve the precision of bipolar illness diagnoses, according to a study published in *JAMA Psychiatry*. This test was found to be very helpful when used in conjunction with a digital mental health assessment. It can identify up to 30% of bipolar individuals with accuracy.

Bipolar disorder and major depressive disorder are diseases that have similar symptoms but require

distinct pharmacological treatments; biomarker testing may help physicians differentiate between them.

This study's findings suggest that the blood test can complement existing psychiatric diagnostic methods while shedding light on the biological underpinnings of mental health disorders. Notably, around 1% of the population experiences bipolar disorder, yet nearly 40% of those affected receive a misdiagnosis of major depressive disorder. The researchers utilized samples and data from the Delta study conducted in the UK from 2018 to 2020. The data included information of individuals previously diagnosed with major depressive disorder within the last 5 years, and who were currently displaying depressive symptoms.

The study identified a distinct biomarker signal for bipolar disorder, even after adjusting for confounding factors like medication. The combination of patient-reported information and the biomarker test significantly enhanced diagnostic accuracy for individuals with bipolar disorder, particularly in cases where the diagnosis was less evident.

(Source: <https://www.tribuneindia.com/news/health/simple-blood-test-can-help-diagnose-bipolar-disorder-accurately-study-557857>)

Study: Extreme Heat Linked to More Cardiovascular Death

A study published in *Circulation* suggests that extreme heat will drive an increase in cardiovascular-related fatalities in the US between 2036 and 2065. The impact of underlying health issues and socioeconomic challenges will be disproportionately felt by vulnerable groups, particularly those 65 years of age and older and persons of color. The study projects an increase in summer days with temperatures reaching at least 90 degrees, as indicated by the heat index, which takes humidity into account. As a result, this tendency is anticipated to change. Although extreme heat currently contributes to less than 1% of cardiovascular deaths, the modeling analysis forecasts a change in this pattern. While most individuals can adapt to extreme heat through mechanisms like perspiration, those with underlying health issues, including diabetes and heart disease, face heightened risks of heart attacks, irregular heart rhythms or strokes.

The study's predictions were generated by evaluating county-level data from 48 states between May and September in the years 2008-2019, during which more than 12 million cardiovascular-related deaths occurred. Environmental modeling estimates indicated that the heat

index exceeded 90 degrees approximately 54 times each summer. Researchers linked these extreme temperatures to an average of 1,651 annual cardiovascular deaths nationally. Further modeling analyses, incorporating environmental and population changes, anticipate that between 2036 and 2065, there will be about 71 to 80 days each summer with temperatures feeling 90 degrees or hotter. The general population is expected to experience a 2.6-fold increase in heat-related cardiovascular deaths, requiring minimal greenhouse gas emissions. If these emissions increase and are not controlled, then extreme heat would potentially triple the fatality.

(Source: <https://www.daijiworld.com/news/newsDisplay?newsID=1135159>)

Research Reveals Mobile Phone Use Linked to Lower Semen Quality

A University of Geneva study published in *Fertility & Sterility* revealed that frequent mobile phone usage can reduce sperm concentration and total count. However, it found no connection between mobile phone use and sperm motility and morphology.

The study analyzed data from 2,886 Swiss men aged 18 to 22 (recruited between 2005 and 2018) and found a significant decrease of 21% in sperm concentration for those who used their phones more than 20 times a day compared to those who used them less than once a week. Sperm quality is evaluated based on parameters including sperm concentration, total count, motility and morphology. Over the past half-century, numerous studies have reported a decline in semen quality, with sperm count dropping from an average of 99 million per milliliter to 47 million per milliliter. This decrease is believed to result from a combination of environmental factors like endocrine disruptors, pesticides and radiation, as well as lifestyle factors such as diet, alcohol consumption, stress and smoking. Notably, the study did not find a correlation between the position of the phone, such as being in a trouser pocket, and lower semen parameters.

(Source: <https://www.daijiworld.com/news/newsDisplay?newsID=1135820>)

Impact of Surgical Treatment of Endometriosis

Women who undergo surgical treatment for endometriosis had significant improvement in their quality of life on several domains, according to a study published in the journal *Revista da Associação Médica Brasileira*.^{1,2}

A total of 102 women with pelvic pain and endometriosis were included in this observational, longitudinal and

prospective analytical study. Their condition had not improved with clinical treatment. These participants, with mean age of 35.96 years, underwent surgical treatment from September 2020 to May 2022. Through this study, the researchers aimed to examine their pre- and post-surgery (3 months and 6 months) quality of life, which was assessed with the help of the Endometriosis Health Profile-30 (EHP-30) questionnaire. The score ranged from 0 to 100; lower scores denoted better quality of life.

Based on the revised endometriosis classification of the American Society of Reproductive Medicine (rASRM), 9 women were categorized as having minimal endometriosis, 18 (17.6%) with mild endometriosis, 35 (34.3%) moderate endometriosis, while 40 (39.3%) women had severe endometriosis. The different surgical procedures adopted were: excision of only endometriotic lesions (20.5%), excision + myomectomy (29.5%), excision + hysterectomy (22.6%), excision + rectosigmoidectomy + hysterectomy (22.5%), excision + myomectomy + rectosigmoidectomy (~5%).

Comparison of the EHP-30 scores before and after the surgery showed that the scores reduced 3 and 6 months after surgery in the central questionnaire (Part 1) and in Sections A, B, C, E and F. Compared to 3 months after the surgery, the scores further reduced 6 months post-surgery.

The mean quality of life score in the central questionnaire (Part 1) before the surgery was 46.67, which reduced to 16.25 at 3 months after surgery and 7.5 at 6 months after the surgery. The scores in Section A (work) before the surgery and 3 and 6 months after the surgery were 35, 10 and 0. Section B (relationship with children) scores reduced to 0 at 3- and 6-months post-surgery compared to the score of 50 before the procedure. The scores in Sections C (Sexual Relations; 15 and 0 vs. 50), E (Treatment; 16.6 and 0 vs. 41.6) and F (Infertility; 25 and 6.25 vs. 50) were found to reduce at 3 and 6 months after surgery compared with before surgery, respectively. Reduction in scores for Section D (Relationship with Physician) was observed 6 months after surgery compared to before surgery.

The severity of endometriosis had no correlation with the EHP-30 quality of life scores before and after surgery. Quality of life is an integral and critical component of management of endometriosis. This study highlights the good prognosis in women who undergo surgery for endometriosis in terms of improved quality of life. The study group comprised of women with "all forms of endometriosis", who underwent different types of

procedures. Hence, women who do not respond to medical treatment should be offered surgical treatment to reduce their symptoms thereby improving their quality of life.

References

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2. Welsh ET. Available at: <https://www.healio.com/news/womens-health-ob-gyn/20231018/treating-endometriosis-with-surgery-improves-quality-of-life>. Dated Oct. 20, 2023. Accessed Nov. 2, 2023.

Study: No Increased Miscarriage Risk with Pre-pregnancy COVID Vaccine

A study featured in *Human Reproduction* has confirmed that receiving a coronavirus disease 2019 (COVID-19) vaccine prior to conceiving does not elevate the risk of early or late miscarriage. This study was conducted by Boston University School of Public Health (BUSPH) researchers and is the first to assess the risk of early miscarriage (before 8 weeks' gestation) following COVID-19 vaccination.

The research analyzed COVID-19 vaccination and miscarriage data from 1,815 female participants in the BUSPH-based Pregnancy Study Online (PRESTO). Notably, 75% of these participants had already been given at least one dose of a COVID-19 vaccine before pregnancy. Approximately a quarter of pregnancies ended in miscarriage, with 75% occurring prior to 8 weeks' gestation. However, the study found no increased risk of miscarriage. The risk percentages were as follows: 26.6% for unvaccinated participants, 23.9% for those who received one vaccine dose before conception, and 24.5% for those who completed the full primary vaccine series before conception. For those who completed the vaccine series 3 months before conception, the risk was 22.1%, and for those who received only one dose of a two-dose vaccine before conception, it was 21.1%.

(Source: <https://health.economictimes.indiatimes.com/news/industry/research-shows-covid-vaccination-before-pregnancy-doesnt-increase-risk-of-miscarriage/104886474>)

Benefits of High-flow Nasal Cannula in COPD Patients with Chronic Hypercapnia

Use of home high-flow nasal cannula (HFNC) for chronic hypercapnic respiratory failure in patients with chronic obstructive pulmonary disease (COPD) may reduce acute exacerbations and hospital admissions, according to a recent study published in the journal *Respiratory Medicine*.^{1,2}

This study, which was a systematic review and meta-analysis, was conducted by researchers from University of Toronto, McMaster University and Dalhousie University in Canada to investigate if HFNC versus standard care was effective in COPD patients with chronic hypercapnia. Four randomized controlled trials involving 440 adults with stable COPD (no exacerbations in the preceding month) who had started HFNC for at least 1 month were included in the meta-analysis after a comprehensive search of Cochrane CENTRAL, SCOPUS, MEDLINE, EMBASE and Clinicaltrials.gov databases. Acute COPD exacerbations, hospitalizations and change in St. George Respiratory Questionnaire (SGRQ) scores and all-cause mortality were selected as the primary study endpoints. The duration of follow-up ranged from 12 months to 15 months in the studies included. The forced expiratory volume in 1 second (FEV1) percent predicted at the start of the study was 26% to 45%. The highest CO₂ level at baseline was 51.9 mmHg and the lowest was 48.3 mmHg.

Analysis showed that compared to standard care, the risk of acute exacerbations was probably reduced by HFNC with relative risk (RR) of 0.77 (moderate certainty), suggesting that there were 69 fewer acute exacerbations per 1,000 patients. Use of HFNC (vs. standard care) was also likely associated with reduced risk of hospitalization (RR 0.87; low certainty) suggesting that there were 20 fewer hospitalizations per 1,000 patients. The researchers also found that the SGRQ score may also decline with mean difference -8.12 units suggesting an improvement in quality of life of the patients. But, no effect on mortality (RR 1.22) was noted with HFNC versus standard care.

These results suggest that home HFNC may be effective for patients with COPD and chronic hypercapnia. Although its effect on mortality was debatable, use of HFNC might lead to fewer acute exacerbations and hospital admissions in COPD patients with chronic hypercapnia resulting in better quality of life as shown in this study. The authors conclude by recommending further studies "with longer follow-up periods to provide more robust evidence on the efficacy of HFNC" and its comparative efficacy with noninvasive ventilation in patients with COPD.

References

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Research Shows Positive Outlook Reduces Aging Anxiety

In a recent study, the researchers have discovered that maintaining a positive attitude towards physical activity is linked to reduced anxiety related to the aging process.

Given the aging demographic, it becomes crucial to promote health-enhancing behaviors and emphasize preventive measures for chronic diseases. The anxiety surrounding aging encompasses concerns about losing independence, relationships, physical and psychological changes, as well as discomfort or dissatisfaction with interactions among older individuals.

While factors like gender, age, marital status and financial status influence one's perceptions of exercise and aging, a shift in how these topics are presented can encourage healthier behaviors.

A multi-state study involving 1,250 participants from Washington, DC, and six states revealed that African-American individuals were more interested in health-related programs. The most prominent aging-related concern was the fear of loss, particularly pronounced among those with lower incomes and individuals living alone. Women aged 40 to 49 expressed more anxiety about changes in their physical appearance compared to their male counterparts and older age groups.

A positive attitude towards physical activity correlates with reduced aging-related anxiety, likely due to the holistic benefits of staying physically, mentally and socially active, leading to an improved perception of the aging process and a subsequent reduction in anxiety associated with growing older.

These study findings can guide the development of educational workshops addressing aging-related anxiety while highlighting the health advantages of engaging in physical activity.

(Source: <https://www.hindustantimes.com/lifestyle/health/positive-attitude-towards-physical-activity-may-be-associated-with-less-anxiety-about-ageing-research-101698983902369.html>)

Study: COVID-19 has no Impact on MS Activity

A study discovered that the COVID-19 virus does not elevate the likelihood of clinical and magnetic resonance imaging (MRI) disease progression or motor and cognitive decline in multiple sclerosis (MS) patients.

The study compared 136 individuals with MS, both with and without a history of COVID-19. It encompassed regular neurologic check-ups, brain MRI scans, neuropsychological assessments, and evaluations of fatigue,

depression, anxiety, sleep and psychological impacts related to COVID-19.

Over the 18 to 24 months following a COVID infection, there were no noteworthy distinctions between the groups in terms of EDSS (Expanded Disability Status Scale) worsening, the percentage of patients experiencing relapses, the need to alter disease-modifying therapies, the appearance of new or enlarged brain lesions visible on T2-weighted MRI scans, and gadolinium-enhancing lesions. Upon follow-up, 22% of MS patients with a history of COVID and 23% of those without COVID history displayed cognitive impairment. However, there were no substantial variations in overall cognitive functions, verbal and visual memory, and information processing speed, attention and verbal fluency.

Scores in assessments for the Modified Fatigue Impact Scale (MFIS), Hospital Anxiety and Depression Scale (HADS) for anxiety and depression, Pittsburgh Sleep Quality Index (PSQI), and Impact of Event Scale-Revised (IES-R), as well as tests for cellular immune responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), did not exhibit significant differences. In light of these findings, the authors propose that individuals with MS may gradually resume their everyday lives. Nevertheless, they emphasize the importance of maintaining good hygiene practices, as the virus can still pose a threat, and the potential emergence of new variants may present a different range of neurological symptoms.

(Source: <https://www.medscape.com/viewarticle/998044?src=>)

Impact of Early Testosterone on Mental Health in Transgender and Gender-Diverse Adults

Prompt initiation of testosterone in transgender and gender-diverse individuals significantly reduces gender dysphoria, depression and suicidality compared to starting testosterone after waiting for 3 months, according to new research published in *JAMA Network Open*.¹

This 3-month study included 64 transgender and gender-diverse adults, aged 18 to 70 years, seeking initiation of testosterone therapy. The median age of the participants was 22.5 years. They attended the endocrinology OPDs and primary care clinics that specialized in transgender and gender-diverse health in Melbourne, Australia between November 2021 to July 2022. None of the selected participants had been treated with testosterone earlier. The selected subjects were randomized to immediate intervention with testosterone or to standard care with testosterone started after the usual wait period of 3 months. Testosterone was administered

via intramuscular or transdermal routes, based on the preference of the participant. Gender dysphoria measured by the Gender Preoccupation and Stability Questionnaire (GPSQ) was the primary outcome of the study. The secondary outcomes were depression and suicidal ideation. Depression was assessed with the Patient Health Questionnaire-9 (PHQ-9) and suicidal ideation was evaluated with the help of the Suicidal Ideation Attributes Scale (SIDAS) at baseline and at 3 months. In the immediate intervention group, 74% had depression and 65% had anxiety. In the standard care group, 58% had depression and 65% had anxiety. At baseline, the mean testosterone levels in the immediate treatment group was 37.5 ng/L; in the standard treatment group, the mean testosterone levels were 25.9 ng/dL. After 3 months, the mean testosterone levels were ~392 ng/dL.

Participants in whom testosterone was started immediately showed substantial reduction in gender dysphoria compared to those receiving standard care with a 7.2 point decrease in GPSQ score. There was a clinically significant reduction in depression with a mean difference of -5.6 points in the PHQ-9 score as well as a significant decrease in suicidality with a mean difference of -6.5 points in SIDAS score was also seen. In over half (52%), the suicidal ideation was resolved as per the PHQ-9 item 9 following immediate intervention with testosterone compared to just one (5%) in the standard care group. Adverse effects with intramuscular testosterone undecanoate included injection site pain or discomfort and transient headache lasting for a day. None developed polycythemia.

Gender dysphoria due to incongruity of gender identity is a cause of significant distress and can cause depression affecting day to day life and may even lead to suicidal ideation. This trial has for the first time included a “transgender and gender-diverse control group randomized to no treatment” as controls, who started testosterone after 3 months. It is the first trial to demonstrate the benefits of early initiation of testosterone in transgender and gender-diverse adults who desired testosterone therapy on their mental health. Marked reduction in gender dysphoria, depression and suicidality was seen. “These findings have critical implications for service access and delivery to ensure timely access to gender-affirming hormone therapy”, concluded the researchers.

Reference

1. Nolan BJ, et al. Early access to testosterone therapy in transgender and gender-diverse adults seeking masculinization: a randomized clinical trial. *JAMA Netw Open*. 2023;6(9):e2331919.