News and Views

Benefits of Finerenone in Heart Failure with Preserved or Mildly Reduced Ejection Fraction

Treating patients who have heart failure with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF) with finerenone reduces their risk of worsening HF events and cardiovascular mortality, according to the results of the FINEARTS-HF study published in the *New England Journal of Medicine*[1,2].

To study the impact of finerenone on symptomatic HFmrEF or HFpEF, researchers selected 6,001 patients with HF and a left ventricular ejection fraction (LVEF) of ≥40%. Most patients were in New York Heart Association (NYHA) class II. A total of 3,003 patients were randomized to receive finerenone (20 mg or 40 mg once daily) and 2,998 patients received placebo, in a 1:1 ratio, along with standard care. The primary study outcome was a composite of total worsening HF events and cardiovascular mortality. An urgent visit for HF or the first or recurrent unplanned hospital admission was defined as an event.

There were 1,083 primary-outcome events in 624 patients in the finerenone group over a median follow-up of 32 months, while 1,283 primary-outcome events occurred in 719 patients receiving placebo. "First worsening HF events or death from cardiovascular causes was similarly reduced with finerenone". The rate ratio was 0.84. Overall, total worsening HF events were reduced by 18% with finerenone. The total number of worsening HF events was 842 in the finerenone group and 1,024 in the placebo group with rate ratio of 0.82. Cardiovascular mortality was comparable between the two groups, 8.1% and 8.7%, respectively, with hazard ratio (HR) of 0.93. However, the risk of hyperkalemia (>5.5 mmol/L) was increased in the finerenone group (14.3%) compared to placebo group 6.9%). The rate of hypokalemia was lower in patients treated with finerenone.

Finerenone was FDA approved in 2021 for patients with chronic kidney disease associated with type 2 diabetes.

The findings of this study support the use of finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist (MRA), in this patient group. However, sounding a note of caution, the authors state that despite fewer side effects than other MRAs, finerenone is associated with risk of hyperkalemia. Hence, patients, especially those with impaired kidney function, should be closely monitored for this adverse effect. This study also demonstrated the lower risk of hypokalemia with finerenone, which is also associated with worse outcomes.

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Anticancer Drugs may Lower Alzheimer's Risk: Study

A study in Scientific Reports found that certain anticancer drugs, specifically molecular targeted therapies and antimetabolites, may reduce the risk of Alzheimer's dementia in older adults. However, these drugs showed no significant impact on vascular dementia risk.

In a recent study published in *Scientific Reports*, researchers observed that specific anticancer drugs may reduce the risk of Alzheimer's dementia (DAT) in older adults. The study, which analyzed data from the Korea National Health Insurance Service database, focused on more than 1,00,000 cancer patients aged 65 and above who were prescribed anticancer medication between January 2008 and December 2018.

The researchers found that two classes of anticancer drugs—molecular targeted therapies and antimetabolites—were associated with a reduced risk of DAT. Specifically; the study reported HR of 0.91 for antimetabolites and 0.60 for molecular targeted therapies in reducing the risk of DAT. However, these drugs showed no significant impact on the risk of vascular dementia, the second most common type of dementia.

The average age of patients receiving anticancer treatments was 71.64 years, with a majority of the patients (64.4%) female. The most frequently used classes of anticancer drugs were platinum (39.0%), antimetabolites (30.5%), and antibiotics (21.3%). Among molecular targeted therapies, epidermal growth factor receptor (EGFR) inhibitors were the most common, accounting for nearly half of the usage.

Further analysis using the Cox proportional HR revealed that antimetabolites (HR = 0.93) and molecular-targeted therapies (HR = 0.67) significantly reduced the DAT risk. When examining molecular-targeted therapies more closely, the study found multikinase inhibitors had the most substantial protective effect (HR = 0.50), followed by EGFR inhibitors (HR = 0.66).

Specialized Medication Management Reduces Hospital Stays and Mortality in Older Patients

A study in JAMDA found that specialized medication management for older patients reduces their hospital stays and mortality risk. One in 10 older patients experienced adverse drug reactions, which significantly impacted their outcomes.

New research published in the *Journal of the American Medical Directors Association (JAMDA)* suggested that specialized medication management for older hospital patients can shorten their hospital stays and lower their risk of death. The study found that 1 in 10 older patients experienced adverse drug reactions (ADRs) during hospitalization, significantly affecting their outcomes.

Examining over 700 patients aged 65 and older, the study revealed that ADRs from medications such as those for high blood pressure, strong painkillers, and antibiotics significantly increased the likelihood of prolonged hospital stays and mortality. Each ADR was associated with a higher risk of extended hospitalization and death, underscoring the importance of careful medication management in this vulnerable population.

Study Links High Diastolic Blood Pressure to Increased Migraine Risk in Women

A study in Neurology found that high diastolic blood pressure slightly increases the risk of migraines in women. No similar associations were found with other cardiovascular risk factors or in men.

A new study published in *Neurology* showed that high diastolic blood pressure—the blood pressure measurement when the heart is resting between beats—is linked to a slightly higher likelihood of having migraines in women. The study, however, did not find any increased migraine risk associated with other cardiovascular factors.

The research involved 7,266 male and female participants with a median age of 67 years, of whom 15% reported having experienced migraines at some point. All participants underwent physical exams, provided blood samples, and answered questions about their migraine history, including whether they had ever had a headache with severe pain that impacted daily activities.

After adjusting for various cardiovascular risk factors and education levels, researchers discovered that female participants with higher diastolic blood pressure had a 16% increased odds of experiencing migraines for each standard deviation increase in diastolic blood pressure. This finding suggested that migraines may be linked to a slightly reduced function of small blood vessels rather than large ones.

No associations were found between migraines and systolic blood pressure, high cholesterol, or obesity in women. Interestingly, current smoking was associated with 28% lower odds of having migraines, and diabetes was linked to 26% lower odds of migraines. No significant associations between cardiovascular risk factors and migraines were observed in male participants.

Extreme HDL-C Levels Linked to Increased Kidney Disease Risk in Women with Type 2 Diabetes

A study in Scientific Reports found that very high and very low levels of HDL-C are linked to an increased risk of kidney disease in women with type 2 diabetes but not in men. Women with HDL-C levels outside the 0.95-1.54 mmol/L range faced significantly higher risks.

A study published in *Scientific Reports* showed that very high and very low levels of high-density lipoprotein cholesterol (HDL-C) are associated with a higher risk of kidney disease in women with type 2 diabetes but not in men.

Researchers conducted a cross-sectional observational study involving 936 patients with type 2 diabetes (mean age around 60 years; 41% women; 33% with diabetic kidney disease) from the Endocrinology Department at Jinhua Hospital between September 2020 and July 2021.

The study used logistic regression and a restricted cubic spline curve to analyze the relationship between HDL-C levels and the risk of diabetic kidney disease. The researchers identified a U-shaped association between HDL-C levels and kidney disease risk, with significant threshold values at 0.95 and 1.54 mmol/L.

Women with HDL-C levels below 0.95 mmol/L or above 1.54 mmol/L had a 128% and 77% increased risk of diabetic kidney disease, respectively, compared to those with levels within the 0.95-1.54 mmol/L range. After adjusting for confounding factors, this association was significant in women but not men. Continuous HDL-C levels were unrelated to kidney disease risk.

Higher Risk of Autoimmune and Psychiatric Disorders in Alopecia Areata Patients, Study Finds

A JAMA Dermatology study found that alopecia areata patients are at higher risk for autoimmune and psychiatric comorbidities both at diagnosis and afterward. The risk for conditions like systemic lupus erythematosus and anxiety was significantly elevated in these patients.

A study published in *JAMA Dermatology* revealed that patients with alopecia areata face a higher prevalence of autoimmune and psychiatric comorbidities at diagnosis and an increased risk of these conditions developing afterward. Analyzing data from the Merative MarketScan Research Database, the study involved 63,384 patients with alopecia areata and 3,309,107 without. At the time of diagnosis, 30.9% of alopecia areata patients had psychiatric comorbidities, compared to 26.8% of unmatched controls without the condition. Additionally, 16.1% of patients with alopecia areata had autoimmune comorbidities, compared to 8.9% of controls. After matching for sex, age, and geographic region, the incidence of psychiatric diseases within the first year of diagnosis was 10.2% for alopecia areata patients and 6.8% for controls. The incidence of autoimmune or immune-mediated diseases was 6.2% for patients with alopecia areata, compared to 1.5% for the control group.

The study highlighted that patients with alopecia areata have a significantly higher risk of developing psychiatric comorbidities, with an adjusted hazard ratio (aHR) of 1.3, and autoimmune comorbidities, with an aHR of 2.7. Notably, psychiatric disorders with the highest risk included adjustment disorder (aHR 1.5), panic disorder (aHR 1.4), and sexual dysfunction (aHR 1.4). Among autoimmune and immune-mediated disorders, systemic lupus erythematosus had the highest risk (aHR 5.7), followed by atopic dermatitis (aHR 4.3) and vitiligo (aHR 3.8).

Approach to Postpartum Hemorrhage in the Lower Uterine Segment

Pulling down the cervix and packing in the vaginal fornix (PC-PVF) can effectively control postpartum hemorrhage in the lower uterine segment (PPH-LUS), according to a study published online August 4, 2024 in the *Journal of Maternal-Fetal and Neonatal Medicine*[1].

In this study, researchers retrospectively analyzed data of 127 women with PPH-LUS at two tertiary care hospitals. The selected participants had undergone vaginal delivery at these hospitals between 2019 and 2022. Three women underwent laparotomy because of failure of hemostasis. The remaining 124 women who were successfully managed conservatively were further categorized into three subgroups: routine treatment only with uterine massage, uterotonics and tranexamic acid (40 patients), routine treatment + early PC-PVF (simultaneous application of routine treatment and PC-PVF) (33 patients), and routine treatment + late PC-PVF (application of PC-PVF after routine treatment was ineffective) (51 patients). PC-PVF involves continuous external compression of the LUS by pulling down the cervix and packing the posterior and anterior fornices of the vagina with gauze soaked in iodophor. The volume and rate of bleeding within 24 hours after childbirth was compared between the three groups. Data analysis revealed that treatment efficacy rate was 44% in the routine treatment alone group, whereas women who also received PC-PVF along with routine treatment showed treatment efficacy of 100% after excluding PPH due to laceration and patients with incomplete rupture of the LUS. No impact of maternal age, gestational week, Apgar score, and neonatal weight was observed on the outcomes. "All tamponade gauzes remained in place until they were removed, and no tamponade-related complications were observed", note the authors. However, between-group differences were noted for blood loss and bleeding rate with significantly lower total blood loss in the routine treatment + early PC-PVF group. The mean total blood loss was 657.27 mL in patients receiving routine treatment + early PC-PVF versus 847.13 mL in those receiving routine treatment alone and 1040.78 mL in patients receiving routine treatment + late PC-PVF.

Bleeding rate was faster in the routine treatment + early PC-PVF group versus the routine treatment + late PC-PVF treatment group. After tamponade, a significant decrease in bleeding rate was noted in both, but bleeding rate was slower in the routine treatment + early PC-PVF group. This study illustrates the role of PC-PVF as a safe and effective treatment for LUS PPH. Early diagnosis followed by prompt use of this technique may help to reduce blood loss after vaginal delivery. PC-PVF helps to achieve hemostasis by continuously pressing on the LUS from outside to inside. This pressure closes the peripheral blood vessels within the myometrium of the LUS and checks the bleeding. This noninvasive, rapid and simple to perform technique can be easily adopted in routine day-to-day practice as an effective method to control PPH-LUS after vaginal delivery, especially in resource-crunched settings.

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Bleeding Risks after Untreated Respiratory Infections in Patients on Oral Anticoagulants

In patients on oral anticoagulants, the risk of both major and non-major bleeding is more than doubled during the first 2 weeks after an untreated respiratory tract infection, according to a study published in *BMJ*[1].

This study sought to determine the association between untreated, community-acquired, respiratory tract infections and bleeding in patients on oral anticoagulants, warfarin or direct oral anticoagulants (DOAC). A total of 1,208 patients, who had experienced a bleeding event between January 2010 and December 2019 and also had a history of untreated community-acquired respiratory tract infection, i.e., no antibiotics were prescribed were enrolled in the study. Data was obtained from the Clinical Practice Research Datalink GOLD. Men comprised 58% of the study population and the first bleeding episode occurred at the median age of 79 years.

Over the median observation period of 2.4 years, there were 292 major bleeds during unexposed time periods and 41 in the 0 to 14 days following a consultation for a respiratory tract infection. The number of clinically relevant non-major bleeds during unexposed time periods was 1,003 and after consultation for a respiratory tract infection, this number was 81.

The incidence rate ratio (IRR) for major bleeding was 2.68 after controlling for confounders such as age, season, and calendar year. The IRR for clinically relevant non-major bleeding was 2.32. The IRR for both types of bleeding was found to increase in the 0 to 14 days after an untreated respiratory tract infection. This association was not affected by gender or the type of anticoagulant administered.

Patients on oral anticoagulants are at high-risk for bleeding and therefore require close monitoring, especially during acute infections such as those involving the respiratory tract. Early and effective treatment of respiratory infections may reduce the risk of major bleeding in patients taking anticoagulants.

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Assessing Cardiovascular Risk

Measuring low-density lipoprotein "bad" cholesterol (LDL-C) levels along with lipoprotein(a) and high-sensitivity C-reactive protein (hsCRP) levels at middle age is a better predictor of 30-year risk of future cardiovascular events in women, according to a study published in the *New England Journal of Medicine*[1-3]. These findings were also presented at the recently concluded European Society of Cardiology Congress 2024 in London.

Baseline data of LDL-C, hsCRP, and lipoprotein(a) or Lp(a) levels were collected from 27,939 initially healthy participants of the Women's Health Study. They were followed for a duration of 30 years from the time they were recruited for the study between 1992 and 1995 at an average age of ~55 years. Occurrence of the first major adverse cardiovascular event (MACE), a composite of myocardial infarction, stroke, coronary revascularization, or cardiovascular mortality was the primary end point of the study. The objective of the study was how the three biomarkers correlated with these events, alone and all together.

The study subjects were categorized into five groups based on the highest to lowest level of each biomarker. The highest quintile for LDL-C was >150 mg/dL, for hsCRP it was >5 mg/dL and for Lp(a) it was >44 mg/dL. The mean body mass index (BMI) at the time of enrollment was 25.9 kg/m^2. Twenty-five percent were hypertensive, 12% were current smokers, and 2.5% had diabetes.

A total of 3,662 first MACE were recorded over three decades of follow-up. The increasing levels of all the three biomarkers were predictive of the primary endpoint by 30 years. Analysis of data revealed that the risk of cardiovascular events increased by 36% among the participants with the highest levels of LDL-C with covariable-adjusted hazard ratio of 1.36 versus women with the lowest LDL-C levels. Showing a similar trend, the risk of MACE increased by 33% in women with highest levels of Lp(a) (aHR 1.33) and 70% in those with the highest levels of hsCRP (aHR 1.70) compared to those with the lowest levels. Risk was greater as the number of biomarkers increased. The HR for one biomarker in the highest quintile was 1.27, 1.66 for two biomarkers and 2.63 for three biomarkers than those who had none. Collective assessment of LDL-C, Lp(a) and CRP demonstrated more than threefold increased risk for coronary heart disease and 1.5 times heightened risk for stroke vis-a-vis women with the lowest levels of these biomarkers.

Traditionally, the 10-year risk of developing cardiovascular disease is usually estimated. While LDL-C is a routinely ordered test, hsCRP and Lp(a) are usually not advised. But all three are easily available tests.

This study shows that the three biomarkers, when assessed individually, are predictive of cardiovascular risk; the strongest predictor of long-term risk was hsCRP.

Using them in combination enhances their ability to anticipate acute cardiovascular events and therefore is a more comprehensive approach to evaluating long-term cardiovascular risk as shown in this study with over 30 years of follow-up. This allows targeted interventions as they can be "modified either with behavior changes and/or drug therapy". Hence, for primary prevention, risk stratification for atherosclerotic cardiovascular disease should look beyond just measuring cholesterol levels.

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Psychiatric Safety of Semaglutide in Obesity Treatment

The use of semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), in patients with obesity without a known major mental health disorder does not increase the risk of developing depression or suicidal ideation thoughts compared to placebo, as per a study, which analyzed the STEP trials, published September 3, 2024 in *JAMA Internal Medicine*[1,2].

This post hoc analysis of the phase 3a STEP 1, 2, and 3 trials and phase 3b STEP 5 trial was conducted to examine the psychiatric outcomes of subcutaneous semaglutide, 2.4 mg, administered once weekly (vs. placebo) in patients without any known major psychopathology. The participants were overweight or had obesity, while those in the STEP 2 trial also had type 2 diabetes. Depressive symptoms, the main outcomes of the present study, were assessed with the help of Patient Health Questionnaire (PHQ-9). Suicidal ideation/behavior was also a major study outcome and was measured with the Columbia-Suicide Severity Rating Scale.

The study group consisted of 3,377 participants in the STEP 1, 2, and 3 trials and 304 participants in the STEP 5 trial. All the trials had a female preponderance.

Analysis of pooled data showed that the mean PHQ-9 score at baseline for patients in the STEP 1, 2, and 3 trials treated with semaglutide was 2.0 suggesting that the study subjects had no or minimal symptoms of depression. In the placebo group, the mean PHQ-9 score at baseline was 1.8. At week 68, the PHQ-9 scores were 2.0 and 2.4 in the semaglutide and placebo groups, respectively. The estimated between-group treatment was −0.56. Patients receiving semaglutide had a lower probability of progressing to a more severe category of depression on PHQ-9 with odds ratio (OR) of 0.63.

Only ≤1% of participants reported experiencing suicidal ideation or behavior during treatment based on the Columbia-Suicide Severity Rating Scale. There were no significant differences between the two groups. The adverse psychiatric events were generally similar between the two groups.

The STEP 5 trial showed similar results.

Semaglutide injection, 2.4 mg once in a week, is FDA approved for chronic weight management in adults with obesity or overweight with at least one weight-associated condition such as type 2 diabetes, high blood pressure, or high cholesterol as adjunct to lifestyle modification.

Obesity has a significant impact on emotional health due to the weight-related stigma leading to reduced self-esteem, feelings of isolation, depression, or anxiety. Monitoring their mental health is of utmost importance.

An earlier study published in August this year in *JAMA Network Open* had shown 45% higher risk of suicidal ideation with semaglutide[2]. The current study has thrown up opposite results regarding psychiatric effects. Semaglutide was not associated with increased risk of any unintended psychiatric effects such as depression and suicidal ideation or behavior. It was associated with "a small but statistically significant reduction in depressive symptoms (not considered clinically meaningful)", according to the authors.

These findings should alleviate the concerns of both patients and clinicians regarding the psychiatric safety of semaglutide treatment. It can therefore be prescribed for weight management in patients with obesity, who have no significant underlying mental health issues, without major apprehensions about potential psychiatric adverse effects.

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Hypertonic Saline Nasal Drops: A Remedy for Pediatric URTIs?

Use of hypertonic saline nasal drops can shorten the duration of a upper respiratory tract infections (URTI) in children by 2 days, according to the results of ELVIS-Kids randomized controlled trial presented at the ongoing European Respiratory Society (ERS) Congress being held in Vienna, Austria[1,2]. Transmission of infection in the household contacts was also reduced.

The study enrolled 301 children, aged up to 6 years, within 48 hours of development of URTI. They were otherwise healthy. One hundred fifty children in the intervention group were administered hypertonic saline nasal drops (2.6%) by the parents in the dose of 3 drops per nostril, at least 4 times in a day until they recovered, while 151 children in the control group received the usual care (UC) for colds. A daily diary was maintained with a record of side effects, symptoms and compliance as assessed by the Canadian Acute Respiratory Illness and Flu Scale (CARIF). Nasal mid-turbinate swabs were collected daily for 5 days to test for viruses using a respiratory polymerase chain reaction (PCR) panel; 17 URTI viruses were identified. The aim was to study the impact of the nasal drops on the duration of URTI.

The median duration of symptoms decreased by 2 days in children who used the hypertonic saline nasal drops for 5 days (median). Children in the nasal drops group had the symptoms for an average of 6 days (interquartile range [IQR], 5-9 days), whereas children in the UC group remained symptomatic for 8 days (IQR, 5-11 days). The saline nasal drops reduced the duration of symptoms in cases where virus was detected (hypertonic saline drops [n = 102], median 6 days; UC [n = 101], median 8 days), but not where virus was not detected. The most frequently isolated virus was Rhinovirus, detected in 73%. Children who received the drops also had significantly fewer episodes of wheeze; 5% vs. 19%, respectively.

The spread of infection among household contacts of children who received hypertonic saline nasal drops was also reduced compared to the UC group. There were 66 infections (41%) among household members in the hypertonic saline nasal drops group vs. 92 (58%) in the UC group.

"Eighty-two percent of parents said the nose drops helped the child get better quickly and 81% said they would use nose drops in the future"[2].

The side effects were rare and included sneezing, runny nose, and pain. These were mild in nature. No serious adverse effects were observed.

The authors also explained the mechanism by which the hypertonic salt nasal drops exert their beneficial effect. They said, "Salt is made up of sodium and chloride. Chloride is used by the cells lining the nose and windpipes to produce hypochlorous acid within cells, which they use to defend against virus infection. By giving extra chloride to the lining cells this helps the cells produce more hypochlorous acid, which helps suppress viral replication, reducing the length of the virus infection, and therefore the duration of symptoms"[2].

These findings demonstrate the benefits of hypertonic saline nasal drops in children with URTIs as well as in their family members as a simple and cost-effective intervention. Faster recovery of children translates to fewer infections among their household contact with "clear implications for how quickly a household feels better and can return to their usual activities like school and work etc.[2]"

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