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Late-Breaking Data Highlighting Benefits of Ultrafiltration Therapy Using the Aquadex System for Heart Failure Patients was Presented at the Technology and Heart Failure Therapeutics Conference

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- Analysis demonstrates the statistically superior benefits of ultrafiltration therapy in heart failure events and heart failure hospitalizations compared to intravenous loop diuretics
- Artificial intelligence and machine learning-based model show that lifestyle and clinical factors can be strong predictors of heart failure events

MINNEAPOLIS, March 07, 2024 (GLOBE NEWSWIRE) -- [Nuwellis, Inc.](#) (Nasdaq: NUWE), a medical technology company focused on transforming the lives of people with fluid overload, announced results from two new clinical data analyses from the AVOID-HF trial, which demonstrate the benefits of its Aquadex System in reducing heart failure readmissions at 30 days. Results from the analyses were presented in a late-breaking session at the Technology and Heart Failure Therapeutics (THT) conference in Boston.

"Through these studies, we can provide strong evidence demonstrating ultrafiltration as a superior therapy compared to adjustable intravenous diuretics in helping to reduce heart failure events and heart failure hospitalizations for patients, in addition to establishing a potential method for accurately predicting patient response to treatment with Aquadex," said John Jefferies, M.D., chief medical officer of Nuwellis. "The re-appraisal of the AVOID-HF data give us even greater confidence in [REVERSE-HF](#), our ongoing prospective, multicenter, randomized controlled trial. We look forward to gathering additional evidence supporting Aquadex as an effective treatment option for heart failure patients suffering from fluid overload."

Aquapheresis for Management of Decompensated Heart Failure: A Re-appraisal of AVOID-HF Trial

The data was presented by Dr. Sean P. Pinney, M.D., Professor of Medicine and director of the Heart Failure and Transplantation Program at the Mount Sinai Health System, and evaluated the clinical benefit of adjustable ultrafiltration (AUF) therapy with Nuwellis' Aquadex System compared to adjustable loop diuretics (ALD) by re-analyzing data from the AVOID-HF (Aquapheresis vs. Intravenous Diuretics and Hospitalizations for Heart Failure) clinical trial¹ using the Finkelstein-Schoenfeld method of Win-Ratios.

In the trial, 221 study participants were randomized to AUF (n=110) or ALD (n=111), and 213 (AUF=105, ALD= 108) patients who completed index treatment and discharge were included in the analysis. Data were independently adjudicated by a blinded clinical events committee, which evaluated AUF compared to ALD within the three-factor composite endpoint of cardiovascular mortality, heart failure events and quality of life. Key findings demonstrating the benefits of AUF include:

- **Fewer heart failure events and heart failure hospitalizations:** AUF patients had significantly fewer heart failure events within 30 days compared to ALD (90% vs 77.3% p=0.0138) and fewer heart failure hospitalizations for the AUF patients compared to the ALD patients (90.0% vs. 79.2% p=0.0321) within 30 days.
- **Results of the Hierarchical Win-Ratio:** In the primary composite outcome, 72.6% resulted in either a "win" or "loss" and the remaining 27.4% resulted in a "tie". AUF won in 71.0% of the heart failure event related paired comparisons (versus 29.0% for ALD) and in 53.4% of the quality-of-life comparisons (versus 46.6% for ALD) resulting in a WR=1.43 (p=0.056) favoring ultrafiltration.
- Other statistically significant results presented from the original AVOID-HF trial¹ included:
 - Fewer patients re-hospitalized for heart failure (p=0.034)
 - Fewer days in the hospital due to heart failure readmissions (p=0.029)
 - Lower rehospitalization rates due to a cardiovascular event (p=0.037)
 - Fewer rehospitalization days due to a cardiovascular event (p=0.018)
 - Fewer patients re-hospitalized for a cardiovascular event (p=0.042)

AI Assisted Identification of Super-Responders for Ultrafiltration can Reduce 90-Day Readmission Rates: Evidence from AVOID-HF Trial

This study, presented by Deya Alkhatib, M.D., Section of Cardiovascular Medicine, Yale School of Medicine, aimed to develop a model for pretreatment and identification of risk for 90-day heart failure events among heart failure patients who have undergone AUF therapy. Using artificial intelligence (AI) and machine learning (ML), a predictive model was developed based on data from the AVOID-HF trial. The model was designed to be used before initiating AUF to anticipate which patients will respond well to the therapy and which will be at high risk for future heart failure events. Key findings from the analysis include:

- **Top predictors for 90-day heart failure events:** Using ML, the study identified the top 10 predictors for 90-day heart failure events. Notably, "intimate relationships with loved ones" was a strong predictor of response to AUF therapy. Other predictors

included valvular heart disease, history of arrhythmia, poor adherence to medical therapy, history of diabetes mellitus, suboptimal diuretic therapy response, chronic obstructive lung disease, ALD use during acute decompensated heart failure hospitalization, history of cerebrovascular disease, and intravenous bumetanide use.

- **Successful prediction of outcomes:** The ML model used in the study was more successful in predicting the outcome for heart failure patients treated with AUF. The predictive model anticipated 90-day heart failure events with better statistical accuracy than existing classic models.
- **Strong results for super-responders:** 90% of patients categorized as super-responders to AUF therapy within this model did not experience any 90-day heart failure events.
- **Accurate predictions for high-risk patients:** The model assigned 41% of patients in the study to the high-risk category. Among these patients, 57% experienced a 90-day heart failure event.

"Nuwellis is dedicated to making Aquadex therapy the standard of care for fluid management in heart failure patients who don't respond to diuretics, and this new evidence provides strong validation that we're on the right track," said Nestor Jaramillo, Jr., president and CEO of Nuwellis. "The Aquadex System has demonstrated that it not only helps improve patient quality of life, but also helps relieve the financial burden that repeated heart failure hospitalizations and readmissions take on hospitals, health systems, and patients themselves."

About the AVOID-HF Trial

The AVOID-HF prospective, multicenter, randomized controlled trial tested the hypothesis that patients hospitalized for heart failure (HF) and treated with ultrafiltration would have a longer time to their first heart failure event within 90 days after hospital discharge compared to those receiving IV loop diuretics. The study was trending favorably when the study sponsor terminated it before reaching full enrollment for reasons unrelated to patient safety or clinical futility. At the time, analysis of the AVOID-HF trial data was inconclusive due to the lower-than-planned sample size. However, new statistical analysis methods such as the Finkelstein-Schoenfeld method of hierarchical Win Ratios increases statistical precision in demonstrating significant differences in clinical outcomes between treatment arms, while requiring a smaller study sample size.

About the Aquadex SmartFlow® System

The Aquadex SmartFlow system delivers clinically proven therapy using a simple, flexible and smart method of removing excess fluid from patients suffering from hypervolemia (fluid overload). The Aquadex SmartFlow system is indicated for temporary (up to 8 hours) or extended (longer than 8 hours in patients who require hospitalization) use in adult and pediatric patients weighing 20 kg or more whose fluid overload is unresponsive to medical management, including diuretics. All treatments must be administered by a health care provider, within an outpatient or inpatient clinical setting, under physician prescription, both having received training in extracorporeal therapies.

About Nuwellis

Nuwellis, Inc. (Nasdaq: NUWE) is a medical technology company dedicated to transforming the lives of patients suffering from fluid overload through science, collaboration, and innovation. The company is focused on commercializing the Aquadex SmartFlow® system for ultrafiltration therapy. Nuwellis is headquartered in Minneapolis, with a wholly owned subsidiary in Ireland. For more information visit www.nuwellis.com or visit us on [LinkedIn](#) or [X](#).

Forward-Looking Statements

Certain statements in this release may be considered forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, including without limitation, statements regarding the new market opportunities and anticipated growth in 2024 and beyond. Forward-looking statements are predictions, projections and other statements about future events that are based on current expectations and assumptions and, as a result, are subject to risks and uncertainties. Many factors could cause actual future events to differ materially from the forward-looking statements in this release, including, without limitation, those risks associated with our ability to execute on our commercialization strategy, the impact of the COVID-19 pandemic, the possibility that we may be unable to raise sufficient funds necessary for our anticipated operations, our post-market clinical data collection activities, benefits of our products to patients, our expectations with respect to product development and commercialization efforts, our ability to increase market and physician acceptance of our products, potentially competitive product offerings, intellectual property protection, our ability to integrate acquired businesses, our expectations regarding anticipated synergies with and benefits from acquired businesses, and other risks and uncertainties described in our filings with the SEC. Forward-looking statements speak only as of the date when made. Nuwellis does not assume any obligation to publicly update or revise any forward-looking statements, whether due to new information, future events or otherwise.

1) Costanzo, M.R., et al., Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure. *JACC Heart Fail.* 2016. 4(2): p. 95-105.

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