cooling to a lower-temperature target does not improve outcomes of unconscious survivors of out-of-hospital cardiac arrest (OHCA) compared with cooling to standard temperature targets.

OHCA carries a high risk of death and poor neurological outcomes. Since induced hypothermia is associated with improved outcomes in these patients, its use is recommended in clinical guidelines. However, the optimal target temperature is unknown [Nielsen N et al. *Int J Cardiol* 2011].

The TTM trial [Nielsen N et al. *N Engl J Med* 2013] is the largest trial to study hypothermia in cardiac arrest patients. This international, multicenter, randomized trial was designed to evaluate whether cooling to a target temperature of 33°C compared with 36°C improved outcome in patients with OHCA.

Inclusion criteria were OHCA, age ≥18 years, unconscious, presumed cardiac cause, and stable return of spontaneous circulation (ROSC).

Exclusion criteria included unwitnessed cardiac arrest with initial rhythm of asystole, ROSC to screening interval >240 minutes, known or suspected acute intracranial hemorrhage or stroke, and body temperature <30°C.

The primary endpoint of the study was all-cause mortality through the end of the trial, and the main secondary outcome was a composite of death or poor neurologic function at 180 days, as evaluated by the Cerebral Performance Category scale and modified Rankin scale.

A total of 939 OHCA patients were enrolled in the study and randomized 1:1 to either target temperature managements of 33°C (n=473) or 36°C (n=466) for 24 hours.

At the end of the trial, there was no significant difference in the primary endpoint of patient mortality between the 33°C and 36°C groups (50% vs 48%; p=0.51).

And similarly, at 180-day follow-up, there was no significant difference in the percentage of patients who had died or had poor neurologic function, as evaluated with either the Cerebral Performance Category scale (54% vs 52%; p=0.78), or the modified Rankin scale (both 52%; p=0.87).

Serious adverse events, including bleeding, pneumonia, and electrolyte disturbances, were frequent in both the 33°C group and the 36°C group (93% vs 90%; p=0.09), with a significant increase in the incidence of hypokalemia (19% vs 13%; p=0.02)

Prof. Nielsen concluded that these results do not suggest any benefit for a target body temperature of 33°C in unconscious OHCA patients compared with 36°C. The optimal temperature for therapeutic hypothermia in this patient population therefore remains unclear, and further study is needed to determine the optimal temperature goal for patients with OHCA being treated with therapeutic hypothermia.

Results From the ROSE AHF Study

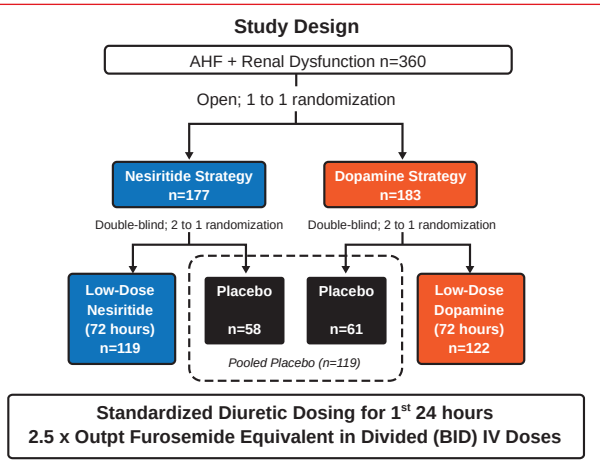
Written by **Mary Mosley**

In the Renal Optimization Strategies Evaluation in Acute Heart Failure Study [ROSE AHF; NCT01132846] treatment with low-dose dopamine or low-dose nesiritide did not improve renal dysfunction compared with placebo. The results of the National Heart, Lung, and Blood Institute -funded study were presented by Horng H. Chen, MD, Mayo Clinic, Rochester, Minnesota, USA.

ROSE-AHF examined whether the addition of low-dose dopamine (2 µg/kg/min) or low-dose nesiritide (0.005 µg/kg/min without bolus) to diuretic therapy would enhance decongestion and preserve renal function when compared with placebo in patients with acute heart failure (AHF) and ≥1 symptom (dyspnea, orthopnea, edema) or ≥1 sign (rales, edema, ascites, chest x-ray), and an estimated glomerular filtration rate (eGFR) 15 to 60 mL/min/1.73 m^2. For the first 24 hours, all patients received standardized diuretic dosing (2.5-times the outpatient dose) and patients were enrolled within 24 hours of hospitalization.

The randomization schema and number of patients in each group are shown in Figure 1. The two coprimary endpoints were cumulative urinary volume from randomization through 72 hours (decongestion endpoint), and change in serum cystatin-C concentration from randomization to 72 hours (renal function endpoint).

Figure 1. ROSE AHF Study Design



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Patients randomized had a median age of 70 years, 73% were male, and 26% had an ejection fraction (EF) >50%. Over half of patients (67%) had been hospitalized for AHF in the prior year. Their median eGFR was 44.5 mL/min/1.73 m^2, NT-proBNP was 4972 pg/mL, and the median outpatient dose of furosemide was 80 mg/day.

Results for the dopamine strategy showed no significant difference between active treatment and placebo in 72-hour urine volume (8.5 vs 8.3 L, respectively; p=0.58), or cystatin-C concentration (0.12 vs 0.11 mg/L; p=0.72). The lack of effect was consistent across prespecified subgroups, except for patients with preserved EF (>50%) who tended to have lower urine volume with dopamine compared with placebo (p=0.01).

No significant treatment effect was seen with dopamine on secondary endpoints related to decongestion, renal function, or symptom relief. There was less study drug dose reduction or discontinuation due to hypotension in the dopamine group, but they were more likely to have study drug dose reduction or discontinuation due to tachycardia. The overall incidence of study drug discontinuation before 72 hours due to any cause was similar between the two groups. As for clinical outcomes, the composite of 60-day death, unscheduled visits, or HF readmission was similar between the two groups (HR, 1.15; 95% CI, 0.74 to 1.78; p=0.53), as was the rate of 180-day mortality (HR, 0.95; 95% CI, 0.54 to 1.68; p=0.87).

In the nesiritide group, there was no significant difference between active treatment and placebo in 72-hour urine volume (8.6 vs 8.3 L, respectively; p=0.25), or cystatin-C concentration (0.07 vs 0.11 mg/L, respectively; p=0.35). The lack of benefit was consistent across prespecified subgroups. There was a nonsignificant trend suggesting a differential effect in patients with reduced EF compared with patients with preserved EF. Patients with reduced EF who received nesiritide tended to have greater urine output volume (p=0.06) and less change in cystatin-C concentration when compared with patients receiving placebo (p=0.09). There was no significant treatment effect on secondary endpoints related to decongestion, renal function, or symptom relief. Patients receiving nesiritide had rates of study drug dose reduction or discontinuation due to hypotension that were numerically higher than in patients receiving placebo (18.8% vs 10.4%; p=0.07). The overall incidence of study drug discontinuation before 72 hours for any reason was similar in both the treatment and placebo group (25% vs 25%; p=0.94). The rate of 180-day mortality was similar between the groups (HR, 0.91; 95% CI, 0.51 to 1.61; p=0.74). The composite rate of 60-day death, unscheduled visits, or HF readmission, however, showed a nonsignificant trend favoring nesiritide (HR, 0.71; 95% CI, 0.44 to 1.15; p=0.16).

In patients with AHF and underlying renal dysfunction, neither low-dose dopamine nor low-dose nesiritide when added to diuretics enhanced decongestion or improved renal function. Further investigations of these, or other, AHF therapies should assess the potential for differential responses in HF with preserved versus reduced EF, stated Dr. Chen.

TOPCAT: Effects of Spironolactone on CV Outcomes in Patients With Heart Failure With Preserved Ejection Fraction

Written by **Mary Mosley**

In adults with heart failure and preserved ejection fraction (HFpEF), the mineralocorticoid receptor antagonist spironolactone did not significantly reduce the composite primary outcome of cardiovascular (CV) mortality, aborted cardiac arrest, or hospitalization for heart failure (HF) compared with placebo, but it did reduce HF hospitalizations (Table 1). Marc A. Pfeffer, MD, PhD, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented the results of the Treatment of Preserved Cardiac Function With an Aldosterone Antagonist [TOPCAT; NCT00094302] study.

Table 1. Results for Primary Outcome and Its Components

Outcome	Number and Percentage of Subjects With Event and Event Rate		
	Spironolactone (n=1722)	Placebo (n=1723)	HR (95% CI) p Value
Primary outcome	320 (18.6%) 5.9/100 pt-yr	351 (20.4%) 6.6/100 pt-yr	0.89 (0.77–1.04) p=0.138
Primary components			
CV mortality	160 (9.3%) 2.8/100 pt-yr	176 (10.2%) 3.1/100 pt-yr	0.90 (0.73–1.12) p=0.354
Aborted cardiac arrest	3 (<1%) 0.05/100 pt-yr	5 (<1%) 0.09/100 pt-yr	0.60 (0.14–2.50) p=0.482
Hospitalization for heart failure	206 (12.0%) 3.8/100 pt-yr	245 (14.2%) 4.6/100 pt-yr	0.83 (0.69–0.99) p=0.042

CV=cardiovascular; pt-yr=patient-years.

The hypothesis for the benefit of aldosterone antagonism in HFpEF patients was based upon mechanistic data in combination with the benefits observed in outcomes trials of patients with heart failure and reduced ejection fraction (HFrEF) as well as in the post-myocardial infarction (MI) setting. These included the RALES [Pitt B et al. *N Engl J Med* 1999], EMPHASIS [Zannad F et al. *N Engl J Med* 2011], and the EPHESUS studies [Pitt B et al. *N Engl J Med* 2003].

The National Heart, Lung and Blood Institute-funded, international, multicenter, double-blind, placebo-controlled TOPCAT study randomized 3445 patients with symptomatic HF (NYHA II to IV), left ventricular ejection fraction (LVEF) ≥45%, and either HF hospitalization within 1 year prior to randomization or elevated natriuretic peptide levels (BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL) within 60 days prior to randomization. Stratification based on