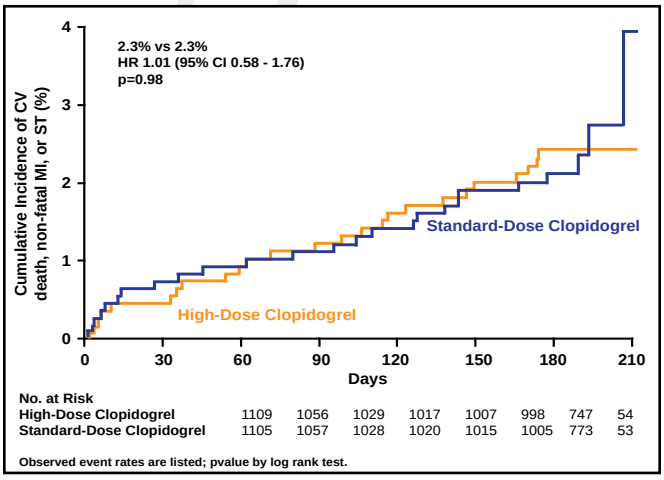
had high residual platelet reactivity (platelet reactivity units [PRU] >230) and were randomized to continue on the 75-mg standard clopidogrel dose or to receive another 600-mg loading dose and a higher maintenance dose of 150 mg daily. Follow-up VerifyNow assays, the results of which were not available to the treating physician, were performed at 30 days and 6 months to assess the effect of the intervention on platelet reactivity. All participants also received daily low-dose aspirin.

The primary efficacy endpoint was CV death, nonfatal myocardial infarction (MI), or stent thrombosis at 6 months. The key safety endpoint was moderate or severe bleeding at 6 months.

Most enrolled patients were at relatively low risk at baseline, with 84% having stable coronary artery disease or low-risk unstable angina. Results showed no significant differences between the 6-month rate of CV death, MI, or stent thrombosis, which was 2.3% for both groups (HR, 1.01; 95% CI, 0.58 to 1.76; p=0.98; Figure 1). Rates of bleeding, whether moderate or severe, were also similar in both groups (1.4% vs 2.3%, high dose and standard dose respectively; p=0.10).

Figure 1. Primary Endpoint: CV Death, MI, Stent Thrombosis.



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Persistently high PRU levels (> 230) were significantly more common in the standard-dose group at 30 days (62% vs 40%; p<0.001), although achieving a lower PRU with higher-dose clopidogrel did not translate into improved clinical outcomes. One possible explanation is that the magnitude of the effect on platelet reactivity was not sufficient to demonstrate a clinically significant difference between these two dosing strategies of clopidogrel.

Dr. Price noted that high-dose clopidogrel was safe and that future trials should investigate more potent antiplatelet agents, focus on different populations, and test different treatment strategies—eg, treating to a specific PRU target rather than basing treatment upon a single post-PCI assessment of platelet function.

Results From the ASCEND-HF Trial

Results from a large, prospective clinical trial that was designed to assess the safety and efficacy of nesiritide that was added to standard care in patients with acute decompensated heart failure (ADHF) showed that nesiritide is safe but offers no significant benefit in terms of mortality or HF rehospitalization rates. There was a modest improvement in dyspnea. Renal function was not compromised.

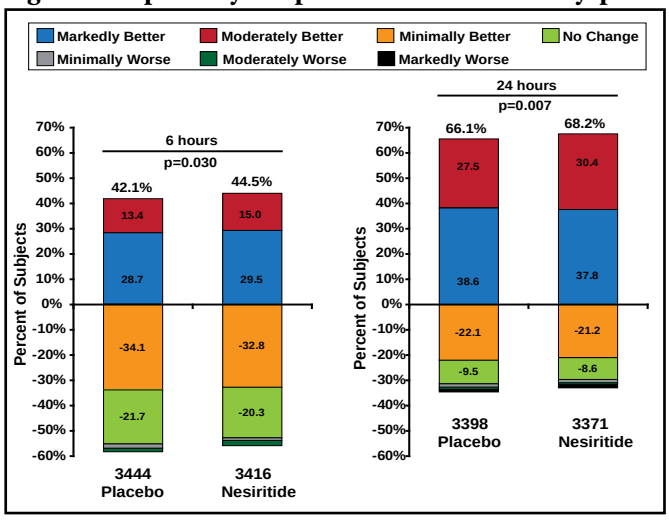
Nesiritide is a recombinant intravenous (IV) formulation of human B-type natriuretic peptide that is known to reduce dyspnea and intracardiac filling pressures within 3 hours of administration in patients with ADHF. It was approved in 2001 to reduce pulmonary capillary wedge pressure and improve dyspnea and was widely used until 2005, when the results of two meta-analyses questioned its safety, noting a higher mortality rate [Sackner-Bernstein JD et al. *JAMA* 2005] and increased risk of kidney injury [Sackner-Bernstein JD et al. *Circulation* 2005]. The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF; NCT00475852) was designed as the result of an independent safety and efficacy review of nesiritide data in an attempt to assess the concerns that were raised by the 2005 reports more fully.

ASCEND-HF was a prospective, double-blind, randomized trial in 7141 patients (median age 67 years; ~34% women) with ADHF, dyspnea at rest or with minimal activity, and one clinical sign and one objective measure of HF. Within 24 hours of hospitalization, subjects were randomly assigned to receive either IV nesiritide (n=3496; initial IV bolus of 2 µg/kg at the discretion of the investigator, followed by continuous IV infusion of 0.01 µg/kg) or matching placebo (n=3511) for up to 7 days, along with usual care. The duration of treatment was based on the investigator's assessment of clinical improvement.

The two coprimary endpoints were rehospitalization for HF/all-cause mortality within 30 days and dyspnea at 6 or 24 hours (p-value for significance prespecified at ≤0.005 for both assessments or ≤0.0025 for either assessment). Improvement in dyspnea was self-reported using a 7-point Likert scale: markedly worse, moderately worse, minimally worse, no change, minimally better, moderately better, and markedly better. Safety endpoints included impact on renal function (25% decrease in eGFR through Day 30) and hypotension.

There was no difference in either of the coprimary endpoints between treatment groups. The rate of HF rehospitalization or 30-day all-cause mortality was 9.4% for subjects who were treated with nesiritide versus 10.1% for placebo-treated patients (HR, 0.93; 95% CI, 0.81 to 1.08; p=0.31). The observed reduction in overall dyspnea was modest and did not meet the preestablished criteria for significance. At 6 hours, 44.5% of nesiritide subjects reported markedly or moderately better dyspnea versus 42.1% of subjects who received placebo (p=0.030). At 24 hours, the rates were 68.2% for nesiritide patients versus 66.1% for placebo patients (p=0.007; Figure 1). Marked improvement in dyspnea was less frequent with nesiritide at 6 hours (15.0% vs 13.4%; p=0.03) and 24 hours (30.4% vs 27.5%; p=0.007). Neither finding was statistically significant, based on the predefined significant p-value of ≤0.005.

Figure 1. Coprimary Endpoint: 6- and 24-Hour Dyspnea.



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There was no difference in renal function between treatment groups (p=0.11). Subjects who received nesiritide experienced significantly (p<0.001) more hypotension compared with those who received placebo through Day 10 or discharge (HR, 11.3; 95% CI, 9.4 to 13.1).

No Reduction in Recurrent AF With Omega-3 Fatty Acids

Treatment with prescription omega-3 (P-OM3) fatty acids failed to reduce the risk of recurrent atrial fibrillation (AF) after 6 months compared with placebo in patients with paroxysmal AF, according to findings from a large randomized study. P-OM3 was also ineffective in reducing the risk of symptomatic recurrence in patients with persistent AF.

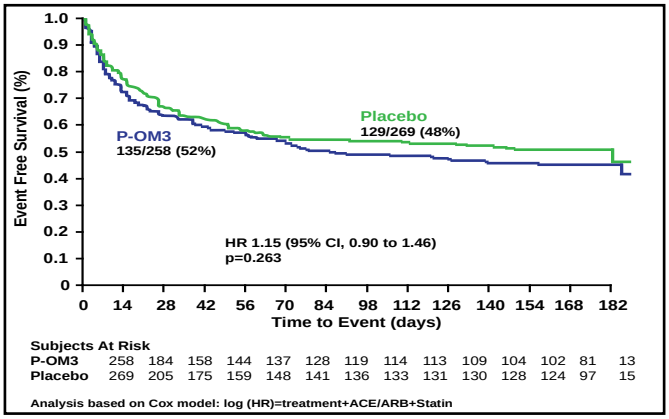
Various doses and preparations of fish oil products have been evaluated to reduce cardiovascular endpoints, with mixed results. The current study examined a high-dose form of pure P-OM3 in patients with AF. Each 1-g capsule of P-OM3 contained approximately 465 mg eicosapentaenoic acid and 375 mg docosahexaenoic acid. Patients were randomized to 8 g daily for the first week, then 4 g daily (n=332) versus placebo (n = 331).

In the prospective, multicenter, double-blind study, 663 patients with paroxysmal (n=542) or persistent (n=121) AF were randomly assigned to treatment with P-OM3 4 g once daily or placebo for 24 weeks. All patients were free from substantial structural heart disease and had normal sinus rhythm at baseline. The primary endpoint was the time to first symptomatic recurrence of AF or atrial flutter in patients with paroxysmal AF. Secondary endpoints included the efficacy and safety of P-OM3 in patients with persistent AF.

Peter R. Kowey, MD, Lankenau Institute for Medical Research, Wynnewood, Pennsylvania, USA, presented the results during a late-breaking clinical trials session.

Among patients with paroxysmal AF, P-OM3 failed to reduce the risk of symptomatic recurrence compared with placebo (52% with P-OM3 vs 48% with placebo; HR, 1.15; 95% CI, 0.90 to 1.46; p=0.26; Figure 1). The risk of recurrent AF or atrial flutter was similar in the P-OM3 and placebo groups across patient subgroups, defined by age, gender, race, smoking status, alcohol consumption, angiotensin-converting enzyme inhibitor and angiotensin receptor blocker use, and geographical region.

Figure 1. Time to First Recurrence of Symptomatic AF or Atrial Flutter in Patients with Paroxysmal AF.



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In an analysis of secondary endpoints, P-OM3 did not reduce the risk of recurrence relative to placebo in patients with persistent AF (50% vs 33%; HR, 1.64; 95% CI, 0.92 to 2.92; p=0.09) or in the combined study group of paroxysmal and persistent AF (52% vs 46%; HR, 1.22; 95% CI, 0.98 to 1.52; p=0.08). P-OM3 also failed to reduce the annualized