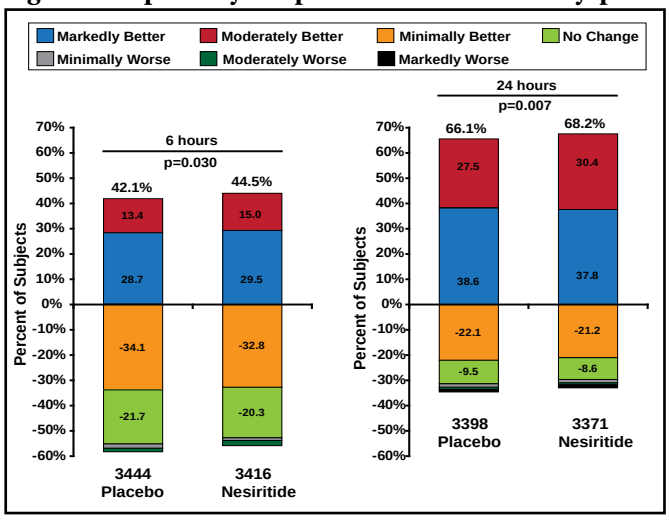
There was no difference in either of the coprimary endpoints between treatment groups. The rate of HF rehospitalization or 30-day all-cause mortality was 9.4% for subjects who were treated with nesiritide versus 10.1% for placebo-treated patients (HR, 0.93; 95% CI, 0.81 to 1.08; p=0.31). The observed 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.

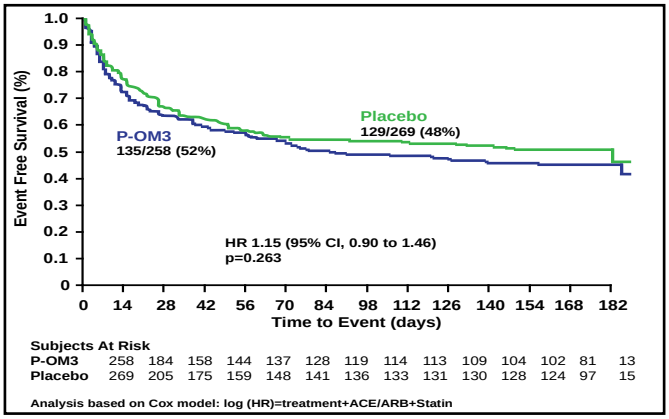
Various doses and preparations of fish oil products have been evaluated to reduce cardiovascular endpoints, with mixed results. The current study examined a high-dose form of pure P-OM3 in patients with AF. Each 1-g capsule of P-OM3 contained approximately 465 mg eicosapentaenoic acid and 375 mg docosahexaenoic 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

number of rescue episodes versus placebo (4.2 vs 2.4; p=0.07), the cumulative frequency of symptomatic AF or atrial flutter episodes (8.3 vs 6.8; p=0.32), or symptomatic AF recurrences (8.3 vs 6.9; p=0.24).

Although P-OM3 did not provide a clinical benefit, fish oil treatment did result in several favorable biological changes. Compared with the placebo group, the P-OM3 group had a lower ventricular rate during the first AF recurrence. Patients in the P-OM3 group also had decreased triglyceride and very low-density lipoprotein levels at Week 24, lower systolic blood pressure levels at Week 24, and increased plasma levels of the omega-3 fish oils eicosapentaenoic acid and docosahexaenoic acid at Week 4 and Week 24.

P-OM3 was well tolerated. Adverse events occurred with similar frequency in the P-OM3 and placebo groups, including nausea (5% vs 4%), dizziness (4% vs 3%), urinary tract infection (4% vs 4%), sinusitis (3% vs 4%), and peripheral edema (4% vs 2%).

In summary, findings from this large prospective trial do not support the use of P-OM3 to reduce the risk of recurrent AF, investigators said. However, the results do not exclude the potential for a benefit with high-dose P-OM3 therapy in combination with other antiarrhythmic drugs or in different patient populations, such as high-risk primary prevention patients or in postoperative AF. Future prospective trials may examine the role of P-OM3 in these clinical settings.

Results of this study were published simultaneously in the *Journal of the American Medical Association*. Kowel P et al. *JAMA* 2010.

CLOSURE I: No Reduction in Recurrent Stroke or TIA With Septal Closure

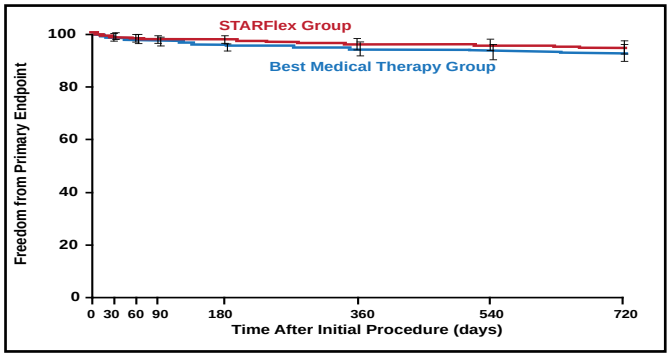
Percutaneous closure of patent foramen ovale (PFO), an atrial septal defect that epidemiological studies have suggested is associated with cryptogenic stroke, does not reduce the risk of recurrent stroke or transient ischemic attack (TIA) of unknown origin compared with standard medical therapy alone, according to new findings from the CLOSURE I trial.

The prospective, randomized, multicenter CLOSURE I trial included 909 patients aged 60 years or younger with a history of cryptogenic stroke or TIA and PFO that was documented by transesophageal echocardiography (TEE) within 6 months of enrollment. Patients were randomly assigned to PFO closure using the STARFlex closure device within 30 days plus 6 months of aspirin and clopidogrel, followed by an additional 18 months of aspirin (n=447) or best medical therapy (n=462), defined as aspirin, warfarin, or the combination of aspirin and warfarin for 24 months.

The composite primary endpoint included the 2-year incidence of stroke or TIA, all-cause mortality at 30 days, and neurological mortality between 31 days and 2 years. Anthony J. Furlan, MD, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA, presented findings from the CLOSURE I study.

Among the patients who were randomized to the STARFlex closure device, the mean age was 46 years, 52% were male, and 38% had an atrial septal aneurysm ≥10 mm. Procedural success was achieved in 90%. In an intent-to-treat analysis, 5.9% of patients in the PFO closure group and 7.7% of those who were treated with medical therapy alone reached the primary endpoint (p=0.30; Figure 1). Stroke risk was also similar in the PFO closure and the medical therapy groups (3.1% vs 3.4%; p=0.77), as was the risk for TIA (3.3% vs 4.6%; p=0.39).

Figure 1. Risk of Recurrent Stroke or TIA, All-Cause Mortality, and Neurological Mortality at 2 Years.



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Percutaneous PFO closure was associated with significantly more major vascular complications than medical therapy (3.2% versus 0.0%; p<0.001), as well as an increased risk of atrial fibrillation (5.7% versus 0.7%; p<0.001). Most cases of atrial fibrillation in the device closure group (60%) were periprocedural. Patients in the PFO closure group also showed a trend toward increased major bleeding (2.6% vs 1.1%; p=0.11) but experienced no increase in the risk of nonendpoint deaths (0.5% vs 0.7%) or other serious adverse events (16.9% vs 16.6%).

Given the high procedural success rate, the lack of benefit with PFO closure was not due to device failure. Thrombus formation was observed by TEE in 4 patients (1.0%), including 2 patients with a recurrent stroke on Days 4 and 52, respectively. The majority of patients maintained effective PFO closure, defined as no residual leaks by TEE at 6 months (86.1%), 12 months (86.4%), and 24 months (86.7%). Furthermore, there were no recurrent strokes or TIA in any of the patients with residual leaks. Finally, within