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

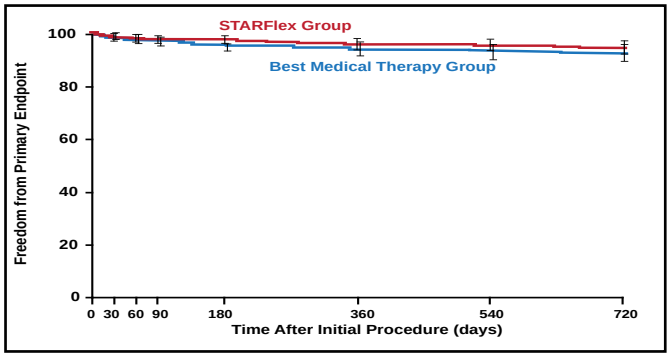
Percutaneous closure of patent foramen ovale (PFO), an atrial septal defect that epidemiological studies have suggested is associated with cryptogenic stroke, does not reduce the risk of recurrent stroke or transient ischemic attack (TIA) of unknown origin compared with standard medical therapy alone,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

the medical treatment group, there was no difference in the primary endpoint between aspirin alone and warfarin alone.

Among patients in the CLOSURE I trial who experienced recurrent stroke or TIA during follow-up, approximately 80% had an alternative explanation other than paradoxical embolism, Dr. Furlan said. These findings suggest that cryptogenic stroke and TIA include multiple etiologies other than PFO that are not adequately addressed with PFO closure or current medical therapy.

Although the CLOSURE I trial showed no significant improvement with PFO closure over medical therapy alone, PFO closure may be beneficial in better-defined patient subgroups, Dr. Furlan said. Ongoing trials, including the Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE) and Patent Foramen Ovale and Cryptogenic Embolism (PC) trials, are examining the role of PFO closure in other patient groups.

Results from the ASCOT Trial

Peter S. Sever, MD, Imperial College, London, UK, presented an analysis from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) database, showing that screening for high-sensitivity C-reactive protein (hsCRP) only minimally improved risk assessment in middle-aged patients with traditional cardiovascular disease risk factors.

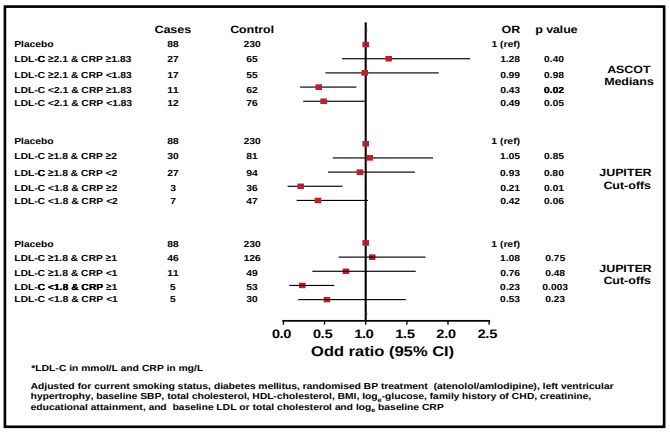
This retrospective, nested, case-control study explored the relationship between hsCRP prior to and during treatment with statins and their association with cardiovascular (CV) events. ASCOT randomized 19,342 hypertensive adults aged 40-79 years with no prior CHD but with 3 or more additional CV risk factors to either a calcium channel blocker (amlodipine) or beta-blocker (atenolol) (ASCOT blood pressure-lowering arm) [Dahlöf B et al. *Lancet* 2005]. Patients (n=10,305) with total cholesterol ≤6.5 mmol/L (250 mg/dL) were further randomized to atorvastatin (10 mg) or placebo (ASCOT lipid-lowering arm) [Sever PS et al. *Lancet* 2003].

For the present analyses, cases were confined to those that occurred in ASCOT patients who were recruited in the UK and Ireland in whom stored blood samples for hsCRP analysis were available. Four hundred eighty-five cases (fatal coronary heart disease, nonfatal MI, coronary revascularization, fatal and nonfatal stroke) that occurred during the 5.5 years of follow-up from ASCOT were age- and sex-matched with 1367 controls from within the group. Cases were more likely to be smokers; have diabetes or increased systolic blood pressure and higher CRP, glucose, and creatinine levels; and be receiving statin therapy. Conditional logistic regression models were used to evaluate the association between CV events and LDL-cholesterol (LDL-C) and hsCRP.

There was a direct linear association between baseline CRP with CV events with an odds ratio (OR) of 1.21 (p=0.0004). Inclusion of hsCRP in the Framingham risk model did not significantly improve prediction of CV events (p=0.20).

At 6 months, atorvastatin reduced median LDL-C by 40.3% and hsCRP by 27.4% (Figure 1). In subjects who were randomized to atorvastatin, lower in-trial median LDL-C (2.1 mmol/L or 77 mg/dL) was associated with a highly significant reduction in CV events (OR, 0.41; 95% CI, 0.22 to 0.75; p<0.004). In contrast, in subjects who were randomized to atorvastatin in the fully adjusted model, lower hsCRP at 6 months was not associated with CV events (OR, 0.86; 95% CI, 0.49 to 1.51; p=0.60) and, thus, was not an indicator of the magnitude of the effect of atorvastatin on CV outcome.

Figure 1. Risk of CV Events (CHD or Stroke) by On-Treatment (6 Month Trial) LDL-C and CRP*.



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In this nested case study, the addition of on-treatment hsCRP to on-treatment LDL-C did not improve prediction of statin efficacy. This modestly sized retrospective analysis does not support the hypothesis that either baseline or on-treatment hsCRP usefully improves CV risk factor prediction or provides useful information about the efficacy of statin treatment to reduce CV events beyond LDL-C reduction. These data are in contrast to those from the JUPITER trial, which studied statin therapy in a lower-risk primary prevention cohort with elevated baseline CRP, and demonstrated a significant reduction in CV endpoints. Potential explanations for the discrepant findings include the use of a lower-intensity and different statin in ASCOT (10 mg atorvastatin may not reduce CRP to the same degree as 20 mg rosuvastatin) compared with JUPITER, incomplete adjustment for baseline differences in the case-control design, and differences in study populations and outcome assessments.