(HR, 0.72; 95% CI, 0.62 to 0.83; p<0.001). Moreover, the risk reduction was particularly related to the annual risk of non-hemorrhagic stroke in the aspirin alone (3.2%) and clopidogrel plus aspirin (2.1%) groups (RR, 0.68; 95% CI, 0.59 to 0.80; p<0.001). The annual risk of hemorrhagic stroke was 0.2% in both treatment groups (RR, 1.37; 95% CI, 0.79 to 2.37; p=0.27).

There was also a nonsignificant trend toward a reduction in the risk of MI from 0.9% with aspirin alone to 0.7% with dual antiplatelet therapy (HR, 0.78; 95% CI, 0.59 to 1.03; p=0.08). However, there were no differences between treatment groups in the risk of vascular death (4.7% per year in both groups; p=0.97) or non-CNS systemic embolism (0.4% per year in both groups; p=0.84).

Clopidogrel increased the risk of bleeding in patients on long-term aspirin therapy. Compared with patients taking aspirin alone, those taking clopidogrel and aspirin had a higher rate of major bleeding (1.3% vs 2.0% per year; RR, 1.57; 95% CI, 1.29 to 1.92; p<0.001), including severe bleeding (1.0% vs 1.5% per year; p<0.001), with a trend toward increased fatal bleeding (0.2% vs 0.3% per year; p=0.07). The excess risk of major bleeding included both intracranial bleeding (0.2% vs 0.4% per year; p=0.006) and extracranial bleeding (1.1% vs 1.6%; p<0.001).

Overall, adding clopidogrel to aspirin therapy for 3 years in 1000 patients with atrial fibrillation unsuitable for anticoagulation will prevent 28 strokes, including 17 fatal or disabling strokes, and 6 MIs. This strategy will also cause 20 major bleeds, including 3 fatal bleeds, which is an acceptable balance of clinical benefits and hemorrhagic risks, Dr. Connolly concluded.

Findings from the ACTIVE-A trial were simultaneously published online in the *New England Journal of Medicine.*

Adding Cardiac Resynchronization Therapy (CRT) May Prevent Disease Progression In Asymptomatic and Mildly Symptomatic Heart Failure (HF) Patients Already on OMT

The 24-month results of the European cohort of the Resynchronization Reverses Remodeling in Systolic left ventricular dysfunction (REVERSE; NCT00271154) trial showed that CRT that is combined with optimal medical therapy (OMT) produces improved clinical outcomes, as well as improved ventricular structure and function in persons with NYHA Class I-II HF patients. Jean-Claude Daubert, MD, Centre Hospitalier Universitaire, Rennes, France, suggested that CRT may prevent disease progression in these patients.

The 1-year results from REVERSE failed to show that adding CRT to OMT significantly influenced the primary endpoint, which was percentage of worsening. This subset analysis (from the European dataset) included 261 patients with HF that was associated with a QRS duration ≥120 ms, an LVEF ≤40%, and left ventricular end diastolic diameter (LVEDD) ≥55 mm who received a CRT device with or without a defibrillator. Patients in REVERSE were randomly assigned to an active CRT group (CRT on; 180 patients) or a control group (CRT off; 82 patients) for 24 months, while OMT for HF was maintained. The primary endpoint was the HF clinical composite response (including all-cause mortality, HF hospitalizations, crossover due to worsening HF, NYHA class, and the patient global assessment), which compared the proportion of improved, unchanged, or worsened patients in the CRT-off versus CRT-on groups. The prospectively powered secondary endpoint was LV end-systolic volume index (LVESVi).

After 24 months, the clinical composite response was significantly (p=0.01) worsened in more patients in the CRT-off (34%) versus the CRT-on group (p=0.0006). Significant differences were noted at 6 months and remained for the duration of the study. Worsening was attributed to death or HF hospitalization in 69% of patients in the CRT-off group. Compared with patients in the CRT-off group, CRT-on patients experienced a significant reduction in LVESVi (p<0.0001) and other measures of LV remodeling. Time to first HF hospitalization or any death was significantly delayed in CRT on compared with CRT off (HR, 0.38; 95% CI, 0.20 to 0.73; p=0.003). Minnesota living with HF score, 6-minute Hall Walk score, and NYHA class score were not significantly different between the CRT-on and CRT-off groups.

Most of the results of this study concur with the earlier 12-month North American/Canadian arm of the REVERSE study [Linde C et al. *J Am Coll Cardiol* 2008], except in that analysis, the HF clinical composite response endpoint was not significantly different between patients who worsened in the CRT-on (16%) group compared with those in the CRT-off (21%) group (p=0.10). When questioned about this disparity, Dr. Daubert responded, "It was probably due to differences in study length."