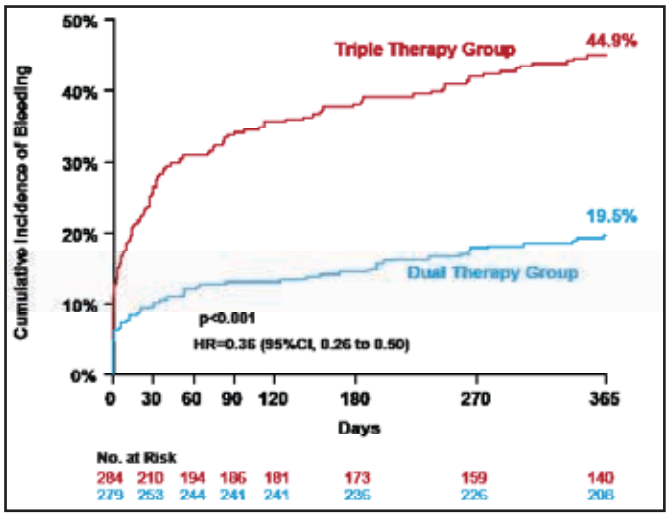
Long-term OAC therapy is necessary in most patients with atrial fibrillation (AF) or a mechanical heart valve. The addition of aspirin and clopidogrel are indicated when these patients undergo percutaneous coronary intervention (PCI), but when all 3 drugs are coadministered, the risk of major bleeding is substantially increased [Sorensen et al. *Lancet* 2009]. In this context, the What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting [WOEST; NCT00769938] trial was designed to test the hypothesis that in patients on OAC therapy undergoing PCI, the addition of clopidogrel alone is superior to the combination of aspirin and clopidogrel with respect to bleeding. The results of the trial were presented by Willem Dewilde, MD, Twee Steden Hospital, Tilburg, the Netherlands.

WOEST was an investigator-initiated, prospective, randomized study conducted in 15 Danish and Belgium hospitals between November 2008 and November 2011. Patients with a prior history of AF (69%), a mechanical heart valve (10%), or other indication for OAC (eg, thromboembolic disease or severe systolic heart failure) were openly randomized to either dual (warfarin+clopidogrel 75 mg QD; n=279) or triple (warfarin+clopidogrel 75 mg QD+aspirin 80 mg QD; n=284) therapy. Patients were treated with clopidogrel for a minimum of 1 month after placement of a bare-metal stent (~30% of patients) and 1 year after placement of a drug-eluting stent (~65%). All patients were followed for 1 year. The primary outcome was the occurrence of any bleeding event (Thrombolysis in Myocardial Infarction [TIMI] major or minor criteria), and the study was statistically powered to detect a 60% reduction in bleeding based on prior cohort data (annual expected bleeding rate on triple therapy was projected to be 12%). Secondary exploratory endpoints included ischemic events, a combination of stroke, death, myocardial infarction (MI); stent thrombosis (ST) and target vessel revascularization (TVR); and individual components of these endpoints [Dewilde W and Berg JT. *Am Heart J* 2009].

Baseline characteristics in the WOEST study revealed the mean age of patients was ~70 years, ~80% were men, ~70% had a history of hypertension, 70% had hypercholesterolemia, and 25% to 30% had a prior history of either diabetes, MI, or heart failure. Concurrent use of proton pump inhibitors was ~35%. Despite the exclusion of patients with a recent history of major bleeding, peptic ulcer disease, or other major risk factors, bleeding in this study was higher than expected (~45% of patients assigned to triple therapy experienced a bleeding endpoint within 1 year). However, patients treated with dual therapy experienced significantly less bleeding compared with triple therapy (19.5% vs 44.9%; HR, 0.36; 95% CI, 0.26 to 0.50; p<0.001; Figure 1).

Figure 1. Primary Endpoint: Total Number of Bleeding Events (TIMI Criteria).



TIMI=thrombolysis in myocardial infarction.
Reproduced with permission from W. Dewilde, MD.

Results were consistent among major subgroups, including when analyzed by a threshold age of 75 years, gender, presentation with acute coronary syndrome, indication for OAC, and stent received. The difference in bleeding between the 2 treatment groups was driven predominantly by TIMI minimal and minor bleeding from the access site, gastrointestinal, and superficial locations. There was no difference between the 2 groups in TIMI major bleeding (3.3% vs 5.8%; p=0.159) or intracranial bleeds (3 in each group).

Patients receiving dual therapy experienced significantly fewer composite ischemic events compared with those receiving triple therapy (11.3% vs 17.7%; HR, 0.60; 95% CI, 0.38 to 0.94; p=0.025). Each component of the composite ischemic endpoint was consistently less frequent among patients assigned dual therapy except for TVR.

The investigators concluded that a strategy of omitting aspirin is an option in high-risk patients on chronic anticoagulation undergoing PCI. Although it was an open-label study, this provocative trial will hopefully open the door for further investigations of the optimal long-term treatment strategy to balance ischemic and bleeding outcomes in high-risk patients.

Results from the Aldo-DHF Trial

Written by Maria Vinall

Results from the Aldosterone Receptor Blockade in Diastolic Heart Failure [Aldo-DHF; ISCRTN94726526] trial, presented by Burkert Mathias Pieske, MD,

Medical University of Graz, Graz, Austria, showed that spironolactone significantly improves diastolic function and blood pressure (BP) control, but not exercise capacity, in patients with diastolic heart failure (DHF).

DHF accounts for more than 50% of all HF cases and clinical outcomes for these patients are poor. While no established therapy exists for DHF, there is strong evidence for a benefit from aldosterone antagonists in patients with reduced left ventricular ejection fraction (LVEF) [Chatterjee S et al. *Am J Med* 2012], and aldosterone has been implicated in the pathogenesis of DHF via aldosterone receptor mediated myocardial fibrosis, hypertrophy, and vascular stiffening.

Aldo-DHF was a multicenter, randomized, placebo-controlled, double-blind, parallel-group study conducted to assess the safety and efficacy of the aldosterone receptor antagonist spironolactone on diastolic function and exercise capacity in patients with DHF after 1 year of therapy. Subjects were required to have documented stable chronic HF (NYHA II/III), echocardiographic evidence of diastolic dysfunction ≥Grade 1 or atrial fibrillation, EF ≥50%, and peak VO_2 <25 mL/kg/min. Co-primary endpoints were change in diastolic function (mitral inflow E velocity to tissue Doppler e´ [E/e´ ratio]) and maximal exercise capacity (peak VO_2 on bicycle spiroergometry) at 12 months [Edelmann F et al. *Eur J Heart Fail* 2010].

Subjects (mean age 67 years, 52% women, ≥85% NYHA class II) were randomized to spironolactone (n=213) or placebo (n=209). Baseline E/e´ was 12.7±3.6 and 12.8±4.4 and peak VO_2 was 16.3±3.6 and 16.4±3.5 mL/kg/min in the spironolactone and placebo groups, respectively. Median NT-proBNP was 179 ng/L in the spironolactone group (range, 81 to 276) and 148 ng/L (range, 80 to 276) in the placebo group. Approximately 92% of patients had controlled hypertension at study entry. Mean estimated glomerular filtration rate was ~78 mL/min/1.73 m^2.

Spironolactone (25 mg QD) significantly improved diastolic function (p<0.001) but did not improve exercise capacity. Treatment effects were consistent across all subgroups analyzed. Spironolactone induced significant structural reverse remodeling (LV mass index p=0.009) and significant reductions in NT-proBNP plasma levels (p=0.03), but did not improve NYHA class, left atrial volume index, or quality of life.

Spironolactone was also associated with significant reductions in both systolic and diastolic BP beginning at 3 months, yet the effects of spironolactone on cardiac structure and function remained significant after adjusting for BP changes. Adverse events occurred significantly more often with spironolactone, including mild worsening of renal function (36% of spironolactone subjects vs 21% of placebo subjects; p<0.001); new or worsening anemia (16% vs 9%; p=0.03), gynecomastia (4% vs <1%; p=0.02), and nonsevere (<5.0 mmol/L) increases in serum potassium levels (21% vs 11%; p=0.005). One patient in the spironolactone group died (vs none of the placebo subjects). There was no difference in the rate of hospitalization.

Additional data on the long-term efficacy and safety of spironolactone in patients with DHF will come from the Trial of Aldosterone Antagonist Therapy in Adults With Preserved Ejection Fraction Congestive Heart Failure [TOPCAT; NCT00094302] study, which is expected to report during 2013. TOPCAT is a multicenter, international, randomized, double-blind, placebo-controlled trial of spironolactone in 3515 adults with HF and LVEF ≥45%. The trial duration is ~6 years with an expected average subject follow-up of 3.45 years. The primary endpoint is a composite of cardiovascular mortality, aborted cardiac arrest, or hospitalization for the management of HF.

FAME 2 Results

Written by Lori Alexander

Percutaneous coronary intervention (PCI) guided by fractional flow reserve (FFR) plus the best available medical therapy (MT) improves outcomes in patients with stable coronary artery disease (CAD) compared with optimal MT alone. The benefit is primarily due to a lower rate of rehospitalization for urgent revascularization (UR). These findings, from the Fractional Flow Reserve-Guided Percutaneous Coronary Intervention Plus Optimal Medical Therapy versus Optimal Medical Therapy Alone in Patients with Stable Coronary Artery Disease [FAME 2; NCT01132495] trial, were reported by Bernard De Bruyne, MD, PhD, Onze-Lieve-Vrouw Clinic, Aalst, Belgium.

In prior studies, PCI has failed to to improve the prognosis for patients with stable CAD. However, Prof. De Bruyne and the FAME 2 investigators hypothesized that PCI plus MT would improve outcomes for patients with stable CAD if the presence of lesions that produced ischemia were confirmed by measurement of FFR. FFR-guided PCI was superior to angiography-guided PCI in the initial FAME trial [Tonino PA et al. *N Engl J Med* 2009]. The results of FAME 2 were simultaneously published to coincide with the presentation of the study [De Bruyne B et al. *N Engl J Med* 2012].

The researchers measured FFR in patients with stable CAD for whom PCI was being considered. Patients who had at least 1 functionally significant stenosis (FFR ≤0.80)