

number of primary events in both study groups. Basically the primary endpoint could not be more neutral than this,” commented Dr. Tardif. Heart failure hospitalizations were higher in the succinobucol group. Succinobucol also caused a significant rise in low density lipoprotein-cholesterol (LDL-C; $p < 0.0001$) and a significant decrease in high density lipoprotein-cholesterol (HDL-C; $p < 0.0001$).

In a secondary measure of combined athero-thrombotic endpoints including CV death, cardiac arrest, MI, and stroke, a significant decrease was observed with succinobucol therapy (hazard ratio=0.81; 95% CI, 0.68 to 0.98; $p=0.028$). Other secondary analyses indicated that the time to new onset of diabetes was significantly reduced in the succinobucol arm, a finding that was further supported by improvement in glycated hemoglobin A1c and glucose (all $p < 0.001$ vs placebo).

Serious adverse event rates were similar between the two groups. The most common adverse event associated with succinobucol was diarrhea (23% vs 8% for placebo). Although the study did not meet its primary endpoint, the investigators remain optimistic about the future of the drug.

Hawthorn Extract in CHF Patients: Results of a Controlled Study

Millions of patients worldwide purchase herbal supplements for their health and trust the manufacturers’ claims. This burgeoning market, however, is often unregulated and a paucity of controlled data exist that support claims of safety and effectiveness. For this reason, the results of the randomized, double-blind, placebo-controlled multicenter Survival and Prognosis: Investigation of Crataegus Extract (SPICE) trial were greatly anticipated. Crataegus extract in the form of the compound WS 1442 was studied versus placebo in patients with congestive heart failure (CHF). Crataegus extract (more commonly known as hawthorn extract) is available as an over the counter medication for the treatment of mild CHF (NYHA class 1 and class 2). Its purported mechanisms of action include vasodilation, positive inotropic effect, antioxidative properties, anti-ischemic effects, and anti-arrhythmic effects.

Dr. Christian Holubarsch, Median Kliniken Hospitals, Bad Krozingen, Germany presented the results of the study. The objectives of SPICE were to determine 1) if it was safe for patients to take WS 1442 concomitantly with existing medications and 2) what effects WS 1442 would have on measures of mortality and morbidity. The study was conducted at 156 centers in 13 European countries in patients with NYHA Class 3 CHF with a left ventricular ejection fraction of $\leq 35\%$. Patients received either WS 1442 900 mg/day or placebo and were followed for 24 months. The primary efficacy endpoint was a composite of cardiac mortality, non-fatal myocardial infarction, or hospitalization due to exacerbation of heart failure.

A total of 1,338 patients were randomly assigned to WS 1442 treatment; 1,343 received placebo. The study did not demonstrate significant differences between the two treatment groups in the composite primary endpoint. In a subanalysis, treatment with WS 1442 showed a significant effect in reduction of sudden cardiac death in patients with an LVEF $\geq 25\%$ ($p=0.025$ at 24 months). In terms of safety, adverse event rates were similar between the two groups.

In conclusion WS 1442 is safe when patients take it in addition to their regular therapies, but did not reduce the composite of cardiac mortality, MI, or hospitalization for CHF. WS 1442 may reduce sudden cardiac death in a subpopulation of patients. The investigators were congratulated for undertaking a large controlled study of an herbal treatment, as well designed clinical trials in alternative and complementary medicine are sparse.

Reconstituted HDL Infusions Look Promising

Higher levels of high density lipoprotein cholesterol (HDL-C) have been associated with a reduction in risk of cardiovascular disease, largely through its reverse transport of cholesterol, anti-inflammatory and anti-oxidative properties. CSL-111 is a reconstituted HDL that is similar to native HDL. It is isolated from human plasma, with appropriate donor screening and purification steps to minimize the risk of disease transmission. The findings from the Effect of Reconstituted High-Density Lipoprotein

on Atherosclerosis: Safety and Efficacy (ERASE) trial (Tardif et al. *JAMA*. 2007 doi:10.1001/jama.297.15.jpc70004) were presented by Jean-Claude Tardif, MD, of the Montreal Heart Institute.

Patients with recent acute coronary syndrome (ACS) were randomly assigned to either 4 weekly infusions of CSL-111 (40 mg/kg or 80 mg/kg) or volume-matched placebo. Patients were assessed via intravascular ultrasound (IVUS) and quantitative coronary angiography (QCA) at baseline and follow-up. The primary endpoint was the percentage change in atheroma volume as measured by IVUS. Secondary efficacy endpoints included nominal change in plaque volume on IVUS, change in plaque characterization on IVUS, and change in coronary score of QCA. The original statistical analysis plan was to compare the differences between all 3 treatment groups, but the safety review committee recommended stopping the 80 mg/kg arm because of observed liver function test abnormalities. The statistical plan and protocol were therefore amended to adjust the primary analysis to the change from baseline to final assessment within the active treatment group.

Twelve (12) patients were randomly assigned to the 80 mg/kg group (before the treatment group was discontinued), 60 to placebo, and 111 to CSL-111 40 mg/kg. Patients treated with CSL-111 40 mg/kg had a statistically significant reduction in the median percent and nominal changes in atheroma volume compared with baseline ($p < 0.001$), but these changes were not significant when compared to placebo. The change in plaque composition characterization and change in coronary score ($p = 0.03$) were significantly different between the treatment groups.

Thirty-three percent (33%) of the 80 mg/kg group had an ALT >10 times the upper limit of normal, compared with 0.9% in the 40 mg/kg group. Dr. Tardif noted that the liver enzyme elevations were transient, returned to normal after CSL-111 discontinuation, and there was no evidence of hepatic dysfunction/failure. The most common adverse events in the 80 mg/kg group were fatigue (25%) and diarrhea (16.7%), and the most frequent adverse events in the 40 mg/kg group were hypotension (13.8%) and fatigue (10.1%).

Dr. Tardif concluded by saying that, although the clinical significance of these findings is not fully understood, the compound demonstrated great promise in this small, proof-of-concept study.

Metabolic Syndrome Needs Intervention

Roger S. Blumenthal, MD, Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, Maryland, described the six risk conditions associated with the metabolic syndrome, and their appropriate interventions:

Risk	Interventions
Abdominal obesity	Diet and exercise
Atherogenic dyslipidemia	Statins, fibrates
Elevated blood pressure	ACE inhibitors, angiotensin receptor blockers
Insulin resistance/glucose intolerance	Lifestyle changes, thiazolidinedione, metformin
Proinflammatory state	Diet, statins
Prothrombotic state	Aspirin

Intensive lifestyle changes can reduce the progression to diabetes by nearly 60%, Dr. Blumenthal noted, largely through robust dietary interventions and a regular exercise program of 30 minutes of moderate activity per day—or “10,000 steps.” “These actions are just as important as giving aspirin or a cholesterol-lowering pill every day,” he remarked.

Gail Underbakke, MS, RD, of the University of Wisconsin, Madison, noted that diet has an effect on endothelial function. Fruits, vegetables, folic acid, and omega-3 fatty acids improve vascular function, while high-fat diets (especially saturated and trans fats) worsen postprandial vascular function. Studies with antioxidant vitamins show mixed results, she said.

In the optimal diet, calories should be appropriate for weight management. Carbohydrates should be <60% of calories (high fiber, limit concentrated sugars), fat should be 25% to 35% of calories (emphasize monounsaturated fat, omega-3 from fish and plants, and 1 ounce of nuts per day), protein should be 15% to 20% of calories (from

Continued on page 34