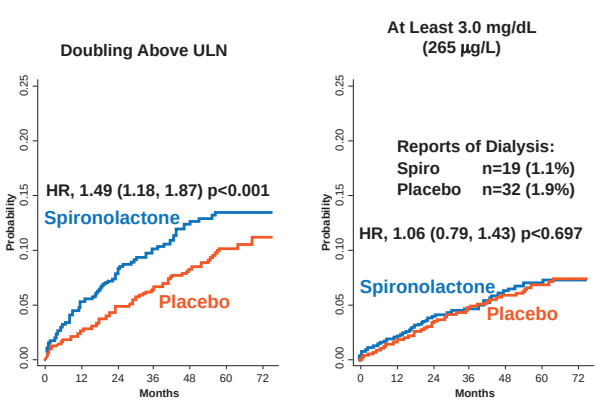
hospitalization in the past year for HF management was performed [Desai A et al. *Am Heart J* 2011]. Patients were started on spironolactone 15 mg/placebo with titration to 30 mg at 4 weeks if there were no tolerability concerns; further titration to 45 mg daily was based on investigator discretion. At 8 months, the mean spironolactone dose was 25 mg. The mean follow-up was 3.3 years. Discontinuation of the study drug increased each year, with 34.3% of spironolactone patients and 31.4% of placebo patients discontinuing by 3 years. Vital status was unknown for 67 spironolactone patients (3.9%) and 65 placebo patients (3.8%).

Within each stratum, 71.5% were hospitalized within the prior year for HF and 28.5% had elevated natriuretic peptides. Baseline characteristics included a median age of 69 years and 52% were women. The median LVEF was 56%. NYHA II was present in 63% and NYHA III in 33% patients. Pertinent baseline findings included history of MI (26%), diabetes mellitus (33%), median systolic blood pressure 130 mm Hg, and eGFR <60 mL/min/1.73 m^2 (39%).

No overall differences were found in the rate of serious adverse events (48.5% spironolactone vs 49.6% placebo). Significantly more patients in the spironolactone group had hyperkalemia (≥5.5 mmol/L; 18.7% vs 9.1%; p<0.001) but fewer had hypokalemia compared with placebo (≤3.5 mmol/L; 16.2% vs 22.9%; p<0.001). In addition, the spironolactone group had a significantly increased risk of elevated creatinine (2x upper limit of normal). However, the percentage of patients requiring dialysis or having a creatinine level of at least 3.0 mg/dL was similar between the groups (Figure 1). Dr. Pfeffer stated that the use of spironolactone in patients with HFpEF requires careful monitoring of potassium and creatinine.

Figure 1. The Effect of Spironolactone on Creatinine and Risk of Dialysis



ULN=upper limit of normal.

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The overall trial results were consistent across 21 of 22 prespecified subgroups, except in patients with elevated natriuretic peptides who demonstrated a significant reduction in the primary endpoint with spironolactone (HR, 0.65; 95% CI, 0.49 to 0.87; p=0.003). An exploratory post hoc analysis also revealed a significant geographic variation in the placebo event rates and the reduction of the primary endpoint (p=0.122). The primary outcome occurred in 31.8% of the placebo patients in the United States, Canada, Argentina, and Brazil; in these countries, spironolactone was associated with a HR of 0.82 (95% CI, 0.69 to 0.98). In Russia and the Republic of Georgia, the primary outcomes occurred in 8.4%; in these countries, spironolactone was not associated with better outcomes (HR, 1.10; 95% CI, 0.79 to 1.51). Physician judgment should guide the decision whether to use spironolactone to reduce HF hospitalization in a specific patient. However, these data do not support the broad use of spironolactone in patients with HFpEF to reduce CV events.

Adverse Effects Associated With Varespladib in the VISTA-16 Trial

Written by Muriel Cunningham

Inflammation has been implicated in atherosclerosis, and evidence suggests that some of the benefit seen with statin treatment may be related to an anti-inflammatory effect. Secretory phospholipase A_2 ($sPLA_2$) is found in atherosclerotic plaques and has been shown to participate in the inflammatory pathway. The objective of the Vascular Inflammation Suppression to Treat Acute Coronary Syndrome for 16 Weeks study [VISTA-16; Nicholls SJ et al. *JAMA* 2013] was to determine whether varespladib, a pan-$sPLA_2$ inhibitor, would have an effect on cardiovascular (CV) outcomes in patients treated for the first 16 weeks after an acute coronary syndrome (ACS).

Stephen J. Nicholls, MD, South Australian Health and Medical Research Institute, Adelaide, Australia, presented the results of the VISTA-16 trial. A total of 5145 patients with ACS were randomized in a double-blind fashion to treatment with varespladib 500 mg/day (n=2572) or placebo (n=2573) in addition to atorvastatin (at least 20 mg/day) and standard care. Eligible patients also had to have one of the following additional risk factors for cardiovascular (CV) events: diabetes, metabolic syndrome, high-density lipoprotein cholesterol <42 mg/dL, estimated glomerular filtration rate <60 mL/minute, stroke or transient ischemic attack, peripheral artery disease, myocardial infarction (MI), or coronary revascularization. Randomized patients began treatment within 96 hours of an ACS and double-blind treatment was continued for 16 weeks. The primary endpoint was the composite of CV death, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina.

Baseline clinical characteristics were well-balanced in the randomized treatment groups Table 1. The data safety monitoring board (DSMB) conducted a prespecified interim analysis on 212 primary events, 55% of the projected total. In March 2012, the DSMB recommended stopping the trial for futility and possible harm.

Table 1. Clinical Characteristics of Randomized Patients in the VISTA-16 Trial

Parameter	Placebo (n=2573)	Varespladib (n=2572)
Mean age (years)	60.7	61.0
Males	74.3%	73.1%
Caucasian	88.5%	88.4%
Mean body mass index (kg/m^3)	29.6	29.8
History of hypertension	77.8%	75.2%
History of diabetes	31.3%	31.3%
Current smoker	33.6%	33.4%
Prior myocardial infarction	29.6%	30.2%
Prior percutaneous coronary intervention	18.6%	17.7%
Prior coronary artery bypass graft	7.1%	6.3%
Prior lipid-modifying therapy	36.5%	35.8%

There were no statistically significant differences between the treatment groups.

There was no significant difference between treatment groups in the primary endpoint (HR, 1.25; 95% CI, 0.97 to 1.61; p=0.08). However, secondary efficacy endpoint analyses indicated a significantly higher risk in the composite CV death/MI/stroke endpoint for varespladib treatment compared with placebo (p=0.04). This finding was driven by the 66% increase in risk of nonfatal MI seen in varespladib-treated patients compared with placebo-treated patients (HR, 1.66; 95% CI, 1.16 to 2.39; p=0.005). The trial was designed to also assess 6-month mortality; however, the sponsor obtained 6-month mortality for only 31% of the patients (1588 out of 5145). Dr. Nicholls believes the sponsor was remiss in study follow-up activities, as the lack of 6-month survival data in the majority of patients led to difficulties in determining whether the higher rate of MI led to more deaths.

In a subgroup analysis of the primary endpoint, there was no heterogeneity in the outcomes for any specific subgroup treated with varespladib. Additional analyses found that patients randomized to varespladib that did not undergo percutaneous coronary intervention were at significantly higher risk for MI (p=0.04), with a similar trend observed in patients with non-ST segment elevation MI (p=0.06). Patients randomized to varespladib also had higher rates of discontinuation due to adverse events (n=72 vs n=36 placebo) and more cases of elevated liver enzymes (n=38 vs n=6 for placebo). This highlights the importance of performing outcome trials of novel agents, concluded Dr. Nicholls, since varespladib proved to be harmful despite promising smaller Phase 2 studies.

Endovascular Revascularization Plus Supervised Exercise May Benefit Intermittent Claudication Patients

Written by Muriel Cunningham

Peripheral artery disease (PAD) is often accompanied by intermittent claudication, which may lead to functional disability. Supervised exercise therapy (SET) is the recommended first-line therapy for intermittent claudication. The Endovascular Revascularization and Supervised Exercise for Claudication study [ERASE] sought to determine whether endovascular revascularization (EVR) with SET led to greater improvement in walking distance and claudication symptoms than SET alone.

Farzin Fakhry, MSc, Erasmus Medical Center, Rotterdam, The Netherlands, presented the results from the ERASE trial. The study, conducted at 10 sites in The Netherlands, enrolled patients with stable (>3 months) intermittent claudication, a vascular obstruction >50% at the aortoiliac and/or femoropopliteal level, a target lesion suitable for EVR, no ambulation limitations attributed to other conditions, and no prior treatment (including exercise therapy). Patients were randomized to EVR plus SET (n=106) or SET alone (n=106). EVR consisted of balloon angioplasty of aortoiliac and/or femoropopliteal lesion with selective stenting. SET sessions lasted 1 hour and were administered by trained physical therapists. Patients had SET sessions 2 to 3 times per week during the first 3 months, 1 to 2 times per week during Months 3 to 6, and once every 4 weeks for Months 6 to 12.

The primary endpoint was the maximum walking distance on the graded treadmill test (Gardner protocol, 30 minutes). Secondary endpoints included pain-free walking distance (Gardner protocol, 30 minutes), ankle brachial index (ABI) at rest and after treadmill walking, self-reported quality of life (QoL) scores (VascuQoL, Short-Form 36 Health Survey [SF-36] rating score, and EuroQoL), leg amputations, and secondary interventions.

In the EVR plus SET group, 94% of patients completed the 12-month study versus 92% in the SET group. After 12 months, the EVR plus SET group had significantly greater improvement in maximum walking distance than the SET group, with a mean difference of 282 m (99% CI, 60 to 505 m; p=0.001). Significant improvements were also noted in pain-free walking distance, resting and postexercise ABI, the disease-specific VascuQoL, and the SF-36 physical functioning measure (all p<0.01). In addition, there was a significantly lower proportion of patients requiring interventions in the EVR plus SET group (p<0.01). Fakhry concluded that the combination of EVR and SET led to