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

improved walking distance and QoL for patients with intermittent claudication compared with SET alone.

Discussant Mary McGrae McDermott, MD, Northwestern University, Chicago, Illinois, USA, pointed out several limitations of the ERASE study. The benefits seen in the EVR plus SET group were greatest early in the study, and therefore may diminish over time. Additionally, because the primary endpoint, treadmill walking, is not representative of walking in real life, the 6-minute walk test and physical activity results may be more clinically relevant if measured in an uncontrolled environment. Dr. McDermott also noted that the amount of exercise in the study was considerably less frequent than current recommendations (3 times per week); raising the hypothesis that less of a difference may have been seen with a more intensive SET program. Lastly, reimbursement and accessibility issues could potentially complicate SET implementation. Dr. McDermott encouraged researchers to devise treatments that take these obstacles into account.

EU-PACT Study: Initial Warfarin Dosing Improved by Clinical Variables and Genotype to Guide Therapy

Written by Muriel Cunningham

Response to warfarin is highly variable, making it difficult to select the optimal dose. Typical doses can range from 0.5 to 20 mg per day, and various factors, such as genetics, can influence an individual's daily dose. Cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase complex 1 (VKORC1) are two genes that can affect warfarin dosing. The purpose of the European Union Pharmacogenetics of Anticoagulant Therapy Warfarin Study [EU-PACT; Pirmohamed M et al. *N Engl J Med* 2013] was to compare whether the use of clinical variables and genotype information improves the time in therapeutic range (TTR) compared with "standard" dosing (ie, only considering age ≤75 years or not). Munir Pirmohamed, PhD, University of Liverpool, Liverpool, United Kingdom, presented the EU-PACT results.

EU-PACT was a randomized, single-blind (the patient), parallel, controlled trial conducted in the United Kingdom and Sweden. Patients with atrial fibrillation (AF) or venous thromboembolism (VTE) who were previously naïve to warfarin were enrolled and genotyped for CYP2C9 and VKORC1 using a point-of-care test that provided results in <2 hours. For the first 5 days, the experimental arm used an algorithm incorporating age (in years), height, weight, amiodarone use, and genotype data. Patients randomized to the standard-therapy arm were treated using a standard 3-day loading dose followed by adjustment on Day 4 according to clinical practice. After the first 5 days, all patients in both groups were managed according to usual clinical care. The primary outcome measure was the percentage of TTR of 2.0 to 3.0 for the international normalized ratio (INR) during the 12 weeks after warfarin therapy was started.

Of 455 patients enrolled, 227 were randomized to the genotype-guided arm and 228 to the standard dosing arm. The majority of patients (98.5%) were Caucasian, 61% were male, 72.1% had AF, and the mean age was 67.3±13.7 years. Genotype distributions were comparable between the two arms. There were no major bleeds, but three clinically serious bleeds and one thromboembolic event occurred in the control group. The occurrence of minor bleeds was comparable between the two groups (35.1% for genotype-guided and 36.9% for control). Prof. Pirmohamed noted that a limitation of the trial was that it was not powered to detect whether the dosing strategies affected clinical events.

In the primary endpoint analysis, the mean TTR in the algorithm-guided arm was 67.4% compared with 60.3% in the control group (7%; 95% CI, 3.3 to 10.6; p<0.001). The mean TTR was significantly better for the algorithm-guided arm in the first 8 weeks, but not during Weeks 9 through 12 (Table 1). The control group had higher INRs initially but this difference diminished over time. Patients in the algorithm-guided arm reached a therapeutic INR and stable dose more quickly than the control group. Algorithm-guided therapy also had fewer patients with an INR ≥4.0 (57 vs 79 in the control group; 0.63; 95% CI, 0.41 to 0.97; p=0.03) and required fewer dose adjustments (4.9 vs 5.4; 0.91; 95% CI, 0.83 to 0.99; p=0.02).

Table 1. Percentage of Time in Therapeutic Range by Treatment Month

	Genotype-Guided Therapy Arm	Standard Dosing Arm	Difference (%)	p Value
Adjusted mean percentage of time in range (95% CI):				
Weeks 1 to 4	55.72 (52.12, 59.33)	46.96 (43.36, 50.56)	8.77 (4.39, 13.14)	<0.001
Weeks 5 to 8	74.36 (69.57, 79.16)	64.19 (59.40, 68.98)	10.17 (4.36, 15.99)	<0.001
Weeks 9 to 12	75.47 (71.21, 79.72)	74.11 (69.81, 78.40)	1.36 (–3.84, 6.57)	0.607

These study results suggest that clinical variables and genetic information can be valuable in selecting initial warfarin dosing. Whether genotype information provides incremental benefit on top of clinical variables, and whether such testing is cost effective was not assessed in this study.