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.