Pharmacogenetic-Guided Dosing of Warfarin: Results of the Couma-Gen Study

More than 2 million patients in the United States take warfarin as anticoagulant therapy. The dose of warfarin may vary depending on patient genotypes, which has resulted in changes in the prescribing guidelines for this agent. The effect of pharmacogenetic (PG)-guided dosing, however, has not been established in controlled studies.

The Couma-Gen study was a prospective, randomized, double-blind trial of a PG-guided algorithm for warfarin dosing compared with standard dosing in patients starting oral anticoagulation therapy [Anderson JL, Horne BD, Stevens SM et al. *Circulation* 2007]. Jeffrey Anderson, MD, Intermountain Medical Center, Murray UT, presented the results of the study. Patients ≥18 years of age with an indication for anticoagulation therapy and a target international normalization ratio (INR) of 2-3 were eligible for participation. The trial excluded women of child-bearing potential, patients with severe comorbidity or those taking medications that could confound the measurement of the INR. The standard dosing protocol consisted of 10 mg/day for the first 2 days followed by 5 mg/day (35 mg weekly dose), and then modified as indicated from INR results. The PG-guided algorithm was derived from the patient's genotype, age, weight, and gender. Genotyping was performed using buccal swabs obtained from the patients. Results were generated in, approximately 1 hour. Patients were followed for up to 3 months and INRs were obtained on Days 0, 3, 5, 8, 21, 60, and 90 or longer, if necessary. The primary outcome measure was the percentage of INRs out of range (OOR), characterized by a value either <1.8 or >3.2.

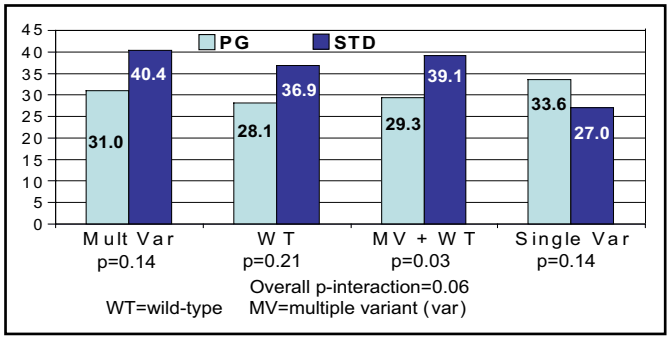
A total of 200 patients were enrolled in the study – 101 in the PG group and 99 in the standard group. The mean follow-up was 46 days, and a mean number of 7.6 INR measurements were made. The groups were well matched, although PG-guided patients were slightly older (63.2 years vs 58.9; p<0.02) and more likely to have hypertension (63.5% vs 47.5%; p<0.02). In terms of genotyping, significantly more patients in the standard group had the VKORC1 1173 CT allele (50.0% vs 35.4%; p<0.05) and any genetic variant (79.6% vs 61.0%; p<0.01). The study did not meet the primary endpoint, as the PG-guided group had 30.7% INRs OOR as compared with 33.1% INRs OOR in the standard therapy group (p=0.47). The PG algorithm, however, did result in significantly fewer INRs per patient and fewer dose changes per patient (Table 1). PG guidance appeared beneficial in wild-type patients and those with multiple variant alleles (Figure 1). "These promising subset analyses will require validation, but for the moment we must consider the clinical benefit of PG-guided warfarin dose initiation to remain unproven," said Dr. Anderson.

Table 1. Secondary Endpoints.

Endpoint	PG	STD	Rel. Risk	p
1 st ↑INR (d)	53.4	47.1	0.88 (0.6-1.3)	0.53
TTR (%)	69.7	68.6	--	0.74
Thera INR on d 5 (%)	69.7	68.3	1.07 (0.6-2.0)	0.85
Thera INR on d 8 (%)	68.8	63.0	1.29 (0.7-2.4)	0.41
#INRs /pt	7.2 (2.3)	8.1 (3.5)	--	0.06
#ΔDoses/pt	3.0 (2.0)	3.6 (2.0)	--	0.035
%INR ≥ 4/AE	34.7	42.4	0.72 (0.4-1.3)	0.26
SAE (% pt)	4.0	5.1	0.78 (0.2-3.0)	0.71

*Significant stenosis was defined as more than 50% stenosis.

Figure 1. Primary Endpoint Subset Analysis: %OOR INR by Variant Status.



In conclusion, Dr. Anderson stressed that larger trials are needed and are now being planned with a National Institutes of Health trial involving 2,000 patients to begin next year.

Outcomes in Drug-Eluting Stents Comparable to Bare Metal Stents: Results of the MASS Stent Trial

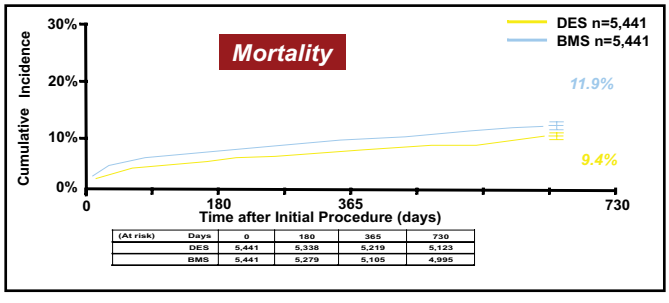
The safety of drug-eluting stents (DES) has been a matter of controversy with a recent FDA Advisory Panel meeting convened. Laura Mauri, MD, MSc, Harvard Medical School and Brigham and Women's Hospital, Boston, MA, presented the results of the Massachusetts Stent (MASS Stent) Trial sponsored by the Massachusetts Department of Public Health. This study reviewed medical records of all patients who

underwent percutaneous coronary intervention (PCI) with stents from April 1, 2003 through September 30, 2004 at non-government hospitals in Massachusetts. The time period included the introduction of DES to the market, and patients were followed for 24 months following stent placement. The goal of the study was to determine long-term patient outcomes by stent type in a population representative of current United States medical practice.

A propensity score-matched analysis was performed using a logistic regression model created from 63 variables. The primary outcome measure was the matched risk differences between the two groups in mortality, myocardial infarction (MI), and revascularization at 2 years. A total of 17,726 patients that underwent placement of a bare metal stent (BMS) or DES were identified; patients that received both stent types were excluded. Sixty-five percent (11,516) of patients received DES compared with 35% (6,210) who received BMS. Of the DES, 72% were sirolimus-eluting, and 28% were paclitaxel-eluting stents. A total of 5,441 propensity matched pairs were analyzed for each of the 2-year outcomes. The DES group was significantly better in terms of mortality, 9.4% versus 11.9% (p<0.0001).

"Previous studies had presented differences in early and late hazards of DES compared to BMS. In fact, what we saw were consistent findings across all time periods," noted Dr. Mauri (Figure 1). Sensitivity analyses were employed in the following two areas to ensure that residual confounding was not present after the propensity match. The first sensitivity analysis included DES time on the market versus BMS over time, and the second analysis looked at a time-point where there would not be an expected difference in mortality between groups (2 days). The sensitivity analyses findings were consistent with the primary endpoint analyses, indicating that the data are robust. "This [study] demonstrated no increase in rates of death or myocardial infarction associated with DES compared with BMS use at 2 years," concluded Dr. Mauri.

Figure 1. 2-Year Mortality in Matched Patients After DES and BMS Treatment.



PCI Plus Optimal Medical Therapy Offers Benefit in Moderate-to-Severe Ischemia

A substudy analysis within the COURAGE trial indicated that percutaneous coronary intervention (PCI) plus optimal medical therapy (OMT) led to significantly improved outcomes in patients with moderate-to-severe ischemia. According to lead author Leslee Shaw, PhD, Emory University School of Medicine, Atlanta, GA, the substudy results clarify the primary results of the COURAGE trial, reported earlier this year. The main trial results demonstrated that elective PCI plus OMT did not reduce death or MI compared with OMT alone for patients with stable coronary artery disease.

"These findings do not invalidate the earlier results," said Dr. Shaw. "Rather, they clarify the results and show that there is a differential benefit of PCI in a particular subgroup. The benefit was greatest in patients with more severe ischemia at baseline."

The substudy involved 314 patients from the main COURAGE population who had rest and stress myocardial perfusion SPECT (MPS) before their assigned treatment and again at 6-18 months after randomization. The primary aim of the study was to compare changes in ischemic burden (defined as a reduction of at least 5% in myocardial ischemia) after an average of 1 year following random assignment to either PCI plus OMT or OMT alone.

The burden of ischemia at baseline on MPS was similar for both groups (8.2% for PCI plus OMT vs 8.6% for OMT alone). At an average of 1 year, the percentage of patients with a significant reduction (at least 5%) in ischemia (the primary endpoint) was greater for the PCI plus OMT group (33.3% vs 19.8%; p=0.004; Figure 1A). PCI was especially beneficial for patients who had moderate-to-severe ischemia at baseline (perfusion defect ≈10% of myocardium) (78% for the PCI plus OMT group vs 52%; p=0.007; Figure 1B). The mean reduction in ischemic myocardium was also greater in the PCI plus OMT group (-2.7% vs -0.5% for OMT alone; p<0.0001).

Figure 1A and 1B. Primary Endpoint: % with Ischemia Reduction ≥5% Myocardium (N=314) and % with Ischemia Reduction ≥ 5% Myocardium.