COAG Trial: No Advantage Seen With Genetic-Based Warfarin Dosing

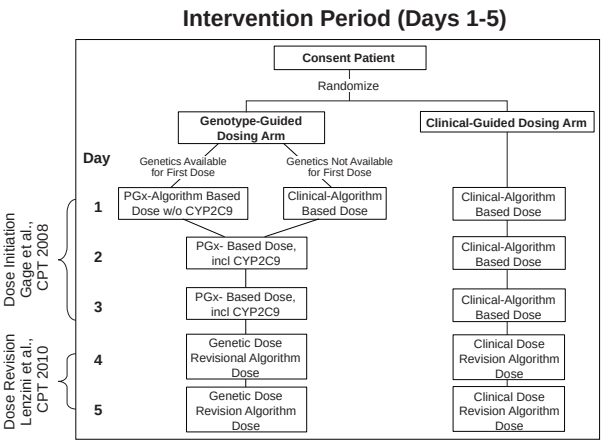
Written by Muriel Cunningham

Warfarin is a widely used medication with a very narrow therapeutic window. Limited evidence suggests that utilizing pharmacogenetic information on top of clinical information could improve warfarin dosing, but large, well-conducted studies are lacking. Stephen E. Kimmel, MD, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA, presented the key results of the Clarification of Optimal Anticoagulation Through Genetics trial [COAG; Kimmel SE et al. *N Engl J Med* 2013]. COAG was a large, randomized double-blind trial conducted at 18 centers in the United States. The study compared warfarin initiation using a clinical algorithm with or without the addition of pharmacogenetic information. The analysis was performed in all randomized patients as well as for those in whom a significant difference in the initial warfarin dose was predicted between the algorithms.

A total of 1015 patients were randomized to the clinical-guided arm (n=501) or the pharmacogenetic-guided (PG) arm (n=514). Genotype information on cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase complex 1 (VKORC1) was available for ≥99% of subjects in each arm. Participants were stratified by clinic center and self-reported race (black vs nonblack). Stratification by race was performed because of a priori knowledge that genotype-guided algorithms do not perform as well in black patients. Clinical variables used to guide warfarin initiation included age, race, body surface area, smoking status, amiodarone use, target international normalized ratio (INR), and indication for warfarin use. A dose-revision algorithm used on Days 4 and/or 5 was used for dose adjustments (Figure 1). Clinical variables in this algorithm included age, race, body surface area, diabetes, stroke, amiodarone use, fluvastatin use, target INR, natural log INR, and prior warfarin doses used. The primary endpoint was the percentage of time in the therapeutic range (TTR) during the first 28 days of warfarin treatment.

Patient demographic and clinical characteristics were similar between the two arms. Approximately two thirds were started on warfarin as an inpatient. Fifty-eight percent of patients were taking warfarin for deep vein thrombosis or pulmonary embolism only, and 22% were taking warfarin for atrial fibrillation/flutter only. Genotypes were well balanced between the groups and the prevalence was as expected.

Figure 1. Intervention Period (Days 1 to 5)



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The mean TTR for the PG arm was 45.2% (SD 26.6) compared with 45.4 (SD 25.8) in the clinical-guided arm after 4 weeks of therapy (mean difference, –0.2; 95% CI, –3.4 to 3.1; p=0.91). The coprimary analysis of the TTR was conducted in those who had a ≥1.0 mg/day difference in starting dose by the two algorithms; this analysis was consistent with the primary results. Race was a highly significant interaction: black patients in the PG group had a lower TTR than nonblacks (mean difference, –8.3; 95% CI, –15 to –2.0; p=0.01). There were no significant differences between treatment groups in any safety endpoint.

In this large randomized trial, initiating warfarin therapy by adding genotype information to a clinical-guided algorithm did not improve anticoagulation control during the first 4 weeks. The clinical-guided algorithm appeared be a more appropriate choice for black patients. Dr. Kimmel concluded that the COAG trial highlights the importance of performing randomized trials for pharmacogenetics, particularly for complex medicine regimens such as warfarin.

No Benefit to Renal Artery Stenting Seen in CORAL Trial

Written by Muriel Cunningham

Atherosclerotic renal artery stenosis (RAS) becomes more prevalent with age and is often incidentally diagnosed, but existing data is unclear as to whether revascularization of RAS prevents major adverse cardiovascular (CV) events. The objective of the Cardiovascular Outcomes in Renal Atherosclerotic Lesions study [CORAL] was to determine

whether renal artery stenting, in combination with optimal medical therapy, could reduce the incidence of major clinical events in patients with both atherosclerotic RAS and a potentially related clinical syndrome—either systolic hypertension or chronic kidney disease (CKD).

Christopher J. Cooper, MD, University of Toledo, Toledo, Ohio, USA, gave an overview of the results from the CORAL trial. CORAL was an international, open-label, randomized, multicenter, controlled clinical trial sponsored by the National Heart, Lung and Blood Institute [Cooper CJ et al. *N Engl J Med* 2013]. Patients were eligible for the study if they had atherosclerotic RAS (defined as angiographic evidence of ≥60% and <100% stenosis, renal artery duplex with systolic velocity of >300 cm/sec, or evidence of RAS on core lab approved magnetic resonance angiography/computed tomography angiography) as well as either hypertension requiring ≥2 antihypertensive medications or Stage 3 or greater CKD. All participants were provided antiplatelet therapy, candesartan plus/minus hydrochlorothiazide, and atorvastatin plus amlodipine. Participants were randomized 1:1 to medical therapy alone or in combination with renal artery stenting. The primary endpoint was a composite of CV or renal death, stroke, myocardial infarction (MI), hospitalization for heart failure, progressive renal insufficiency, or a need for permanent renal replacement therapy.

A total of 947 patients were randomized, 467 to renal stenting plus medical therapy (stent group) and 480 to medical therapy alone. In the stent group, 434 (94.6%) received a stent, and 12 patients (2.5%) in the medical therapy group crossed over to the stent group before the end of the study. The study population was evenly split between men and women, with a mean age of 69 years. The majority of patients (91%) were white, 34% had diabetes, and 13% had heart failure. In the stent group, stenosis was reduced to 16% (p<0.001) with approximately one stent per vessel. None of the participants needed dialysis within 30 days post randomization, and only one patient in the stent group (0.2%) started dialysis between 30 and 90 days after randomization. The median follow up was 43 months.

Overall there was no difference in the rate of the primary endpoint at 3 years between patients treated with stenting plus optimal medical therapy versus optimal medical therapy alone (35.1% vs 35.8%; HR, 0.94; 95% CI, 0.76 to 1.17; p=0.58). Findings were generally consistent across subgroups (Table 1) and for the individual primary endpoint elements as well as secondary endpoints. The stent group did have a significant reduction in systolic blood pressure at 3 years (~2 mm Hg; p=0.03). "Stenting, when added to medical therapy, did not reduce the rate of clinical events," summarized Dr. Cooper.

Table 1. CORAL Subgroup Analysis Results

Subgroup	Stent n (%)	Medical Therapy n (%)	Hazard Ratio (95% CI)	p Value for Interaction
Overall	161/459 (35)	169/472 (36)	0.94 (0.76, 1.17)	
Creatinine				0.09
>1.6 mg/dL	43/84 (51)	34/87 (39)	1.35 (0.86, 2.11)	
≤1.6 mg/dL	112/352 (32)	128/367 (35)	0.87 (0.67, 1.12)	
MDRD eGFR				**0.80**
≥45 mL/min/1.73 m^2	91/288 (32)	105/311 (34)	0.93 (0.70, 1.23)	
<45 mL/min/1.73 m^2	64/148 (43)	57/143 (40)	0.98 (0.68, 1.40)	
Diabetes				0.17
Yes	69/148 (47)	66/162 (41)	1.15 (0.82, 1.61)	
No	92/309 (30)	103/310 (33)	0.84 (0.64, 1.12)	
Gender				0.64
Male	75/234 (32)	78/231 (34)	0.89 (0.65, 1.22)	
Female	86/225 (38)	91/241 (38)	0.99 (0.74, 1.33)	
Global Ischemia				0.32
Yes	39/89 (44)	20/51 (39)	1.07 (0.62, 1.83)	
No	119/356 (33)	106/264 (40)	0.78 (0.60, 1.01)	
Race				0.62
African American	11/29 (38)	10/30 (33)	1.01 (0.42, 2.43)	
Other	126/356 (35)	136/357 (38)	0.88 (0.69, 1.13)	
Baseline SBP				0.55
>160 mm Hg	66/148 (45)	58/139 (42)	1.02 (0.71, 1.45)	
≤160 mm Hg	95/309 (31)	108/328 (33)	0.90 (0.68, 1.18)	
Age				0.56
>70 years	91/226 (40)	94/220 (43)	0.87 (0.65, 1.16)	
≤70 years	70/233 (30)	75/252 (30)	1.00 (0.72, 1.39)	
US Sites				0.38
Yes	137/385 (36)	146/387 (38)	0.90 (0.71 ,1.14)	
No	27/74 (32)	23/85 (27)	1.22 (0.69, 2.16)	
Site-Reported Max Stenosis				**0.66**
>80%	77/198 (39)	64/166 (39)	0.93 (0.67, 1.30)	
≤80%	77/231 (33)	79/208 (38)	0.84 (0.61, 1.14)	

eGFR=estimated glomerular filtration rate; MDRD=modification of diet in renal disease; SBP=systolic blood pressure.

Adapted from Cooper CJ et al. *N Engl J Med* 2013.

The discussant, Dr. Zeller of Universitäts-Herzzentrum Freiburg - Bad Krozingen, Bad Krozingen, Germany, noted several characteristics of the study that might limit its generalizability. First, the anatomic inclusion criteria for RAS were more consistent with moderate to severe stenosis and did not require proof that the lesion was hemodynamically significant. He showed that the degree of stenosis included in the study when reviewed by a core lab was ~67% in each group, consistent with moderate

stenosis. Secondly, he pointed out that these results should not be applied to other etiologies of RAS including arteritis or firbromuscular dysplasia. He concluded by stating that CORAL showed that renal artery stenting for moderate RAS lesions does not improve clinical outcomes but that the impact of treatment for patients with severe lesions could not be definitively concluded through the CORAL results.

Edoxaban Noninferior to Warfarin in the ENGAGE AF-TIMI 48 Trial

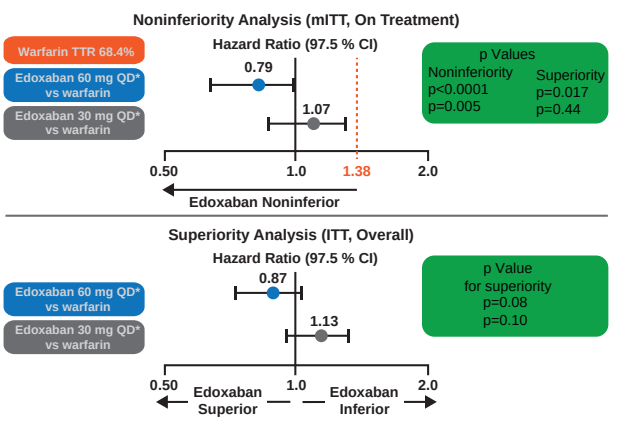
Written by **Muriel Cunningham**

Warfarin is widely used for stroke prevention in patients with atrial fibrillation (AF) but novel oral anticoagulants have been developed that may be just as effective [Dogliotti A et al. *Clin Cardiol* 2013]. Edoxaban is a direct oral factor Xa inhibitor administered once daily with a rapid onset of action. Warfarin and two doses of edoxaban were compared in the Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation – Thrombolysis in Myocardial Infarction 48 study [ENGAGE AF-TIMI 48; Giugliano RP et al. *N Engl J Med* 2013]. This trial enrolled 21,105 patients with AF at moderate to high risk of stroke ($CHADS_2$ ≥2) at 1393 centers in 46 countries. Patients were randomized in a double-blind, double-dummy manner to one of three regimens: 1) warfarin to an international normalized ratio (INR) of 2.0 to 3.0 (n=7036); 2) edoxaban 60 mg/day (high dose; n=7035); or 3) edoxaban 30 mg/day (low dose; n=7034). Edoxaban doses were decreased by 50% if patients had a creatinine clearance of 30 to 50 mL/minute, had a body weight ≤60 kg, or were taking a strong P-glycoprotein inhibitor. The primary endpoint was a composite of stroke or systemic embolic events (SEE). The primary analysis was a noninferiority comparison performed in those patients who took at least one dose of study medications (modified intention-to-treat [mITT] population) during the time that patients were treated (on-treatment time period). Secondary analyses evaluated all patients randomized during the overall treatment period (ITT).

Robert P. Giugliano, MD, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented the primary results from the ENGAGE AF-TIMI 48 trial. Demographic characteristics were well-balanced with no differences between treatment groups in any variable. The median participant age was 72 years (interquartile range, 64 to 78 years), 38% were female, and the mean $CHADS_2$ score was 2.8±1.0. In terms of medical history, 94% had hypertension, 57% had prior congestive heart failure, 36% had diabetes mellitus, and 28% had a prior stroke or transient ischemic attack. A quarter of the patients had an edoxaban dose reduction at randomization.

Over 99% of the patients completed the trial, and only one patient was lost to follow-up. Overall the median time in the therapeutic range was 68.4% (interquartile range, 56.5 to 77.4). The primary endpoint was based on a median follow-up of 2.8 years. Both doses of edoxaban met the noninferiority criteria (p<0.0001 for high-dose edoxaban and p=0.005 for low-dose ; Figure 1) in the mITT population while on treatment. Neither edoxaban regimen was statistically superior for the primary endpoint (p=0.08 for high dose and p=0.10 for low dose in the ITT analysis during the overall time period; Figure 1). Both doses of edoxaban had significant reductions in key secondary outcomes (Figure 2) and safety endpoints (Figure 3).

Figure 1. Primary Endpoint Results



Both dose regimens of edoxaban were noninferior to warfarin in the primary noninferiority analysis. The high-dose regimen tended to be more effective at reducing stroke/SEE compared with warfarin and the low-dose regimen less effective.

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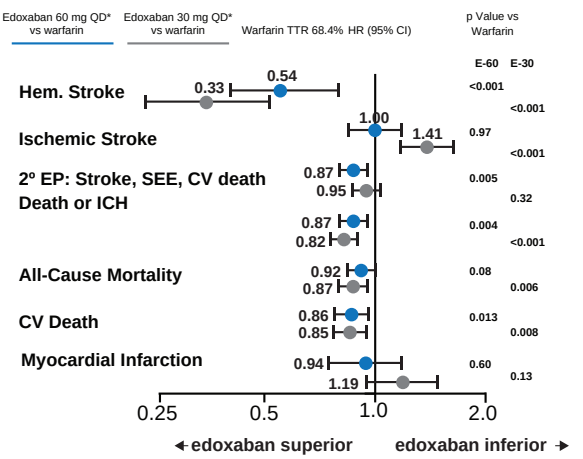
Figure 2. Secondary Endpoint Results



Both dose regimens of edoxaban reduced hemorrhagic stroke, death or ICH, and CV death compared with warfarin. The low-dose regimen was not as effective as warfarin at reducing ischemic stroke. CV=cardiovascular; E-60=edoxaban 60 mg QD dose group; E-30=edoxaban 30 mg QD dose group; ICH=intracerebral hemorrhage; SEE=systemic embolic events, TTR=time in therapeutic range.

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