

Testing Warfarin Sensitivity Cuts Hospital Stays

BY MITCHEL L. ZOLER

ATLANTA — Genotyping patients to determine warfarin sensitivity was associated with a 30% relative cut in hospitalizations during the initial 6 months after the start of warfarin therapy in a controlled study of more than 3,500 patients.

The Medco-Mayo Warfarin Effectiveness Study identified outpatients who filled first-time prescriptions for warfarin through Medco, and invited them to participate in the study and obtain free genotype testing with their physicians' approval. Three-quarters of the warfarin-prescribing physicians approached about the study agreed to receive the genotype information, and they then had the option of modifying the dosages they prescribed based on the genotype reports. There were 890 patients whose physicians received genotype reports and 2,688 in the control group, Dr. Robert S. Epstein said at the annual meeting of the American College of Cardiology.

The test included the gene for cytochrome p450 2C9, an enzyme involved in metabolizing warfarin into its active form, and the gene for VKORC1, an enzyme that produces the active form of vitamin K needed for blood clotting. These two genes together account for a third of the variance in stable warfarin dosing, said Dr. Epstein, chief medical officer of Medco Health Solutions. He estimated that running the two tests, which are approved for U.S. use, costs about \$200-\$400.

Genotyping identified 29% of patients with below-normal warfarin sensitivity, 28% with normal sensitivity, and 43% with varying levels of above-normal sensitivity, which was subdivided in the reports into mild, moderate, high, and very high levels of elevated sensitivity. The genotyping results reached physicians a median of 32 days after warfarin therapy had begun, with a range of 11-60 days.

In the 6 months after the study began, the all-cause hospitalization rate was 18.5% in the patients whose physicians received genotype reports and 25.5% in the control patients, a 28% relative reduction that was statistically significant. Hospitalizations for bleeding or thromboembolic events occurred in 6% of the genotyped patients and in slightly more than 8% of the controls, a 27% relative reduction that was statistically significant.

Warfarin genotyping was linked with a relative drop in all-cause hospitalization of 31%, and a relative drop in hospitalizations for bleeding or thromboembolism of 28%, both statistically significant effects, after the researchers controlled for baseline differences in patients' age, comorbid conditions, other drugs used, warfarin indication, prior gastrointestinal bleeding, venous thromboembolism, history of hospitalization, and propensity score.

"We can reduce hospitalization for a cost savings that is greater than the cost of testing. If testing raises attention that a patient is an outlier [who is] very sensitive or insensitive to warfarin, and brings more precision to warfarin dosing, I think it's a good thing," Dr. Epstein said.

Dr. James B. McClurken, vice chair of surgery at Temple University in Philadelphia, said he "would consider using" the genotyping test. "Warfarin is a good drug, but has a very narrow therapeutic range. Whatever tools we can use to increase its safety, the better," he commented. Dr. Christopher M. O'Connor, director of the heart center at Duke University in Durham, N.C., called the findings "an important advance." Pa-

tients in the intervention arm entered the study during July 2007–February 2009; the controls began their warfarin treatment during July 2006–June 2007. The average age of the patients was 65 years, and 61% were men. The most common reason for warfarin treatment was atrial fibrillation (41%), followed by deep vein thrombosis (25%).

An additional analysis compared the hospitalization rates in the control

group with a second control group of patients who began their warfarin therapy concurrently with the patients in the intervention arm. The researchers saw no statistically significant difference in the incidence of either outcomes in these two groups, showing that the change seen in the intervention group could not be attributed to changes in warfarin use between the two time periods studied. ■

For patients with
type 2 diabetes whose
blood glucose control
is not on track
with orals alone

“YOU MAY WANT TO
HAVE THE INSULIN
TALK SOONER”



“By the time of diagnosis, up to 50% of patients' beta-cell function may have been lost.”⁴

Poor Design Limits Conclusions

MY TAKE

The value of warfarin genotyping in the real world was not established by this study. There is some doubt that warfarin has a disease-modifying effect of equal magnitude on other primary-disease etiologies. One has to assume that we are merely seeing a Hawthorne effect on a population with much closer and better follow-up.

Even when you include propensi-

ty scoring, you can control only for the baseline variables that you can see. The dynamic variables that occur by following patients with warfarin titration are not accounted for by the propensity score analysis. Also, there is considerable doubt as to whether control patients were equally managed post intervention, and there were no data on the international normalized ratio achieved.

My conclusion is that the outcome was more likely the result of closer attention and better follow-up. The trial design was not adequate to answer the question that was posed.

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Clopidogrel Plus Aspirin Cost Effective

BY BRUCE JANCIN

ATLANTA — Adding clopidogrel to aspirin for stroke prevention in warfarin-unsuitable patients with atrial fibrillation is cost neutral, according to a new secondary economic analysis of the ACTIVE-A trial.

What this means is that the substantial cost of adding brand-name clopidogrel (Plavix) to aspirin therapy is canceled out by the resultant considerable savings resulting from fewer strokes, even after taking into account the costs related to clopidogrel-associated bleeding complications, Dr. Andre Lamy said at the annual meeting of the American College of Cardiology.

The good news for health plans is that clopidogrel will go generic in just a few months in the United States and most of the rest of the world. At that point, using clopidogrel plus aspirin instead of aspirin alone to protect against strokes in patients with atrial fibrillation who can't take warfarin will no longer be cost neutral, it will actually become cost saving, according to Dr. Lamy, a surgeon and clinical epidemiologist at McMaster University in Hamilton, Ont.

"It's very unusual to see that with a drug. Health care systems will get good value for the investment. The strokes are quite expensive," he observed in an interview.

ACTIVE-A (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events—Aspirin) was a randomized trial involving 7,554 patients with atrial fibrillation in 33 countries who were deemed unsuitable for warfarin. The primary outcomes have previously been published: a 28% reduction in the risk of stroke with dual preventive therapy compared to aspirin alone during a median 3.6 years of follow-up, which came at the expense of a 57% increase in risk of major hemorrhage (*N. Engl. J. Med.* 2009;360:2066-78).

For every 1,000 patients treated with clopidogrel and aspirin for 3 years, there were 28 fewer strokes than with aspirin alone, including 17 fewer disabling or fatal ones, 6 fewer MIs, and 20 additional major bleeding episodes, 3 of which were fatal.

Dr. Lamy and coinvestigators calculated the direct medical costs associated with these outcomes using Canadian cost rates, which are similar to Medicare costs. They determined that although dual therapy cost an average of \$2,114 Canadian more, this was counterbalanced by the savings achieved through strokes avoided, even after subtracting the costs associated with the major bleeding incidents. ■

Disclosures: Dr. Lamy said that this economic analysis as well as the ACTIVE-A trial were funded by grants from Sanofi-Aventis and Bristol-Myers Squibb.

It's never too early to have the "insulin talk"

Some conversations may be hard to initiate. Take the "insulin talk," for example. According to the American Diabetes Association, insulin is the most effective agent for lowering blood glucose.¹ It works as part of an overall diabetes treatment plan, which may include diet, exercise, and other diabetes medication. Having the "insulin talk" early may help patients accept insulin as a potential treatment option to help them achieve their A1C goals.²

The results of having a positive "insulin talk" can be impactful: in a survey, about 80% of patients with type 2 diabetes on OADs said they'd consider taking insulin if their doctor recommended it.³ So by starting the dialogue now, you can help your patients have a better understanding of insulin as an effective treatment option for lowering blood glucose.

Insulin—a chance for successful glycemic control, not a punishment for failure

Patients may focus on blaming themselves for their uncontrolled blood glucose, but you can help them focus on turning this negative mindset into positive action for managing their disease.² The United Kingdom Prospective Diabetes Study showed that by the time patients with type 2 diabetes are diagnosed, they may already have lost up to 50% of their beta-cell function, and this function may continue to decline.⁴

Because the disease is progressive, many patients with type 2 diabetes may eventually need insulin to achieve or maintain glycemic control.^{2,5} But by the time patients with type 2 diabetes are prescribed insulin, they may have had diabetes for 10 to 15 years and may already have complications due to a prolonged period of uncontrolled blood glucose.⁶ Starting insulin earlier in the disease continuum for appropriate patients can help improve glycemic control. Controlling blood glucose can reduce the risk of diabetes-related complications.^{5,6}

Treatment plans and glycemic targets should be individualized for each patient.

Insulin is indicated to help improve glycemic control in patients with diabetes mellitus.

Important Safety Information About Insulin

Possible side effects may include blood glucose levels that are too low, injection site reactions, and allergic reactions, including itching and rash. Other medications and supplements could change the way insulin works. Glucose monitoring is recommended for patients with diabetes.

THE "INSULIN TALK"

Have the talk early and as needed, to help destigmatize insulin²

- Reassure patients that using insulin doesn't mean failure and that insulin may help replace what the body is no longer adequately making
- Turn the negative mindset of failure into a positive opportunity to take personal control of A1C

Put insulin therapy in context

- Explain the benefits of maintaining blood glucose goals and the risks associated with insulin therapy
- Talk about how insulin may be worth the effort—insulin is an effective treatment option that works as part of an overall treatment plan to lower blood glucose

Identify patients' personal obstacles and help defuse the "scary" factor²

- Today's insulin injections generally cause little discomfort and are administered using small, thin needles^{2,6}
- Insulin pens make insulin more convenient to administer and are discreet²
- Insulin dose may need to be adjusted up or down over the course of treatment depending on how a patient's body responds⁵

INSULIN

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