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." Patients 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. ■

MY TAKE

Poor Design Limits Conclusions

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 propensity 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.*