Rebound Effect Evident After Halting Clopidogrel

BY MARY ANN MOON
Contributing Writer

The risk of myocardial infarction or death spikes during the 90 days after clopidogrel therapy is discontinued among patients treated for acute coronary syndromes, especially those treated medically.

Clustering of adverse coronary events has been reported after cessation of long-term aspirin and heparin therapy in acute coronary syndrome (ACS) patients. Dr. P. Michael Ho of the Denver Veterans Administration Medical Center and his associates assessed whether clopidogrel withdrawal was associated with a similar "rebound" effect.

The investigators analyzed data on all patients with acute MI or unstable angina who were discharged from any of 127 VA medical centers throughout the country between 2003 and 2005 with prescriptions for clopidogrel. A total of 1,568 of these patients who had been treated medically and 1,569 who had undergone PCI took the drug for a mean of 302 and 203 days, respectively, then discontinued the treatment.

In the medically treated patients, the combined end point of all-cause mortality or ACS occurred in 268 patients (17%) after they stopped taking clopidogrel. Significantly more (163) of those events occurred within 90 days of clopidogrel discontinuation than occurred at 91-180 days (57) or 181-270 days (26).

In PCI-treated patients, who took clopidogrel for an average of 278 days after their procedure, death or ACS occurred in 124 (8%) after discontinuation. As with the medically treated patients, significantly more of the primary end point events occurred within 90 days of cessation (73), compared with days 91-180 (29) and days 181-270 (8). Of the PCI-treated patients, almost two-thirds received bare metal stents, while the rest got drug-eluting stents.

"We found a clustering of death or acute MI in the initial 90-day period after stopping treatment with clopidogrel, compared with later follow-up intervals. These findings were consistent among patient subgroups including those who took shorter vs. longer durations of clopidogrel therapy, among patients with and without diabetes, as well as among PCI-treated ACS patients," the researchers said.

The rate of adverse events was nearly twice as high immediately after stopping clopidogrel than it was during later periods. The rate was higher by far in the medically treated patients within 90 days of drug cessation, at 1.31 per 1,000 patient-days, than in those patients during days 91-180 (0.69) or in the PCI group during the same period (0.57).

The findings support the hypothesis that there is a rebound hyperthrombotic period after stopping clopidogrel therapy. Additional studies are needed to confirm the findings and to identify the underlying mechanism so that strategies to prevent or attenuate this effect can be devised, they added (JAMA 2008;299:532-9).

Extended clopidogrel therapy might avoid the rebound effect, or other approaches—tapering clopidogrel, "bridging" the cessation of clopidogrel with another antithrombotic drug, or using alternative antiplatelet agents instead of clopidogrel—might attenuate it, they said.

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Idraparinux Causes More Bleeding Than Vitamin K Antagonists

BY MIRIAM E. TUCKER
Senior Writer

Long-term treatment with idraparinux is as effective as vitamin K antagonists for preventing thromboembolism in patients with atrial fibrillation, but it causes significantly more bleeding.

Those results, from the Sanofi Aventis–funded multinational open-label AMADEUS trial, mark the third recent failure to find an acceptable fixed-dose alternative to adjusted-dose vitamin K antagonists for stroke prevention in patients with atrial fibrillation. The study was stopped early after randomization of 4,576 patients because of excess clinically relevant bleeding with the investigational factor X inhibitor idraparinux, compared with vitamin K antagonists (Lancet 2008;371:315-21).

At the time that AMADEUS was halted (mean follow-up of 10.7 months), 2,283 patients had been randomized to subcutaneous idraparinux 2.5 mg/wk and 2,293 to oral adjusted-dose vitamin K antagonists (warfarin or acenocoumarol, target international normalized ratio of 2.0-3.0). All had nonvalvular atrial fibrillation and at least one indication for long-term anticoagulation. They had a mean age of 70 years; almost two-thirds were men.

In the vitamin K antagonist group, the INR was within target range 63% of the time, below target 18% of the time, and higher for 19%. More patients discontinued in the idraparinux group (13% vs. 10%), mainly because of adverse events, Dr. Harry R. Buller of the department of vascular medicine, Academic Medical Centre, Amsterdam, and associates.

Idraparinux was noninferior to vitamin K antagonists in the prevention of all stroke or non-CNS systemic embolism—the primary efficacy outcome—in both the intent-to-treat analysis (0.9 vs. 1.3 per 100 patient-years) and

in the per-protocol analysis (0.9 vs. 1.2). However, the idraparinux group had overall excesses of clinically relevant bleeding (19.7 vs. 11.3 per 100 patient-years), nonmajor but clinically relevant bleeding (16.4 vs. 10.3), and intracranial hemorrhage (1.1 vs. 0.4). The differences in bleeding incidence became apparent after about 2 months of treatment.

Hemorrhagic stroke occurred in similar numbers in each group. Despite a higher rate

Bleeding was more than double in those taking warfarin or those taking clopidogrel or ticlopidine.

DR. BULLER

of fatal bleeding with idraparinux (0.7 vs. less than 0.1 per 100 patient-years), overall mortality did not differ significantly between the groups (3.2% vs. 2.9%).

Elderly patients and those with renal insufficiency were at significantly increased risk of clinically relevant bleeding with idraparinux, compared with vitamin K antagonists. And irrespective of treatment allocation, clinically relevant bleeding was more than double in the 971 patients who took aspirin with the anticoagulant and in the 126 who took clopidogrel or ticlopidine than it was in those not taking concurrent platelet inhibitor medication. "This combination should be avoided [when] possible," the authors said.

Adjusted-dose anticoagulation with vitamin K antagonists lowers the risk of stroke in high-risk patients by about two-thirds, but the complexity of the dose-adjustment regimen makes it difficult to carry out in clinical practice.

But Dr. Alan S. Go of Kaiser Permanente of Northern California, Oakland, and Dr. Daniel E. Singer of Massachusetts General Hospital, Boston, are optimistic an alternative will be found. "On the basis of positive features of recent trial experiences, one or more approaches . . . will emerge as an alternative to vitamin K antagonists," they wrote in an accompanying comment. But, "We still need dedicated innovative efforts to improve the delivery of vitamin K antagonists for the growing population with atrial fibrillation." ■

Warfarin May Do Harm Unless Target Is Met and Maintained

BY MITCHEL L. ZOLER
Philadelphia Bureau

ORLANDO — Patients with atrial fibrillation who are treated with warfarin must be in their target anticoagulation range at least 50% of the time to get a net benefit from treatment.

The longer a patient stays in the target anticoagulation range the better, but when target anticoagulation is reached less than half the time, a patient gets no net benefit from treatment and actually fares worse than getting no treatment at all, Dr. Alan S. Go said at the annual scientific sessions of the American Heart Association.

The standard, target anticoagulant range for patients with atrial fibrillation treated with warfarin is an international normalized ratio (INR) of 2.0-3.0. The results from Dr. Go's analysis confirmed this range yields the best outcomes. Additional results showed the range to be ideal for all patients, even those at age 80 years or older.

A warfarin regimen that keeps a patient in the INR target range less than half the time may harm patients by causing an excess of thromboembolic events or intracranial hemorrhages, said Dr. Go, assistant director for clinical research at Kaiser Permanente of Northern California in Oakland.

If patients on warfarin have trouble staying at an INR of 2.0-3.0, the problem may be caused by diet, alcohol use, use of other medications that interact with warfarin, or noncompliance, he said in an interview. If a patient can't stay in the target range most of the time, one might need to reconsider whether the patient should remain on the drug because it may be causing more harm than good.

Keeping patients in their target anticoagulation range more than half the time seems to depend on managing pa-

tients in an anticoagulation service. Kaiser Permanente of Northern California operates 21 anticoagulation clinics even though the service loses money, at least in terms of its direct costs.

In the 13,559 patients with atrial fibrillation who were on warfarin in Kaiser during July 1996–September 2003, 58% were kept at their target INR range 60% or more of the time; 75% were kept in their target range at least 50% of the time. During a median follow-up of 6 years, the entire group of atrial fibrillation patients on warfarin had 1,041 thromboembolic events and 279 intracranial hemorrhages.

When the target INR was reached 50% of the time or less, patients had an excess incidence of thromboembolic events and intracranial hemorrhages. When it was maintained 50% of the time, the rate was neutral, and in patients who maintained the target INR more than half the time, there was a direct relationship between the time spent in the target range and a reduced rate of adverse events. Patients maintained at their target INR at least 70% of the time had the lowest rate of adverse events.

Additional analyses showed that all of the Kaiser atrial fibrillation patients were kept in their target INR range for an average of about 65% of the time regardless of their age, including patients younger than 60 years, and patients age 80 years or older. And keeping patients at an INR of 2.0-3.0 led to lower rates of thromboembolic events and intracranial hemorrhages, regardless of age. In fact, because the rate of adverse events in patients who were not treated with warfarin was highest in patients aged 80 years or older, the net clinical benefit from warfarin treatment maintained in the optimal INR range was greatest in patients aged 80 or older, Dr. Go said. ■