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Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents

A science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians*

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Editor's note: The following text represents excerpts of the complete text of the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association science advisory that are pertinent to dentistry. The complete text was published in the Feb. 13 issue of Circulation. The American Dental Association Council on Scientific Affairs has approved this document as it relates to dentistry.

*** Representation does not imply endorsement by the American College of Physicians.**

ABSTRACT

Background and Overview. Dual antiplatelet therapy with aspirin and a thienopyridine has been shown to reduce cardiac events after coronary stenting. However, many patients and health care providers prematurely discontinue dual antiplatelet therapy, which greatly increases the risk of stent thrombosis, myocardial infarction and death.

Conclusions and Clinical Implications. This advisory stresses the importance of 12 months of dual antiplatelet therapy after placement of a drug-eluting stent and educating patients and health care providers about hazards of premature discontinuation. It also recommends postponing elective surgery for one year, and if surgery cannot be deferred, considering the continuation of aspirin during the perioperative period in high-risk patients with drug-eluting stents.

Key Words. American Heart Association scientific statements; anticoagulation therapy; dental care; thrombosis; myocardial infarction; stents; myocardial stunning.
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After placement of a bare-metal stent, thienopyridines (clopidogrel [Plavix, sanofi-aventis, Bridgewater, N.J.] or ticlopidine [Ticlid, Hoffmann-LaRoche, Nutley, N.J.]), in combination with aspirin therapy, have been shown to dramatically reduce the incidence of early major adverse cardiac events after stent placement compared with aspirin alone or in combination with warfarin.[1] In addition, the use of thienopyridine therapy plus aspirin for up to one year after

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acute coronary syndromes is known to decrease the incidence of ischemic cardiovascular events and is recommended in the American College of Cardiology/American Heart Association practice guidelines for the treatment of patients undergoing percutaneous coronary intervention and for the medical treatment of patients with non–ST-segment–elevation acute coronary syndromes.[2-4] Despite these benefits, antiplatelet therapy is sometimes prematurely discontinued within the first year after stent implantation, either by the patient or by a health care provider who may not realize these benefits or the potentially severe consequences of antiplatelet therapy cessation. The leading adverse event associated with early antiplatelet discontinuation is stent thrombosis, and the majority of these events lead to acute myocardial infarction (MI) or death. Therefore, the American Heart Association, working with the American College of Cardiology, the Society for Cardiovascular Angiography and Interventions, the American College of Physicians, the American College of Surgeons, and the American Dental Association, commissioned this advisory to emphasize the potential complications of premature discontinuation of thienopyridine therapy and to address potential strategies to minimize this occurrence.

DUAL ANTIPLATELET THERAPY FOR PREVENTION OF ISCHEMIC CARDIOVASCULAR EVENTS AND STENT THROMBOSIS

Stent thrombosis most commonly occurs in the first month after stent implantation, and in this interval, it is referred to as "subacute stent thrombosis." However, numerous cases of "late" stent thrombosis, particularly in patients who have been treated with drug-eluting stents (DES), have been described as occurring months or even years after stent implantation.[5-17] In the majority of cases, stent thrombosis is a catastrophic event, resulting in life-threatening complications.

In the current era of dual antiplatelet therapy, the average reported occurrence of subacute stent thrombosis is 1 percent.[12-18] The timing of thrombosis appears to be delayed in DES. Late (one to 12 months) stent thrombosis was not readily apparent with bare-metal stents, yet was reported to occur in 0.19 percent of patients in a large DES registry.[14]

On Dec. 7 and 8, 2006, the U.S. Food and Drug Administration convened an advisory panel meeting to discuss stent thrombosis and the overall safety of DES.[19] The advisory panel concurred with the joint clinical practice guideline recommendation[3] for 12 months of dual antiplatelet therapy after placement of a DES in patients who are not at high risk of bleeding.

PREMATURE THIENOPYRIDINE DISCONTINUATION AND STENT THROMBOSIS

The premature discontinuation of thienopyridine therapy is associated with a marked increase in the risk of stent thrombosis and is the leading independent predictor for stent thrombosis in multivariate analyses. Although the number of actual stent thromboses reported in individual studies is modest, the findings are noteworthy.

In a large observational cohort study of patients treated with DES, stent thrombosis occurred in a striking 29 percent of patients in whom antiplatelet therapy was discontinued prematurely.[5]

In a single-site study of 652 patients treated with sirolimus DES, premature discontinuation of clopidogrel was associated with an approximately 30-fold greater risk of stent thrombosis, with greater than 25 percent of patients who discontinued clopidogrel therapy within the first month suffering stent thrombosis.[13]

Spertus and colleagues[15] published an analysis from the PREMIER (Prospective Registry Evaluating Myocardial Infarction: Events and Recovery) registry of 500 patients with acute MI treated with DES. The mortality rate over the next 11 months of those who stopped thienopyridine therapy was 7.5 percent compared with 0.7 percent in those who had not stopped therapy (hazard ratio 9.0, $P < .0001$).

STENT THROMBOSIS AFTER NONCARDIAC SURGERY

Several reports have specifically described incidents of stent thrombosis that occurred after the discontinuation of antiplatelet therapy for noncardiac surgery among patients recently treated with coronary stents.[20-22] Kaluza and colleagues[21] reported on 40 patients treated with bare-metal stents who underwent noncardiac surgery within six weeks of stent implantation. Seven patients

ABBREVIATION KEY. DES: Drug-eluting stent. **MI:** Myocardial infarction.

had an MI, of which six were fatal. In five of seven cases, thienopyridine therapy (ticlopidine) had been withheld before surgery. In a similar analysis of 47 patients who underwent noncardiac surgery within 90 days of bare-metal stent implantation, six of the seven patients in whom thienopyridine therapy was discontinued died "in a manner suggestive of stent thrombosis."[22]

FACTORS RELATED TO PREMATURE CESSATION OF THIENOPYRIDINE THERAPY

Dual antiplatelet therapy is not without risk. Like all antithrombotic agents, both aspirin and clopidogrel increase the risk of bleeding compared with placebo. When compared with aspirin, clopidogrel may be associated with lower risk of gastrointestinal bleeding.[23] However, when clopidogrel was combined with aspirin and administered for prolonged duration, randomized trials demonstrated an absolute increase in major bleeding, compared with aspirin alone.[23]

Antiplatelet therapy may be stopped at the instruction of physicians, dentists, and other health care providers who are to perform an invasive or surgical procedure on the patient because of misguided concerns about excessive procedure-related bleeding. Unfortunately, many patients are routinely instructed to stop "blood thinners" before such procedures without a thorough evaluation of the rationale for such therapy and without distinction between warfarin and antiplatelet agents. Many of these procedures (for example, minor surgery, teeth cleaning, and tooth extraction) can likely be performed at no or only minor risk of bleeding or could be delayed until the prescribed antiplatelet regimen is completed. Although there is a longstanding concern on the part of dental practitioners about the possibility of prolonged bleeding during and after invasive dental procedures on patients receiving antiplatelet drugs, a recent prospective study of single-tooth extractions on patients randomized to aspirin versus a placebo failed to show a statistically significant difference in postoperative bleeding.[24] Although there are no prospective studies of invasive dental procedures on patients taking a thienopyridine alone or in combination with aspirin, there are also no well-documented cases of clinically significant bleeding after dental procedures, including multiple dental extractions. Given the relative ease with which the incidence and severity of oral bleeding can be reduced with local measures during surgery (for example, absorbable gelatin sponge and sutures) and the unlikely occurrence of bleeding once an initial clot has formed, there is little or no indication to interrupt antiplatelet drugs for dental procedures.[25]

The likelihood of increased bleeding and/or an increased requirement for blood transfusion in patients undergoing major noncardiac surgery can be inferred from reports of increased bleeding when cardiac surgery is undertaken in patients taking a thienopyridine drug. Independent documentation of the scope of this risk of increased bleeding during noncardiac surgery, however, is not available. If one must discontinue the thienopyridine drug before major surgery to reduce the risk of excessive bleeding, consideration should be given to continuing aspirin for its antiplatelet action to mitigate the risk of late stent thrombosis and to restarting the thienopyridine as soon as possible.

SUMMARY AND RECOMMENDATIONS

Thienopyridine therapy in combination with aspirin has become the mainstay antiplatelet treatment strategy for the prevention of stent thrombosis. Premature discontinuation of antiplatelet therapy markedly increases the risk of stent thrombosis, a catastrophic event that frequently leads to MI and/or death. Factors contributing to premature cessation of thienopyridine therapy include drug cost, physician/dentist instructions to patients to discontinue therapy before procedures, and inadequate patient education and understanding about the importance of continuing therapy.

To eliminate premature discontinuation of thienopyridine therapy, this advisory group gives the following recommendations:

1. Health care providers who perform invasive or surgical procedures and are concerned about periprocedural and postprocedural bleeding must be made aware of the potentially catastrophic risks of premature discontinuation of thienopyridine therapy. Such professionals who perform these procedures should contact the patient's cardiologist if issues regarding the patient's antiplatelet therapy are unclear, to discuss optimal patient management strategy.

2. Elective procedures for which there is significant risk of perioperative or postoperative bleeding should be deferred until patients have completed an appropriate course of thienopyridine therapy (12 months after DES implantation

if they are not at high risk of bleeding and a minimum of one month for bare-metal stent implantation).

3. For patients treated with DES who are to undergo subsequent procedures that mandate discontinuation of thienopyridine therapy, aspirin should be continued if at all possible and the thienopyridine restarted as soon as possible after the procedure because of concerns about late-stent thrombosis. ■

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