Triple Antithrombotic Therapy After Coronary Stenting
Why Expert Opinion Is Necessary

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Dual antiplatelet therapy has become the cornerstone of the treatment of patients undergoing coronary stenting and of those with acute coronary syndromes with or without stent implantation. Although there is consensus about the indication for dual antiplatelet therapy, there is little evidence about the optimal duration of therapy. In patients surviving non–ST-segment elevation–acute coronary syndromes, 1 year of treatment is advised. Intuitively, cardiologists prefer longer dual antiplatelet therapy rather than single antiplatelet medication (aspirin alone) in patients with drug-eluting stents when compared with carriers of bare metal stents. Consequently, many patients in the cardiology practice in 2011 are on dual antiplatelet therapy, mainly aspirin and clopidogrel. The only important side effect of dual antiplatelet therapy is increased bleeding in comparison to aspirin alone. This has been established in the large trials with clopidogrel in acute coronary syndromes as well as in atrial fibrillation. Especially in the latter, dual antiplatelet therapy has been shown to be as hazardous as oral anticoagulation. Special attention of the risks of dual antiplatelet therapy has been given to patients awaiting coronary artery bypass surgery. Clopidogrel on top of aspirin has been associated with significantly increased blood loss during coronary surgery when compared with aspirin alone. However, this excess bleeding was not significantly associated with an increased risk of reoperation or mortality. Yet, it is generally advised to discontinue clopidogrel 5 days ahead of coronary surgery. Little is known, however, about the optimal strategy in patients on dual antiplatelet therapy undergoing other forms of surgery such as abdominal surgery, orthopedic procedures, neurosurgical operations, or procedures in other vital organs in which bleeding can result in organ loss. Yet, the most vexing problem in this field is the use of dual antiplatelet therapy in patients on oral anticoagulation, usually for long-term stroke prevention in atrial fibrillation. Bleeding is considered the most important side effect and has been shown to be increased, with 43% in the RE-LY trial to 80% in a large Danish registry, when aspirin is combined with warfarin for atrial fibrillation. For dual antiplatelet therapy, the increase is 370%.

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In this issue of Circulation: Cardiovascular Interventions, an expert perspective on this problematic field of interventional cardiology is published. It is written from a North American viewpoint and includes all aspects that must be taken into account in this clinical setting: stroke risk and risk of stent thrombosis on one side, and bleeding on the other. Besides that, the type of stent used and, most importantly, the duration of the various forms of therapy, play a role: anticoagulants in the first place (classic and new) and the antiplatelet agents (classic and novel). Duration of therapy is of explicit importance because discontinuation of antiplatelet therapy in patients awaiting surgical procedures is associated with increased risk of myocardial infarction, stent thrombosis, stroke, and death. Discontinuation of warfarin also may lead to catastrophic thrombotic events including death.

Last year, the European Society of Cardiology’s Working Group on Thrombosis published a position paper on the same topic of triple therapy that shows great similarity to the current North American view: intensity of anticoagulation (INR only between 2.0 and 2.5) and the total avoidance of drug-eluting stents in high bleeding risk.

Differences With the European View on Triple Therapy

The strengths of the European position paper is that a clear and clinically easy differentiation is made between elective stent implantation and procedures in the setting of acute coronary syndromes with and without ST elevation. The American perspective does not address a distinction between elective stenting and acute coronary syndrome procedures and speaks only about “high” and “low” thrombotic risk. Whether this is risk of stent thrombosis, stroke risk, or both is not explained. In acute coronary syndromes, the thrombus load, and thus the thrombotic risk, is larger than in stable coronary disease. This is probably true for both the risk of stent thrombosis as well as the risk of stroke. These differences urge for a more potent approach in the acute setting of acute coronary syndromes, but not necessarily in the long term.

Another important difference is the duration of antiplatelet therapy after stent implantation in the setting of atrial fibrillation. In Europe, a short run of dual antiplatelet therapy (1 month) in elective stenting with a bare metal stent is advised in patients on oral anticoagulants, whereas the American view suggests 1 month of dual antiplatelet therapy followed by single antiplatelet therapy (aspirin or clopidogrel) for 12 months. In a high thrombotic-risk situation, American experts advise dual antiplatelet therapy for a full year after drug-eluting stent implantation on oral anticoagulation, whereas...
the Europeans do so for 3 months for the modern limus stents and 6 months for the paclitaxel stents.

**Future Perspectives**

Unfortunately, randomized, controlled trials on the optimal antithrombotic protection are lacking. Currently, 3 randomized trials are running on the risks and benefits of triple antithrombotic therapy (aspirin, clopidogrel, and warfarin) versus “safer” antithrombotic therapy in anticoagulated patients after coronary stent implantation. One of these studies is initiated from the Netherlands (WOEST), in Germany (ISAR-TRIPLE), and in Spain (MUSICA-2). The outcomes of these trials will guide the treatment of this difficult group of patients. Especially, the absence of aspirin in 1 arm of WOEST is provocative, as well as the short 6-week run of clopidogrel in 1 arm of ISAR-TRIPLE and the interruption of warfarin in MUSICA-2.

**The New Agents**

The novel antiplatelet drugs prasugrel and ticagrelor are more effective than clopidogrel in patients with a high thrombotic risk such as acute coronary syndromes in preventing recurrent ischemic events, but in the setting coronary stenting are certainly not associated with less bleeding. Thus, the views on both sides of the ocean on the warfarin issue will not be influenced by the use of these agents. On the contrary, the duration (and/or dosing) of antiplatelet therapy may be lowered to minimize the extra bleeding hazard.

Different thoughts can be given to the novel anticoagulants. They look certainly safer than warfarin, especially with respect to intracranial hemorrhage. This opens new opportunities for patients with a high bleeding risk such as those on triple therapy after stenting. The only data so far, albeit post hoc and not randomized, comes from the RE-LY trial with dabigatran. Antiplatelet therapy increased bleeding by 60%, irrespective of the anticoagulant used (warfarin, dabigatran 110 mg twice daily, or dabigatran 150 mg twice daily). The reduced risk of bleeding of dabigatran was maintained in the presence of concomitant antiplatelet therapy. The lowest rate of intracranial hemorrhage in combination with antplatelet drugs was seen with the lower dose of dabigatran, even lower than with warfarin alone in the absence of antiplatelet agents. Whether low-dose dabigatran is the preferred anticoagulant when antiplatelet therapy must be combined with antiplatelet drugs should be tested in a new randomized, controlled trial against warfarin in aspirin (plus clopidogrel)-treated patients exclusively. It is unlikely that such a trial would ever be done.

**Long-Term Antiplatelet Therapy**

In each patient on warfarin, the indication for dual antiplatelet therapy should be judged at the moment of decision for stent implantation.

Because in general, the optimal duration of dual antiplatelet therapy in patients who have undergone stent implantation is not fully established, the decision to continue or discontinue double antplatelet therapy after stent implantation is and will be difficult. The only larger study available in this area is ZEST/REAL-LATE, in which patients stable 1 year after drug-eluting stent implantation were randomly assigned to continuation of clopidogrel plus aspirin or to aspirin alone. Nineteen months after discontinuation of clopidogrel, there was significantly more myocardial infarction, stroke, and death in the patients who had continued their clopidogrel treatment compared with those who stopped clopidogrel at random assignment 1 year after implantation. Currently, 2 megatrials are evaluating the optimal duration of dual antiplatelet therapy in stented patients. One is comparing 12 versus 30 months of dual antiplatelet therapy in 20,000 patients with bare metal or drug-eluting stents, using stent thrombosis, major bleeding, and major cardiovascular/cerebrovascular events as end points (the DAPT trial). The second study is the German ISAR-SAFE study, with 6000 patients with drug-eluting stents on dual antiplatelet therapy for 6 versus 12 months; the primary end point is death, stroke, and major bleeding at 15 months.

**Conclusion**

Dual antiplatelet therapy in patients undergoing stent implantation with additional oral anticoagulation increases bleeding risk. Among physicians, large differences in opinion exist about the duration of antiplatelet therapy in these cases: which agent to discontinue first and when? In the lack of results of randomized trials, expert opinion is needed. Both American and European leaders in the field have published their opinions on the optimal patient treatment; however, the American colleagues focus more on prevention of thrombotic events and the Europeans focus more on prevention of bleeding complications.

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