Safety of dual antiplatelet therapy in daily cardiology practice

F.W.A. Verheugt

Dual antiplatelet therapy has become the cornerstone of the treatment of acute coronary syndromes with or without stent implantation.¹ 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 one year of treatment is advised.² 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 2010 are on dual antiplatelet therapy, mainly aspirin and clopidogrel. The only important side effect of dual antiplatelet therapy is increased bleeding in comparison with aspirin alone. This has been established in the large trials with clopidogrel in acute coronary syndromes^{3,4} as well as in atrial fibrillation.⁵ Especially in the latter dual antiplatelet therapy has shown to be as hazardous as oral anticoagulation.⁶ Special attention has been given to the risks of dual antiplatelet therapy in 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.⁷ However, this excess bleeding was not significantly associated with an increased risk of reoperation or mortality. Yet, it is generally advised to discontinue clopidogrel five 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, orthopaedic procedures, neurosurgical op-

erations or procedures in other vital organs where bleeding can result in organ loss. Recently, the first guideline on interruption of antiplatelet therapy in general and of dual antiplatelet therapy in particular was published.⁸ In that guideline, patients with high, medium and low thrombotic risk are identified. In patients with the highest thrombotic risk antiplatelet therapy should be continued, and in the patient with a low thrombotic risk this can be discontinued prior to surgery.

In this issue of *Netherlands Heart Journal* a prospective registry of bleeding complications in patients undergoing implantation of a pacemaker or defibrillator with regard to bleeding complications with single or dual antiplatelet therapy is published.⁹ Interestingly, in this well-performed study dual antiplatelet therapy when continued was not associated with major bleeding complications in comparison with aspirin alone. Only minor complications were seen more frequently with clopidogrel plus aspirin. Furthermore, in patients with major complications, such as cardiac perforation, dual antiplatelet therapy was not associated with a more complicated cause when compared with aspirin alone. Although this study was not randomised for type of therapy or its discontinuation, the results are reassuring in that patients can undergo these implantations safely without discontinuation of dual antiplatelet therapy. This is important since discontinuation of antiplatelet therapy in patients awaiting surgical procedures is associated with increased risk of myocardial infarction, stent thrombosis, stroke and even death.¹⁰⁻¹³

Are these data sufficient to advise cardiologists to routinely continue dual antiplatelet therapy in patients undergoing device implantation? Of course, this study is too small to be conclusive, although the data collection was prospective. Furthermore, it is unclear how many patients used oral anticoagulants on top of dual antiplatelet therapy. Many patients in the need of a dual chamber device and/or a cardiac defibrillator with an indication for antiplatelet dual therapy are also on oral anticoagu-

F.W.A. Verheugt

Department of Cardiology, Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands

Correspondence to: F.W.A. Verheugt
Department of Cardiology, Onze Lieve Vrouwe Gasthuis, PO Box 95500, 1090 HM Amsterdam, the Netherlands
E-mail f.w.a.verheugt@olv.gn.nl

lant therapy. This so-called triple therapy is associated with increased bleeding on one hand, but discontinuation of warfarin on the other may lead to catastrophic thrombotic events including death.¹⁴ Currently, two major randomised trials are running on the risks and benefit of triple antithrombotic therapy (aspirin, clopidogrel and warfarin) versus dual antithrombotic therapy (clopidogrel and warfarin, but without aspirin) in anticoagulated patients after coronary stent implantation.¹⁵ One of these studies is initiated from the Netherlands (WOEST) and the other from Germany (ISAR-TRIPLE). The outcomes of these trials will guide the management of this difficult group of patients.

Finally, in each patient the indication for dual antiplatelet therapy should be judged at the moment the decision is made for implantation. This largely depends on time interval between initiation of dual antiplatelet therapy and the decision to implant a device. Since the optimal duration of dual antiplatelet therapy in patients who have undergone stent implantation is still not fully established, the decision to continue or discontinue dual antiplatelet therapy at the moment of device implantation is and will be difficult. Currently, two 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 endpoints (the DAPT trial). The second study is the German ISAR-SAFE study with 6000 patients with drug-eluting stents on dual antiplatelet therapy for six versus 12 months. Here the primary endpoint is death, stroke and major bleeding at 15 months.

In conclusion, dual antiplatelet therapy in patients undergoing device implantation seems to be as safe as single antiplatelet therapy with aspirin alone, but more studies are necessary especially in patients with additional oral anticoagulation. Still a judgement should be done in each patient on dual antiplatelet therapy awaiting device implantation with regard to safety of the procedure and the consequences of stopping antiplatelet drugs. ■

References

- 1 Van de Werf F. New antithrombotic agents: are they needed and what can they offer to patients with a non-ST-elevation acute coronary syndrome? *Eur Heart J*. 2009;30:1695-702.
- 2 Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non ST-elevation acute coronary syndromes. *Eur Heart J*. 2007;28:1598-660.
- 3 CURE Investigators. Effect of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494-502.
- 4 COMMIT(Clopidogrel and Metoprolol in Myocardial Infarction Trial) Collaborative Group. Addition of clopidogrel to aspirin in 45852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005;366:1607-2.
- 5 ACTIVE Investigators. Effect of clopidogrel added to aspirin in atrial fibrillation. *N Engl J Med*. 2009;360:1266-78.
- 6 Verheugt FWA. Good old warfarin for stroke prevention in atrial fibrillation. *Lancet*. 2006;367:1877-8.
- 7 Fox KAA, Mehta SR, Peters R, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial. *Circulation*. 2004;110:1202-8.
- 8 Douketis JD, Berger PB, Dunn AS, et al. Perioperative management of antithrombotic therapy: American College of Chest Physician evidence-based clinical practice guidelines (8th edition). *Chest*. 2009;133(Suppl 6):299S-339S.
- 9 Przybylski A, Derejko P, Kwasniewski W, Urbańczyk-Świąć D, Zakrzewska J, Orszulak W, et al. Bleeding complications after pacemaker or cardioverter-defibrillator implantation in patients receiving dual antiplatelet therapy: the results of a prospective, two-centre registry. *Neth Heart J*. 2010;18:230-5.
- 10 Collet JP, Montalescot G, Blanchet B, et al. Impact of prior use of recent withdrawal of oral antiplatelet agents on acute coronary syndromes. *Circulation*. 2004;110:2361-7.
- 11 Van Werkum JW, Heestermaans AA, Zomer AC, Kelder JC, Sutorp MJ, Rensing BJ, et al. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. *J Am Coll Cardiol*. 2009;53:1399-409.
- 12 Ferrari E, Benhamou M, Cerboni P, Marcel B. Coronary syndromes following aspirin withdrawal: a special risk for late stent thrombosis. *J Am Coll Cardiol*. 2005;45:456-9.
- 13 Maulaz AB, Bezerra DC, Michel P, Bogousslavsky J. Effect of discontinuing aspirin therapy on the risk of brain ischemic stroke. *Arch Neurol*. 2005;62:1217-20.
- 14 Ruiz-Nodar JM, Marin F, Hurtado JF, et al. Anticoagulant and antiplatelet therapy use in 426 patients with atrial fibrillation undergoing percutaneous coronary intervention and stent implantation: implications for bleeding risk and prognosis. *J Am Coll Cardiol*. 2008;51:818-25.
- 15 Dewilde W, Ten Berg JM. Design and rationale of the WOEST trial: what is the optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary stenting. *Am Heart J*. 2009;158:713-8.