Should dual antiplatelet therapy after drug-eluting stents be continued for more than 1 year?

**Dual Antiplatelet Therapy After Drug-Eluting Stents Should Be Continued for More Than One Year and Preferably Indefinitely**

Adnan K. Chhatriwalla, MD; Deepak L. Bhatt, MD, MPH, FAHA

Since its introduction, percutaneous coronary intervention (PCI) has been limited by 2 major factors: restenosis and vessel closure attributable to thrombosis. The use of coronary stents has had a marked beneficial impact on rates of restenosis.1,2 However, the vessel trauma that occurs during PCI induces platelet activation, and all currently available coronary stents are made of metal and are therefore thrombogenic. The use of drug-eluting stents (DES) can reduce restenosis and target vessel revascularization by >70% compared with bare metal stents (BMS).3,4 However, the polymer coatings and other aspects of DES may result in increased thrombogenicity compared with BMS.5

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Early PCI studies reported rates of acute and subacute vessel closure approaching 25%.6,7 As a result, many antithrombotic and antiplatelet regimens have been investigated to maximize benefit and to reduce complications in patients undergoing PCI. The addition of dipyridamole to aspirin showed no benefit in reducing acute PCI complications compared with aspirin alone.8 Similarly, very high-dose aspirin (1500 mg/d) did not reduce rates of myocardial infarction (MI) or need for surgical revascularization compared with low-dose aspirin therapy (80 mg/d).9 The addition of warfarin to aspirin therapy has been shown to slightly reduce the risk of cardiovascular events; however, this is accompanied by a significant increase in the risk of hemorrhagic complications.10 Dual antiplatelet therapy with aspirin in combination with thienopyridine agents, which have complementary mechanisms of action (Figure 1),10 has resulted in the greatest improvements in PCI outcomes. In the Stent Anticoagulation Restenosis Study (STARS), the incidence of death, target lesion revascularization, vessel thrombosis, or MI at 30 days was 0.5% with aspirin/ticlopidine therapy compared with 2.7% and 3.6%, respectively, with aspirin/warfarin and aspirin alone.11 More recently, because of the rare but severe complication of thrombotic thrombocytic purpura associated with ticlopidine, clopidogrel has become the preferred agent in combination with aspirin after PCI and has been shown to have at least equal efficacy to ticlopidine in the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS)12 and in a meta-analysis.13
Dual Antiplatelet Therapy in Acute Coronary Syndrome

The benefit of antiplatelet therapy with aspirin and clopidogrel is well established in patients with acute coronary syndrome (ACS). In a randomized, blinded trial of Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE), clopidogrel therapy was superior to aspirin, demonstrating an 8.7% relative risk reduction in ischemic stroke, MI, or vascular death over nearly 2-year average follow-up in high-risk patients with recent MI, recent stroke, or symptomatic peripheral arterial disease. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, the addition of clopidogrel therapy to aspirin resulted in a significant reduction in cardiovascular death, MI, or stroke at 1 year in patients with ACS compared with aspirin alone (9.3% versus 11.4%). Furthermore, a subgroup analysis of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study in patients with a history of previous ischemic events (prior MI, prior stroke, or symptomatic peripheral arterial disease) demonstrated a 17.1% relative risk reduction in cardiovascular death, MI, or stroke with aspirin and clopidogrel combination therapy compared with aspirin alone (Figure 2). This benefit seemed to increase out to almost 3 years after randomization.

Dual Antiplatelet Therapy After Stenting

The PCI-CURE study evaluated patients with ACS enrolled in CURE undergoing stenting with BMS and demonstrated an increasing benefit in terms of reduction in cardiovascular death or MI with dual antiplatelet therapy for up to a year versus a few weeks, with no evidence of a plateau effect out to 1 year (8.8% versus 12.6%, Figure 3). A similar increasing benefit of dual antiplatelet therapy was observed in patients undergoing elective PCI with BMS in the Clopidogrel for the Reduction of Events During Observation (CREDO) trial, with a 27% relative risk reduction in death, MI, or stroke at 12 months (Figure 4). Although no prospective study has evaluated extended dual antiplatelet therapy (>1 year) after DES implantation, the event curves from PCI-CURE and CREDO suggest that the benefits of dual antiplatelet therapy may extend beyond 12 months.
Similar findings have recently been demonstrated with the newer thienopyridine agent, prasugrel, which is a more rapid and more effective inhibitor of platelet activation than clopidogrel. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI 38), patients with ACS and planned PCI had lower rates of cardiovascular death, nonfatal MI, or nonfatal stroke when treated with aspirin and prasugrel in combination, as compared with aspirin combined with clopidogrel (9.9% versus 12.1%).20 The benefit of prasugrel over clopidogrel seemed to be increasing out to 15 months, with no evidence of a plateau effect. Furthermore, it was demonstrated in the TRITON-STENT substudy that prasugrel therapy had a beneficial impact on both early (<30 days) and late (>30 days) DES thrombosis (Figure 5), as well as BMS thrombosis.21 When taken collectively, these data suggest that adverse cardiac events are decreased with more complete platelet inhibition as well as with longer-term platelet inhibition after PCI, especially in the ACS patient.

**Late Stent Thrombosis**

The incidence of stent thrombosis in the dual antiplatelet therapy era has approximated 1%,22 and no increased risk of stent thrombosis was initially apparent during <1-year follow-up in clinical trials of DES.23,24 More recently, however, a small but statistically significant risk of very late DES thrombosis has been identified. The first case reports were published by McFadden and colleagues in 2004 and involved both Cypher sirolimus-eluting stents and Taxus paclitaxel-eluting stents.25 The risk of late DES thrombosis was subsequently confirmed in a meta-analysis of clinical trials with >1-year follow-up.26 Furthermore, long term follow-up from the Bern and Rotterdam Registries has demonstrated no attenuation in the risk of late DES thrombosis (0.6% per year) up to 3 years after implantation.27 Similar rates of late thrombosis have been observed with short-term and extended follow-up in pooled analyses of clinical trial data involving Cypher and Taxus DES.28-30

The occurrence of late DES thrombosis is reminiscent of and partially analogous to the well-documented phenomenon of late stent thrombosis after intracoronary brachytherapy.31 As with brachytherapy-associated late stent thrombosis,32 the risk of late DES thrombosis has been attributed to impaired vessel healing, as evidenced by impaired neointimal growth, incomplete endothelialization of the stent struts, and increased inflammation and hypersensitivity reaction at the site of stent deployment (Figure 6).33,34 Clinical factors associated with an increased risk of late stent thrombosis with DES include advanced age, ACS, diabetes mellitus, renal failure, low ejection fraction, prior brachytherapy, and aspirin or clopidogrel resistance.35-39 Furthermore, the risk of late stent thrombosis is increased in small vessels, bifurcation lesions, and with the use of multiple, long, or overlapping stents.36-38 However, the most important risk factor for late stent thrombosis seems to be premature discontinuation of dual antiplatelet therapy.40-42 In a large observational study, DES stent thrombosis was observed in almost 30% of patients who prematurely discontinued antiplatelet therapy.36 Furthermore, a large, retrospective VA study of patients with ACS demonstrated an increased risk of death or MI after discontinuation of clopidogrel, regardless of whether patients were initially treated medically or with PCI, with DES or BMS.43 This risk was highest in the first 90 days after discontinuation of clopidogrel, and it persisted even in patients who completed 9 months of clopidogrel therapy (Figure 7). A large Duke University registry study demonstrated that extended dual antiplatelet therapy with aspirin and clopidogrel was associated with reduced rates of death and MI after DES implantation. Landmark analysis of patients who were event-free at 6-12-month follow-up demonstrated that the benefit of dual antiplatelet therapy was present at 12 months (3.1% versus 7.2%) and at 24 months (0% versus 4.5%); however, no such benefit to extended dual antiplatelet therapy was observed in patients who received BMS.44 Finally, in a study by Brar et al., patients with diabetes mellitus who underwent PCI with DES or BMS had a lower incidence of death or MI with longer duration clopidogrel use; 3.2% in patients treated for >9 months, 9.4% in patients treated for 6 to 9 months, and 16.5% in patients treated for <6 months.45 These collective data provide support for the updated American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guidelines for PCI, which recommend dual antiplatelet therapy for at least 1 year after DES implantation,46 and prompted an American Heart Association/American College of Cardiology/Society for Cardiovascular Angiography and Interventions/American Cancer Society/American Diabetes Association science advisory further stressing the importance of avoiding discontinuation of dual antiplatelet therapy in the first year after DES implantation.47
Dual Antiplatelet Therapy Concerns

Although the early and late benefits of dual antiplatelet therapy have been demonstrated in multiple studies, concerns regarding the extended use of dual antiplatelet therapy persist. Important side effects associated with aspirin include gastrointestinal upset and tinnitus; however, the latter is thought to occur only with large doses of aspirin. Clopidogrel use has been associated with gastrointestinal upset, rash, and diarrhea. However, if aspirin and clopidogrel therapy are initially well-tolerated, then the likelihood of these side effects occurring with extended therapy is very low. The incidence of increased bleeding with dual antiplatelet therapy has been well-examined in several studies. In the CURE trial, clopidogrel and aspirin therapy was associated with a significant increase in major (3.7% versus 2.7%) and minor (5.1% versus 2.4%) bleeding compared with aspirin alone, but no increase in life-threatening bleeding events was observed. Furthermore, the increased risk of major bleeding after 30 days (5 events per 1000 patients) was outweighed by the benefit in cardiovascular death, MI, or stroke (11 events per 1000 patients). A similar result was demonstrated in a subgroup analysis of patients with prior ischemic events in the CHARISMA study, in which the combined end point of cardiovascular death, MI, stroke, or severe bleeding was reduced with combined aspirin and clopidogrel therapy (8.3% versus 9.4%). Furthermore, there was no significant excess of fatal or intracranial bleeding in the trial overall, and little difference in transfusion requirement was observed after the first few months of therapy (Figure 8). Therefore, it seems that in patients at high risk for cardiovascular events, the clinical benefit of dual antiplatelet therapy outweighs the slightly increased risk of moderate bleeding requiring transfusion.

Finally, concern exists regarding the cost of dual antiplatelet therapy, its impact on the health care system as a whole, and on an individual patient’s ability to pay for extended therapy. However, a recent analysis of patients with ACS...
demonstrated that dual antiplatelet therapy with aspirin and clopidogrel was cost-effective at 1 year. Furthermore, the cost per quality-adjusted life year in year 2 of therapy (US$31 600) was similar to that in year 1 (US$26 100).49 Although these data are encouraging, the question of cost-effectiveness of extended dual antiplatelet therapy with clopidogrel may become less important once generic versions are widely available.

**DES for Appropriate Patients**

Although it has been commonly thought that restenosis after BMS use is a benign clinical entity, restenosis can present with ACS in more than one third of cases.50 Several analyses have demonstrated that DES use is associated with a long-term clinical benefit.51,52 It is therefore likely that the beneficial impact of DES on restenosis outweighs the minimally increased risk of late stent thrombosis in many patients. Nevertheless, stent thrombosis is a life-threatening event,22,36,53 and therefore, patients who are not appropriate candidates are best not treated with DES when undergoing PCI. BMS restenosis can be predicted by vessel diameter, lesion length, and presence of diabetes,54 and DES use may be most appropriate for situations in which the risk of BMS restenosis is high. Additional factors that should be considered before deciding on therapy with DES include patient compliance, risk of major bleeding, and foreseeable surgical procedures which might require discontinuation of antiplatelet therapy. Furthermore, dual antiplatelet therapy in patients with indications for anticoagulation therapy (eg, atrial fibrillation, hypercoagulable state, or mechanical heart valve) may pose a prohibitive bleeding risk. As a result, several algorithms have been proposed to evaluate patient risk before deciding on a course of revascularization and if PCI is considered, before deciding on treatment with DES.55,56 In patients who are at high risk for BMS restenosis but are not candidates for extended dual antiplatelet therapy, alternative management strategies, including bypass surgery, should be considered.57

**Future**

Current data seem to indicate that cardiovascular outcomes are improved with extended and more complete platelet inhibition therapy. However, further research is necessary to determine the optimal antiplatelet regimen and the optimal duration of antiplatelet therapy after PCI, particularly in patients receiving DES.

There has been interest in the impact of triple antiplatelet therapy on cardiovascular outcomes after PCI. Addition of
the phosphodiesterase inhibitor cilostazol to aspirin and clopidogrel significantly decreases platelet reactivity.58 Similar regimens have been evaluated after BMS implantation in 2 studies, with some suggestion of decreased restenosis and decreased stent thrombosis.59,60 Triple antiplatelet therapy with cilostazol has also been demonstrated to reduce late restenosis in patients with diabetes receiving DES.61 However, whether triple antiplatelet therapy has any beneficial impact on late DES thrombosis is unknown.

Novel antiplatelet agents, such as prasugrel, AZD6140, and PRT128, may afford more complete and effective platelet inhibition and obviate the need for dual antiplatelet therapy in the future. Such therapies may also overcome complications resulting from aspirin and clopidogrel resistance. Furthermore, advances in genomic medicine and in point-of-care platelet function testing may allow for individualized antiplatelet regimens, tailored to maximize cardiovascular benefit and minimize bleeding risk in each patient.

New stent technology may preclude the need for extended dual antiplatelet therapy in the future. An ideal DES should inhibit neointimal proliferation and therefore reduce the incidence of restenosis, while still allowing sufficient vessel healing to promote endothelialization of the stent struts. Potential areas for design improvement include the shape and thickness of stent struts, choice of antiproliferative agent, and drug-elution pharmacokinetics. The role of different polymers in stent thrombosis deserves more extensive study. Furthermore, bioabsorbable stent technology seems promising and may combine the positive attributes of BMS and DES. Release of antiproliferative agents from the stent platform in the several weeks after stent implantation may retard neointimal growth and minimize restenosis. Once the stent platform degrades, rendering the vessel free from thrombogenic stimulus, dual antiplatelet therapy can theoretically be safely discontinued without an increased risk of vessel thrombosis. However, there may still be a role for extended dual antiplatelet therapy based on the patient’s underlying risk, such as in patients with a history of ACS. Evaluation of a bioabsorbable magnesium alloy stent revealed a 45% rate of target lesion revascularization at 1 year.62 However, the Bioabsorbable Everolimus-eluting Coronary Stent System for Patients with Single De Novo Coronary Artery Lesions (ABSORB) trial recently evaluated the feasibility of a bioabsorbable everolimus-eluting polylactic acid stent platform in 30 patients and reported a 3.3% rate of cardiac death or MI at 1 year, with no episodes of target lesion revascularization.63

**Conclusions**

The current body of randomized and observational evidence demonstrates that patients with ACS, a prior history of ischemic events, or PCI with BMS or DES have improved cardiovascular outcomes with more robust or longer duration antiplatelet therapy. Furthermore, discontinuation of dual antiplatelet therapy seems to be the most potent predictor of late stent thrombosis, and barring a bleeding contraindication, provides sufficient reason to recommend extended dual antiplatelet therapy in patients treated with DES, particularly those with prior ACS. Therefore, until the risk of late stent thrombosis is attenuated with approved novel therapeutic agents or new stent technology, dual antiplatelet therapy with aspirin and clopidogrel should be recommended for >1 year, and perhaps indefinitely, in all patients receiving DES. This recommendation must be prospectively validated through adequately powered randomized clinical trials with long-term follow-up. Although newer transformative stent technologies may emerge, it remains important to clarify the optimal management of patients who have already received current generation DES, and we eagerly await the results of ongoing trials, such as Prospective, Randomized, Double-Blind, Placebo-Controlled Trial of 6 Months Versus 12 Months Clopidogrel Therapy After Implantation of a Drug-Eluting Stent (ISAR-SAFE); Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated With Drug-Eluting Stent Implantation and Late Coronary Arterial Thrombotic Events (REAL-LATE); and Evaluation of the Long-Term Safety After Zotarolimus-Eluting Stent, Sirolimus-Eluting Stent, or Paclitaxel-Eluting Stent Implantation for Coronary Lesions—Late Coronary Arterial Thrombotic Events (ZEST-LATE), which should provide much needed data on this important issue.64

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17. Bavry AA, Kumbhani DJ, Hetlon TJ, Borek PP, Mood GR, Bhatt DL. 
    Late thrombosis of drug-eluting stents: a meta-analysis of randomized 
The article by Chhatriwalla and Bhatt reports on a number of studies supporting the concept of clopidogrel therapy or clopidogrel plus aspirin in significantly reducing ischemic events in patients with atherosclerotic vascular disease. Studies evaluating dual antiplatelet therapy (DAT) after bare metal stent and drug-eluting stent (DES) implantation have confirmed benefit up to 1 year. Prolonged (>12 months) DAT has never been shown in any randomized study to be beneficial post–DES implantation, and the deficiencies in the literature have led to widespread uncertainty. There has, therefore, been an extrapolation of the previous studies using DAT in bare metal stents, patients with high cardiovascular risk, and patients with acute coronary syndromes into patients who are otherwise healthy but have had a DES implanted 12 months earlier. As much as the authors try to elucidate risk factors for “late stent thrombosis,” the reality is that the mechanisms for DES thrombosis are unclear. Moreover, the true prevalence of stent thrombosis per se is unknown and needs to be determined in patients on aspirin and DAT. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial failed to prove any benefit of generalized DAT in secondary prevention, but it may be possible that patients with more severe atherosclerotic disease would have seen greater effects. Termination of DAT at 12 months post–DES implantation could be analogous to discontinuing statin therapy: both approaches are associated with an increased risk of death and myocardial infarction. However, is the DES or the underling atherothrombotic disease the real culprit?
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