Drug-eluting stents (DES) have significantly reduced the occurrence of in-stent restenosis with a coexistent reduction in revascularization compared with bare metal stents (BMS). In September 2006, at the World Congress of Cardiology/European Society of Cardiology in Barcelona, a signal appeared of increased risk with DES more than BMS, namely that of late stent thrombosis. Although the concerns at that time were overemphasized and hyped by the media, when the smoke settled, more rigorous studies and standardized definitions of stent thrombosis demonstrated real ongoing concerns of late stent thrombosis. Potential mechanisms for stent thrombosis are described in Figure and in the Table. Subsequent studies then suggested possible benefits from prolonged (>6 months) dual antiplatelet therapy (DAT) after DES implantation in reduction in clinical events. This prompted the Food and Drug Administration (FDA) to issue a guideline that patients should take DAT for up to 12 months after DES insertion based on indirect data and without a specific prospective study. We think the best way to address these issues is with the following Life Scenario.

**A Life Scenario**

Let us assume that I had symptomatic coronary artery disease with stable angina for which I saw my local cardiologists and he performed noninvasive testing and the stress test was positive. I ended up with a percutaneous coronary intervention (PCI) 2 weeks later, and after a load of clopidogrel, I had 2 stents inserted: a Taxus 3.5×20 mm (Boston Scientific, Natick, Mass) implanted in my proximal right coronary artery and a 3.0×33 mm Cypher (Cordis Corp, Johnson & Johnson Company, Miami Lakes, Fla) in the mid portion of my left anterior descending coronary. Everything went well and I am now asymptomatic with a negative exercise test. After 1 year of clopidogrel and aspirin dual therapy with no side effects, except for having to pay for the extra 6-month treatment because not every country may cover the cost of clopidogrel 6 months beyond PCI, I am now faced with the decision of what to do?

**Why Should I Continue Clopidogrel for 1 Year and Stop It at the End?**

With 2 DES implanted on 2 major epicardial vessels, there is no question that I should continue DAT for ≥6 months.
according to the original guidelines derived from the specific pivotal randomized trials.1–4,32 After having read those trials, I am really perplexed by the evidence supporting the perceived arbitrary decisions of 3 months for Cypher (2 months if you live in Europe)33 and 6 months for the Taxus stent.4 The appearance of late stent thrombosis, occurring after 30 days,8 has made things slightly complicated. First, we ought to step back and try to understand late stent thrombosis. Having continued DAT for \(\frac{1}{2}\) month, I am delighted that I did not experience any late stent thrombosis in the seemingly early period. Now, according to the new recommendations of the American Heart Association/American College of Cardiology/Society for Cardiovascular Angiography and Interventions/American Cancer Society/American Dental Association panel, I may have to extend my DAT to 12 months.31 The original question is now rephrased: Should I continue to take DAT to prevent late thrombosis \(\frac{1}{2}\) months after DES implantation? Unfortunately, the more I try to unfold the puzzle the less clear it becomes. When I look at reports regarding late stent thrombosis and very late stent thrombosis, I see a lot of events occur during the 6- to 12-month and after the 12-month period from stenting.34–36 Some of them happen in patients who stop clopidogrel, some in patients who still receive DAT,20,34,37–41 and some in patients who stop aspirin and clopidogrel.20,34,38 In our recent study,20 we reported that between 6 and 12 months, the stent thrombosis rate was 0.2% in patients who stopped clopidogrel and continued aspirin and 0.4% in patients taking DAT; between 12 and 18 months, stent thrombosis rates were 0.1% and 0.4% in patients without clopidogrel and with DAT, respectively (Figure 2). The perceived constant rise in the risk of very late stent thrombosis as demonstrated in the study of Daemen7 should be evaluated with caution as the main limitation with this conclusion lies in the number of patients at risk, which at 1 year was 5549, whereas at 3 years, it dropped significantly and was 989. The decline in the number at follow-up results in a much larger confidence interval. Having accepted this fact, it means that whatever I do I will never be protected but what I need to understand now is about the possible benefit of continuing clopidogrel beyond the recommendations of American Heart Association/American College of Cardiology/Society for Cardiovascular Angiography and Interventions/American Cancer Society/American Dental Association.31

Table. Potential Predisposing Factors for Stent Thrombosis

<table>
<thead>
<tr>
<th>Reference</th>
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<tbody>
<tr>
<td>Plaque rupture of adjacent lesion</td>
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<tr>
<td>Incomplete endothelization</td>
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<tr>
<td>Noncompliance with DAT</td>
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<tr>
<td>Clopidogrel nonresponsiveness</td>
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<tr>
<td>Small vessels</td>
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<tr>
<td>Long lesions</td>
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<tr>
<td>Bifurcations</td>
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<td>Lack of intravascular ultrasound guidance</td>
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<td>Hypersensitivity to drug or polymer</td>
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<td>Diabetes</td>
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<td>Renal failure</td>
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<td>Low ejection fraction</td>
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<tr>
<td>Prior brachytherapy</td>
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<td>Incomplete stent apposition</td>
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Figure 1. Proposed mechanisms leading to late and very late stent thrombosis. A and B, Late stent malapposition caused by persistent stent malapposition from underexpansion at the time of implantation.12 C and D, Late acquired stent malapposition caused by intrastent reabsorption of thrombus.11 E and F, Late acquired stent malapposition caused by vessel expansion due to remodeling (this last feature is specific for DES).11,12 G, New atherosclerotic lesion develops inside the stent leading to plaque rupture and an acute coronary syndrome.13 H, Hypersensitivity reaction to the drug or to the polymer causes inflammation and thrombosis.14,15
The next area of uncertainty comes after reading the American Heart Association document and trying to figure out why they set the 1 year term. The best answer I can find is by looking at reference 21 of the original article by Eisenstein et al, which reported only the incidence of death and MI without any specific mention of ST. As a matter of fact, one interesting finding from this study is that continuation of DAT for ≥24 months (the time duration of the study) is helpful no matter if you had a DES or BMS implanted. Another study which highlights the concern of very late stent thrombosis is the late follow-up of the Basel Stent Kosten-Effektivitäts Trial (BASKET) trial, in which the event rates after discontinuation of clopidogrel between 7 and 18 months were 4.9% after DES versus 1.3% after BMS implantation. Unfortunately, at best, there were only 499 patients with DES and late follow-up (18 months) in the BASKET-LATE study, with 230 patients who had late follow-up in the Eisenstein et al study.

Now if I turn my attention to the various case reports on late and very late stent thrombosis (occurring after 6 months or 1 year) I can see a considerable number of events occurring after 1 year from stenting at variable time intervals from clopidogrel discontinuation. The most important impression that I can glean from examining these studies is that discontinuation of aspirin and clopidogrel, even at a late time, is very frequently associated with stent thrombosis. This conclusion is also derived from clinical experience as we know that the most patients continue with at least aspirin therefore the denominator of the population not taking aspirin and clopidogrel must be quite small. Unfortunately it is difficult to elaborate in the same manner for clopidogrel because we cannot assume as with aspirin that clopidogrel continues to taken indefinitely. So far, I have come to the following conclusion from my literature search: (1) I am not going to ever stop aspirin and (2) despite the American Heart Association/American College of Cardiology/Society for Cardiovascular Angiography and Interventions/American Cancer Society/American Dental Association guidelines and the lack of proof for sustained DAT, I do not feel too comfortable about stopping clopidogrel after 1 year. I am afraid of the unpredictable occurrence of rare events even if not necessarily correlated to clopidogrel discontinuation.

**Why Should I Continue Clopidogrel Indefinitely?**

Except for one article published from our group, there are no data concerning what happens to patients who stop clopidogrel and to those who continue DAT. Studies have focused on the details in individual patients who stopped clopidogrel then subsequently sustained an adverse event, but basically we lack the common denominator. One study attempted to estimate the risk of DES thrombosis if one stopped clopidogrel calculated a 90% hazard ratio. Moreover, what is frequently overlooked is that the hazard ratio refers to “premature discontinuation,” which means stopping clopidogrel before 6 months from stenting, and nothing is reported regarding the risk of stopping clopidogrel after 6 months. The study by Airoldi et al tried to answer this question and concluded that the risk of late discontinuation of clopidogrel is probably very low or absent, but this conclusion has limitations as there were a low number of patients evaluated. This highlights the problem that all studies face when trying to tease out the etiology of this event. It is
difficult to make definitive statements about a low-frequency event such as late and very late stent thrombosis unless you perform a prospective study aimed to evaluate a difference in stent thrombosis between 1 year and 2 to 3 years. Such a study will need to enroll several thousand patients, depending on the superiority or noninferiority design and on the δ in the incidence of very late stent thrombosis (DAT versus only aspirin). We need to take into account that clopidogrel will be protective against ischemic events not necessarily related to thrombosis of the DES. This situation will increase the prevalence of confounding factors and demand a very large sample size. Figure 3 illustrates this problem: this patient had DES implanted for a totally occluded left anterior descending artery (panel A and B). Eight months later, while still on DAT, he underwent a scheduled routine follow-up angiogram demonstrating a severe stenosis proximal to the stented segment (panel C). It is feasible that without DAT this high-grade stenosis may cause an acute event that could be labeled a definite or probable stent thrombosis. These are the sort of confounding factors present in real life that need to be considered in any prospective study. Moreover, I could get very worried when I look at the 23,500 patients in the Estudio Espanol Sobre Trombosis de Stents Farmacoactivos (ESTROFA) Registry and see that in 90 patients with late stent thrombosis and in 62 patients with very late stent thrombosis, more than 60% of them were only taking aspirin. Therefore, I may instinctively conclude that if I continue to take DAT, then I should be at lower risk because only 22% of the patients with late stent thrombosis and 8% with very late stent thrombosis were taking DAT. This notion is indeed appealing and reassuring but could be false unless we know the total number of patients taking single, dual, and no antiplatelet therapy who did not sustain a thrombotic event. Paradoxically, if in the whole registry there were only 25 patients taking DAT, this combination would be regarded as fatal with regard to stent thrombosis. The fact that the authors did not have information regarding the status of antiplatelet therapy in people who did not sustain stent thrombosis is apparent because the discontinuation of DAT was not listed among the predictors of late or very late stent thrombosis.

Among the confounding risk factors for late stent thrombosis, we should consider that over the natural time course, many patients may discontinue DAT.

In addition, I have to deal with the risk of bleeding associated with DAT over this extended time period. The largest study I could find that provides me with some robust data is the CHARISMA trial, in which the risk of severe bleeding with DAT was 1.7% versus 1.3% on aspirin monotherapy, with an increased relative risk of 1.25; however, the 9-month to 3-year bleeding rate was similar. To conclude on this matter, we need to examine the large network meta-analysis by Stettler, which makes me less depressed at having a DES rather than a BMS in my coronary arteries. This is because the overall risk of experiencing a real hard clinical end point such as death or MI is not higher in the DES cohort. In addition, stent thrombosis is not higher compared with BMS. I know that by having a DES, I will secure for myself a longer period of freedom from a second procedure and the inherent risks associated with that. This study unfortunately provides no information on DAT, but I can presume that the practice in Europe at that time was to prescribe DAT for a maximum of 3 months after Cypher and 6 months after Taxus. Interestingly, I note that in our study (data collected from Italy and Germany), 75% of the patients were taking only aspirin and the risk of stent thrombosis after 1 year was 1.5% to 2% per year. Unfortunately, I do not know the exact figure if I decide to continue DAT long term. The reassuring part is that the 1.5% to 2% risk over 1 year should not generate too much panic if I occasionally forget my clopidogrel.

What Should I Do if I Need Surgery?
The worst thing that could happen would be that I need to undergo urgent surgery in the first 6 months following DES implantation. Assuming that the surgery cannot be delayed, I would do my best to find a surgeon who is willing to operate...
without interruption of DAT. If this goal is unachievable, then I will negotiate that I stop clopidogrel 3 days before surgery and restart 48 to 72 hours after the surgery. The literature has a number of reports even after the implantation of BMS about early discontinuation of DAT and stent thrombosis, MI, and death.45–46 I would certainly not take low-molecular heparin as a substitute to antiplatelet therapy, a strategy commonly perceived by some surgeons as the correct way to bridge antiplatelet therapy around the perisurgical period. Heparin can activate platelets, so without a strong antiplatelet therapy on board, the situation can be compounded and become more deleterious than beneficial.47 If the surgery is not urgent, then I would do my best to delay it as much as possible ideally for 6 to 12 months, and I would still not stop aspirin and accept a very short window of being without clopidogrel. I may even consider storing my own blood before surgery in case I require a blood transfusion. The possibility to bridge the time without clopidogrel with an infusion of IIb/IIIa as suggested48 is an innovative proposal but may encounter some obstacles from surgeons. Furthermore, one study using a new short-acting antiplatelet demonstrated reduced bleeding in patients who required emergency coronary artery bypass graft after acute coronary syndromes.49 The role that this agent could play in this setting is debatable but may be potentially used in the morning of surgery and started the day after because the half life is only 6 hours and the molecule inhibits the P2Y12 receptor competitively and not irreversibly as clopidogrel.50

What Would I Have Chosen if I Could Have Selected My Own Stent?

A BMS would have been an option only for a vessel of 3.5 mm diameter or larger requiring a stent <15 to 20 mm. Outside these parameters, I believe the implantation of DES will undoubtedly still be the best option for me, according to most large-scale studies.45,46,51 Some studies report a significantly lower late stent thrombosis after Cypher compared with that after Taxus.44,52,53 Nevertheless, I think we should refrain from drawing firm conclusion from these analyses that were not prospectively designed to evaluate the differences in outcome between the Cypher and the Taxus stents. In addition, specific studies incorporated in meta-analysis may have different definitions of stent thrombosis, which may translate into a higher risk of stent thrombosis for the Taxus stent without a corresponding impact in clinical outcome such as death or MI.53 An interesting alternative that is gaining a lot of attention may be to ask for an Endeavor stent (Medtronic Vascular, Santa Rosa, Calif). This DES seems to be less potent of attention may be to ask for an Endeavor stent (Medtronic Vascular, Santa Rosa, Calif). This DES seems to be less potent compounded and become more deleterious than beneficial.47 If the surgery is not urgent, then I would do my best to delay it as much as possible ideally for 6 to 12 months, and I would still not stop aspirin and accept a very short window of being without clopidogrel. I may even consider storing my own blood before surgery in case I require a blood transfusion. The possibility to bridge the time without clopidogrel with an infusion of IIb/IIIa as suggested48 is an innovative proposal but may encounter some obstacles from surgeons. Furthermore, one study using a new short-acting antiplatelet demonstrated reduced bleeding in patients who required emergency coronary artery bypass graft after acute coronary syndromes.49 The role that this agent could play in this setting is debatable but may be potentially used in the morning of surgery and started the day after because the half life is only 6 hours and the molecule inhibits the P2Y12 receptor competitively and not irreversibly as clopidogrel.50

Endeavor Versus Cypher Stenting Trial (PROTECT) is an ongoing trial on 8000 patients that was designed to evaluate if the Endeavor has indeed a lower stent thrombosis rate. Even if this study would turn out positive, the final decision on which stent to use needs to take into consideration the lesion characteristics such as length and reference vessel size. There are some speculative reports about the low late thrombosis following discontinuation of DAT after 6 months in patients treated with Everolimus-eluting stents (Xience V, Abbott Vascular, Santa Clara, Calif; Promus, Boston Scientific, Natick, Mass).56 I think we need more patients with longer follow-up before emphasizing these findings.

Conclusions

One year of DAT will be my definite choice. I may then continue beyond 1 year if I tolerate the DAT. However, I certainly will not become overanxious if I have to stop clopidogrel after 12 months and try not to let this issue cloud my later years.

Disclosures

None.

References


Response to Colombo and Gerber

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

Drs Colombo and Gerber provide a very thoughtful review and an important personalized perspective. We agree that there is uncertainty about the optimal duration of dual antiplatelet therapy after implantation of drug-eluting stents. No prospective trials have directly addressed this question, and we are therefore in the uncommon position of using the best available evidence to guide clinical decision making. In the percutaneous coronary intervention (PCI) substudy of the Clopidogrel in Unstable Angina to Prevent Recurrent Events trial (PCI-CURE) and Clopidogrel for the Reduction of Events During Observation trial (CREDIBLE) trials, the event curves continue to diverge, even between 6 and 12 months, suggesting that there is ongoing, incremental benefit of extending therapy—certainly within this timeframe and potentially beyond. Bleeding and cost are legitimate considerations with prolonged dual antiplatelet therapy. However, much of the serious bleeding risk is during the first few months of therapy; therefore, patients without bleeding complications at 1 year are likely to tolerate longer-term therapy. Furthermore, it appears from the available data that the benefit of dual antiplatelet therapy on ischemic endpoints outweighs the risk of bleeding. Finally, the cost will decrease substantially once generic clopidogrel is available. Importantly, the authors acknowledge that the benefit of prolonged dual antiplatelet therapy may be related to the underlying atherosclerotic milieu as well as the stent. Newer-generation drug-eluting stents may prove to be less prone to very late stent thrombosis; however, the underlying disease process is not modified by any current or imminent stent technology. Therefore, until data from prospective trials are available to clarify this issue, we feel that dual antiplatelet therapy after implantation of drug-eluting stents should be continued for more than 1 year and, preferably, indefinitely.
Should dual antiplatelet therapy after drug-eluting stents be continued for more than 1 year?: Dual Antiplatelet Therapy After Drug-Eluting Stents Should Not Be Continued for More Than 1 Year and Preferably Indefinitely
Antonio Colombo and Robert T. Gerber

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