HOSPITAL CHRONICLES 2010, SUPPLEMENT: 39–46

ATHENS CARDIOLOGY UPDATE 2010

Problems Arising From the Prolonged Use of Aspirin and Clopidogrel Imposed by Drug-Eluting Stents/Conundrums in Triple Antithrombotic Therapy: Newer Suggestions

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KEY WORDS: *antithrombotic therapy; antiplatelet agents; anticoagulation; aspirin; clopidogrel; prasugrel; ticagrelor*

ABBREVIATIONS
ACS= acute coronary syndromes
AF= atrial fibrillation
BMS= bare metal stents
CABG= coronary artery bypass graft surgery
CAD= coronary artery disease
DAT= dual antiplateltelet therapy
DES= drug-eluting stents
MACE= major adverse cardiac events
MI= myocardial infarction
NSTEMI= non-ST elevation myocardial infarction
PCI= percutaneous coronary intervention
PDE= phosphodiesterase
PPIs= proton pump inhibitors
RCTs= randomized controlled trials
STEMI= ST-elevation myocardial infarction
TAT= triple antiplateltelet therapy

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ABSTRACT

Dual antiplatelet therapy (DAT) can decrease effectively the rate of major adverse cardiovascular events after drug-eluting stent (DES) implantation in high-risk coronary artery disease (CAD) patients, but its implementation is associated with excess in bleeding events compared with aspirin monotherapy and a considerable treatment failure rate, namely persistence of occurrence of ischemic events, despite the use of the recommended dosage of the standard DAT. All large-scale antiplatelet randomized controlled trials have shown that the prolonged administration of DAT after coronary stenting provides improved thrombotic prevention at a cost of increased bleedings.

Newer antiplatelet regimens including higher maintenance doses of clopidogrel, or using the newer agents, prasugrel or ticagrelor, can effectively reduce rates of myocardial infarction and stent thrombosis during follow-up of high-risk CAD patients undergoing an invasive therapy, but they are accompanied by an increase in bleeding rates and, except for ticagrelor plus aspirin, do not reduce mortality. Therefore, the challenge remains to develop therapies that more effectively inhibit platelet activation and have a beneficial net effect on mortality without increasing bleeding complications.

For patients receiving triple therapy, they are advised to keep the dose of aspirin as low as possible (75 to 81 mg); clopidogrel should be given at its standard dose of 75 mg/day, and warfarin should be administered under tight control to achieve a slightly lower target INR of 2.0 to 2.5. It is also suggested that proton-pump inhibitors (PPIs) should be considered as prophylaxis against gastric bleeds, tending to use *pantoprazole* and *esomeprazole*, which have the least incriminating data regarding an interaction with clopidogrel. In patients with mild or moderate bleeding while on triple therapy, every effort should be made to maintain the INR as close to 2.0 as possible, and the aspirin dose should be kept at <100 mg. If bleeding persists, it is advised that aspirin be discontinued first, as clopidogrel seems to be more important than aspirin in preventing stent thrombosis after PCI.

INTRODUCTION

Stenting and dual antiplateltelet therapy (DAT) – consisting of the combination

of aspirin and a thienopyridine (most commonly clopidogrel) – represent the current practice in percutaneous coronary angioplasty (PCI). Stent use has effectively reduced the risk of restenosis and DAT eliminates the risk of stent thrombosis. Indeed, DAT provides incremental platelet inhibition (compared with either agent alone) and more effective suppression of adverse ischemic events and has been studied in the settings of medical therapy and PCI as well as in stroke prevention and treatment. However, these benefits of DAT are associated with an excess in bleeding events. Moreover, long-term duration of DAT has important implications for the subsequent performance of surgical procedures that require stopping antiplatelet therapy, which can lead to stent thrombosis. Conversely, extended dual therapy prolongs the "window of vulnerability" for bleeding, particularly in scenarios where concomitant warfarin might be necessary.[1-7]

In addition, despite the proven clinical benefits associated with DAT compared with aspirin monotherapy in the treatment of high-risk coronary artery disease (CAD) patients, recurrent ischemic events are seen in a significant percentage of patients during long-term follow-up.[1-7] This observation highlights an unmet need in the treatment of the patient at highest risk. For example, in the TRITON trial, there was an ~10% treatment failure rate (ischemic event occurrence) in the prasugrel arm despite the superior inhibition compared with clopidogrel as demonstrated in ex vivo studies of healthy volunteers and patients treated with the same dose.[8-10]

Accordingly, current DAT can decrease effectively the rate of major adverse cardiovascular events after drug-eluting stent (DES) implantation in high-risk CAD patients, but its implementation is associated with two major problems during long-term follow-up, (a) the excess in bleeding events compared with aspirin monotherapy and (b) the persistence of a considerable treatment failure rate, namely persistence of occurrence of ischemic events, despite the use of the recommended dosage of the standard DAT.[1-7] Because the large-scale trials of dual antiplatelet therapy did not implement simultaneous platelet function measurements, it was impossible to determine whether insufficient P2Y12 blockade marked by high on-treatment platelet reactivity to adenosine diphosphate (ADP) was the major cause of treatment failure and whether excessively low platelet reactivity was the cause of bleeding.[1]

THE BLEEDING RISK

Studies comparing DES and bare-metal stent (BMS) have shown that the timing of stent thrombosis might differ.[11-17] Stent thrombosis tends to occur earlier in BMS, whereas stent thrombosis in DES seems to trend later. Of particular concern is the observation that DES thrombosis might continue to occur (albeit at a very low rate) over time. In an attempt to prevent late thrombosis, a longer (possibly indefinite) duration of dual therapy is frequently recommended, specifically after DES in the setting of documented severe extensive atherosclerotic disease.[18] However, bleeding risks have become more problematic with the advent of widespread and prolonged therapy with the combination of aspirin and a thienopyridine. Thus, these recommendations about long-term DAT have important implications for the subsequent performance of surgical procedures that require stopping antiplatelet therapy, which can lead to stent thrombosis. Conversely, extended dual therapy prolongs the "window of vulnerability" for bleeding, particularly in scenarios where concomitant warfarin might be necessary.[7,20]

All large-scale antiplatelet randomized controlled trials (RCTs) have shown that the prolonged administration of DAT after coronary stenting provides improved thrombotic prevention at a cost of increased bleedings. In addition, despite the proven clinical benefits associated with DAT compared with aspirin monotherapy in the treatment of high-risk CAD patients, the rate of DAT failure continues to remain high.[2-4] Regimens, however, proposed to solve this problem can significantly decrease ischemic events but further increase the incidence of major and life-threatening bleedings.[8,9,19,21,22] Indeed, most antiplatelet and antithrombotic agents that reduce ischemia increase bleeding, or alternatively can reduce bleeding at the cost of increased ischemic complications, thereby cancelling any net survival benefit. Thus, although DAT including prasugrel or higher dose of clopidogrel effectively reduces major adverse cardiac events (MACEs) and stent thrombosis, it enhances the rate of major bleedings and has no effect on the survival.[8-10,19] Of particular concern is the observation that, considering numerous large multicenter RCTs in acute coronary syndromes (ACSs) published before PLATO, only fondaparinux in patients with NSTEMI treated conservatively[23] and bivalirudin in patients with STEMI undergoing primary PCI[24] have reduced all-cause mortality. In both cases this result was achieved by the test agent markedly reducing major bleeding while effectively suppressing (but not reducing) rates of MI compared with control. Ticagrelor now has proven the bleeding-ischemia hypothesis by showing the converse – that an agent which decreases MI without increasing overall major bleeding can also enhance survival.[20]

In particular, among antiplatelet strategies proposed to further reduce the remaining high rate of MACE during long-term follow-up after stenting, prasugrel[8,9] or high-maintenance dose clopidogrel[19] over aspirin compared with the standard DAT can effectively reduce MACE and stent thrombosis but enhance the rate of major bleedings and have no effect on the survival.[8,9,19] Like the above two antiplatelet strategies, ticagrelor compared with clopidogrel in the PLATO trial significantly reduced rates of MI and stent thrombosis, accompanied by an increase in major bleeding that was unrelated to coronary artery bypass graft (CABG) surgery.[21-22] By contrast, however,

ticagrelor compared with clopidogrel significantly reduced all-cause mortality at 12 months in all patients (by 22% [absolute difference of 1.4%], p<0.001),[21] and in those patients undergoing an early invasive strategy (by 19% [absolute difference of 1.1%], p=0.01).[22] Thus, all these three antiplatelet strategies, which have been proposed to further reduce the remaining high rate of MACE during long-term follow-up after stenting, can effectively reduce MACE but at a cost of increased bleedings. As a consequence, except for the case of ticagrelor plus aspirin, these bleedings seem to largely offset the expected life-preserving benefits from prevention of MI and stent thrombosis.[8,9,19,21,22]

Why does *ticagrelor* seem to reduce all-cause mortality whereas most other antiplatelet and antithrombotic agents that reduce ischemia and increase bleeding like ticagrelor have a neutral effect on mortality? There are some possible explanations: (**a**) It has been shown that hemorrhagic complications following antiplatelet therapy have been strongly linked to subsequent mortality.[25-29] It might be supposed that a shorter acting and reversible antiplatelet agent might be advantageous when used in patients who are in increased risk for bleeding. Thus, bleedings should be minor and more manageable after discontinuation of such antiplatelet agent, conditions that are apparently safer and associated with less subsequent risk. In TRITON, prasugrel increased CABG-related bleeding, all-cause bleeding, and transfusions, as well as life-threatening and fatal bleeding which largely offset its expected benefits from prevention of myocardial infarction and stent thrombosis. As a result, total mortality at 15 months was not significantly different with prasugrel and clopidogrel (3.0% vs. 3.2%).[8] By contrast, in PLATO, although ticagrelor was associated with an increase in non-CABG-related bleeding, it tended to reduce major CABG-related bleeding, and did not increase overall major bleeding, transfusions, or life-threatening or fatal bleeding.[21,22] Presumably this difference is explained by the fact that, unlike clopidogrel and prasugrel which bind irreversibly to the platelet surface-membrane P2Y12 receptor, ticagrelor is a reversible P2Y12 blocker, with platelet function returning to normal 2–3 days after discontinuation (compared with 5–10 days after discontinuation of clopidogrel and prasugrel).[30] As a result, while non-CABG-related bleeding might be increased with ticagrelor compared with clopidogrel because of its greater potency, such episodes might paradoxically be more manageable after discontinuation of ticagrelor than of clopidogrel. The reversibility of ticagrelor is even more crucial in mitigating bleeding after CABG, and facilitates the performance of surgery sooner after drug discontinuation, which explains the trend toward less non-CABG-related bleeding with ticagrelor than with clopidogrel. As such, there is no net difference in overall major or life-threatening bleeding between the two agents, despite ticagrelor's greater potency. According to the above, bleeding in the ticagrelor arm was more manageable and the "window of vulnerability" for bleeding very shorter after discontinuation of ticagrelor than of clopidogrel, a fact that led to less blood loss. It is most possible that the avoidance of severe hemorrhagic complications by ticagrelor has allowed the life-preserving benefits of reducing MI and stent thrombosis to emerge. (**b**) By contrast with most other antiplatelets, ticagrelor inhibits adenosine reuptake by red blood cells, an effect that might improve microcirculatory flow and perhaps reduce reperfusion injury in ACS.[31] A potential favorable role for this "off-target" effect cannot be excluded.

According to above mentioned, in an attempt to further reduce the remaining high rate of MACE after stenting despite the standard DAT, three dual antiplatelet strategies emerged. Although these strategies effectively reduced the rate of MI and stent thrombosis, they were associated with an increased rate of bleeding and, except for the combination of ticagrelor and aspirin, did not improve the survival.[8,19,22] However, aside from these DAT strategies in which the increased effectiveness was associated with increased rate of bleeding and, except for ticagrelor, no improvement in survival, some newer promising strategies including three antiplatelet agents have come up.[1] In these strategies, a third antiplatelet agent is added to the standard combination of clopidogrel and aspirin. Of these, the addition of cilostazol to conventional antiplatelet therapy with clopidigrel and aspirin in patients undergoing stenting is a promising regimen reducing both in-hospital and long-term adverse cardiovascular events, including mortality, without any increase in the incidence of major bleeding events. It is interesting that these results are more obvious in patients with high-risk profiles where the DATs including a potent antiplatelet agent, such as prasugrel or ticagrelor, cause more bleeding than in patients with low-risk profiles.[1,32-36] Regarding the addition of an inhibitor of the thrombin-mediated platelet activation to the standard DAT, the available results from two small phase-III preliminary RCTs suggest that this combination can improve clinical outcome without increasing bleeding complications.[1,37-39]

NON-RESPONSIVENESS TO STANDARD DAT WITH CLOPIDOGREL AND ASPIRIN

Although the addition of clopidogrel to aspirin has reduced both short- and long-term incidence of ischemic cardiovascular events related to PCI, the risk of recurrent events remains a major issue in a significant percentage of patients during long-term follow-up.[2,3] Enhanced platelet reactivity, non-responsiveness to any of the currently used antiplatelets, or non-compliance to antiplatelet therapy may underlie the increased rate of adverse cardiovascular events after coronary stenting.[1] In the case of confirmed non-adequate inhibition of platelet aggregation despite the use of recommended dosage of the standard DAT, certain solutions have been suggested.

They include (a) the use of higher doses of clopidogrel, (b) the replacement of clopidogrel in the standard DAT combination of "clopidogrel plus aspirin" with another more potent and improved antiplatelet agent such as prasugrel, ticagrelor, or elinogrel, and (c) the addition a third antiplatelet agent in the standard DAT such as cilostazol or a thrombin receptor blocker (triple antiplatelet therapy [TAT]). Among them, certain solutions have been investigated in RCTs and definite results have been concluded. Others, however, are yet under investigation.

Of the above regimens, prolonged combination of prasugrel[8,9] or higher maintenance doses of clopidogrel[1,19] with aspirin is better than the standard DAT at preventing myocardial infarction (MI) and stent thrombosis in patients with an ACS undergoing PCI. However, proportional to their potency, these oral regimens increase hemorrhagic complications,[1,8,19] the occurrence of which has been strongly linked to subsequent mortality.[1,25-29] As a result, neither of these two thienopyridines has been shown to improve survival in patients who underwent PCI for ACSs.

Ticagrelor is another oral antiplatelet agent. This is a non-thienopyridine P2Y12 antagonist, which like prasugrel is more potent and rapid-acting than clopidogrel. However, ticagrelor reversibly binds to the P2Y12 platelet receptors and inhibits adenosine reuptake by red blood cells, an effect that might improve microcirculatory flow and perhaps reduce reperfusion injury in ACSs.[1] These two characteristics represent the most important advantages of ticagrelor over clopidogrel and prasugrel. In the PLATO trial, this agent was compared with clopidogrel in more than 18 500 patients with ACSs.[21,22] Like prasugrel in TRITON trial, ticagrelor compared with clopidogrel significantly reduced rates of MI and stent thrombosis, accompanied by an increase in major non-CABGS-related bleeding. In contrast to prasugrel, however, ticagrelor compared with clopidogrel significantly reduced all-cause mortality at 12 months both in all patients and in those patients undergoing an early invasive strategy.[21,22]

Accordingly, these newer antiplatelet regimens including higher maintenance doses of clopidogrel, prasugrel or ticagrelor over aspirin compared with standard DAT can effectively reduce rates of MI and stent thrombosis during follow-up of high-risk CAD patients undergoing an invasive therapy, but they are accompanied by an increase in bleeding rates and, except for ticagrelor plus aspirin, do not reduce mortality.[1,8,9,19,21,22] Moreover, although each one of these three therapies significantly reduces the incidence of MACE compared with standard DAT, the treatment failure rates of these three newer options of DAT continue to remain high during long-term follow-up (e.g., treatment failure rate ~10% in the TRITON trial).[8,9] However, the explanation for the high rate of DAT failure remains a critical unresolved and under-investigated issue. Therefore, the challenge remains to develop therapies that more effectively inhibit platelet activation and have a beneficial net effect on mortality without increasing bleeding complications. This topic, however, will be discussed in the next chapter dealing with the addition of a third antiplatelet agent in the standard DAT such as cilostazol or a thrombin receptor blocker.

TRIPLE ANTIPLATELET THERAPY

Clinical manifestations of atherothrombotic disease are major causes of mortality and morbidity worldwide. Platelet activation and aggregation are ultimately responsible for the progression and clinical presentations of atherothrombotic disease. The current standard of care, dual oral antiplatelet therapy with aspirin and the P2Y12 ADP receptor inhibitor clopidogrel, has been shown to improve outcomes in patients with atherothrombotic disease.[2-4,8,9] However, aspirin and P2Y12 inhibitors target the thromboxane A2 and the ADP P2Y12 platelet activation pathways and minimally affect other pathways, while agonists such as thrombin, considered to be the most potent platelet activator, continue to stimulate platelet activation and thrombosis.[1] This may help explain why patients continue to experience recurrent ischemic events despite receiving such therapy. Furthermore, aspirin and P2Y12 receptor antagonists are associated with bleeding risk, as the pathways they inhibit are critical for hemostasis.[2-4,8,9,19] The challenge remains to develop therapies that more effectively inhibit platelet activation without increasing bleeding complications. At present, two promising antiplatelet agents seem to meet this challenge, an inhibitor of the endogenous phosphodiesterase (PDE) activity and an inhibitor of the protease-activated receptor-1 (PAR-1) for thrombin.[1]

CILOSTAZOL

Cilostazol is a quinolone derivative that inhibits the PDE3 enzyme in both platelet and vascular smooth muscle cells similar to dipyridamole, thus increasing cAMP levels. It is believed that this property may be important in explaining the enhancement of platelet inhibition when added to clopidogrel and aspirin therapy. It has been shown that cilostazol treatment has antiproliferative effects on vascular smooth muscle cells and reduces the rate of hyperplasia after balloon angioplasty and BMS implantation compared with aspirin and thienopyridines. In addition, cilostazol has an additive inhibitory effect on platelet p-selectin expression when administered with aspirin and clopidogrel therapy.[1] The addition of cilostazol to standard antiplatelet therapy with one or two other antiplatelets has recently proved out promising as regards enhancement of platelet inhibition and improvement of clinical outcomes without any increase in bleeding.[32-36] According to available studies, cilostazol plus

aspirin is comparable to clopidogrel or ticlopidine plus aspirin in the prevention of 30-day major cardiac events after coronary stenting.[1] Thus, it was proposed that cilostazol can be used as an alternative to thienopyridine therapy to prevent short-term post-stenting complications, including stent thrombosis. In addition to these, subsequent studies compared a triple antiplatelet therapy (TAT) – consisting of cilostazol, clopidogrel and aspirin – with DAT including standard or higher doses of clopidogrel. Their results are summarized as follows: (a) TAT compared with DAT is associated with greater inhibition of ADP-induced platelet aggregation and a lower prevalence of low responsiveness; (b) TAT in patients with AMI undergoing coronary stenting results in a greater antiplatelet effect at 30 days as compared with a high-maintenance dose clopidogrel or standard DAT; (c) adjunctive cilostazol to standard DAT in patients with high post-treatment platelet reactivity undergoing coronary stenting significantly reduces the rate of this high reactivity and intensifies platelet inhibition as compared with a high-maintenance dose clopidogrel of 150 mg/day plus aspirin; (d) TAT significantly reduces late loss at 6 months after DES implantation and the occurrence of target lesion revascularization (TLR) and major adverse cardiac events in patients with long coronary lesions compared with DAT; (e) TAT after DES implantation decreases angiographic restenosis and extent of late loss, resulting in a reduced risk of 9-month TLR compared with DAT in diabetic patients; (f) adding cilostazol at least for 1 month to conventional DAT compared with DAT in STEMI patients undergoing primary PCI is associated with a significantly lower in-hospital and 8-month cardiac death but a similar incidence of major bleeding events, and effectively reduces the 8-month incidence of cardiac death, total death, and total major adverse cardiac events, specifically in older (> 65 years of age), female, and diabetic patients; and (g) TAT compared with DAT in ACS patients undergoing stenting is associated with a significantly lower incidence of the long-term cardiac and cerebral events but similar bleeding events, specifically for patients with high-risk profiles. According to the above, the addition of cilostazol to conventional antiplatelet therapy with one or two other antiplatelets in patients undergoing stenting is a promising regimen reducing both in-hospital and long-term adverse cardiovascular events, including mortality, without any increase in the incidence of major bleeding events, specifically in patients with high-risk profiles. At this time, however, cilostazol is approved by the FDA only for treatment of intermittent claudication.[1-32-36]

INHIBITORS OF PAR-1

The inhibition of the PAR-1 for thrombin has been shown to inhibit thrombin-mediated platelet activation without increasing bleeding in pre-clinical models and small-scale clinical trials. PAR-1 inhibition in fact does not interfere with thrombin-dependent fibrin generation and coagulation, which are essential for hemostasis.[1] Thus PAR-1 antagonism coupled with existing dual oral antiplatelet therapy may potentially offer more comprehensive platelet inhibition without the liability of increased bleeding. Two oral thrombin receptor antagonists are currently in clinical trials for the treatment and prevention of arterial thrombosis, SCH 530348 and E-5555. Regarding SCH 530348, two phase-III preliminary RCTs are available. Their results are summarized as follows: (a) oral SCH 530348 added to standard-of-care [aspirin, ticlopidine, and heparin] compared with standard-of-care in Japanese subjects with NSTE ACS undergoing urgent PCI significantly reduced the incidence of periprocedural MI [by 60%; p=0.013] and it was not associated with any other MACE or death and did not result in excess bleeding both in-hospital and during the 60-day follow-up; [37] and (b) oral SCH 530348 administered concomitantly with aspirin and clopidogrel was generally well tolerated and did not cause increased TIMI bleeding compared with standard DAT in CAD patients undergoing non-urgent PCI.[38] These results suggested that SCH 530348 is a potent and selective PAR-1 antagonist that does not impact bleeding, provided preliminary evidence for the feasibility and safety of thrombin receptor inhibition among patients with CAD undergoing PCI, and supported further clinical evaluation. Large phase-III clinical trials designed to assess the efficacy and safety of SCH 530348 in patients with high-risk ACS receiving the full complement of antithrombotic treatment (TRACER) and in the setting of high-risk secondary prevention (TRA 2P−TIMI 50) are currently underway. As regards E-5555, this is another, newer thrombin receptor inhibitor undergoing investigation. Dose-dependent inhibition of thrombin-induced platelet aggregation by this agent has been demonstrated in healthy volunteers. More than 80% inhibition of thrombin-induced platelet aggregation was achieved by single doses of ≥50 mg. Nearly complete inhibition of thrombin-induced platelet aggregation was achieved at drug steady state after repeated administration of 100- and 200-mg doses. There were no significant adverse effects or effects on ADP-induced platelet aggregation, coagulation, or bleeding time associated with E5555 administration. Two phase-II clinical trials assessing safety, tolerability, and the effect on intravascular inflammation and thrombosis in patients with CAD and with ACS, respectively, are being undertaken. [1,39]

CONCURRENT DAT AND ORAL ANTICOAGULANT ADMINISTRATION

Bleeding risk in patients who need treatment with DAT as well as an anticoagulant such as warfarin is a growing problem, specifically in the context of the aging population.[7] DAT (aspirin plus a thienopyridine, usually clopidogrel) is given routinely in the treatment of ACS and after coronary

stent deployment. On the other hand, anticoagulant therapy might be indicated for stroke prevention in a variety of conditions that include atrial fibrillation (AF) and profound left ventricular dysfunction as well as after mechanical prosthetic heart valve replacement. Triple antithrombotic therapy may be needed when a patient has multiple diseases, the most common situations being patients with AF and/or mechanical prosthetic heart valves who also have CAD and require a stent. This is a growing problem in the context of the aging population. Both AF and the need for prosthetic heart valves rise with age and so does the risk of falling, which further increases bleeding risk. ACS is very common, and given the increasingly widespread use of DES (for which DAT is recommended for at least one year), the significant bleeding hazards associated with triple antithrombotic therapy is a real issue, which will become worse in the future.[7]

Before committing a patient to triple therapy for an indefinite period, the physician should carefully consider alternative approaches. For example, in patients who require long-term oral anticoagulation who are undergoing stenting, serious consideration should be given to the use of BMS, for which dual antiplatelet treatment is recommended for a shorter time. And for AF patients, thought should be given to left atrial appendage occlusion devices or pulmonary vein ablation that could avoid the need for long-term warfarin. For patients needing a heart valve, the new On-X valve should be considered; it has lower warfarin requirements than other valves. New valve technology such as this will help immensely to reduce levels of anticoagulation needed.[7,40-42]

BALANCING THE NEED FOR TREATMENT WITH THE BLEEDING RISK

Patients who are treated with triple therapy present significant clinical challenges because of the imperative to balance bleeding risks against the risk of stopping one of the therapies. Unfortunately, the published information regarding use of triple antithrombotic therapy is very limited. Thus, concrete recommendations are difficult.

Data that are available suggest that up to 21% of patients receiving triple antithrombotic therapy need a transfusion (a figure that might increase with longer treatment durations), and the relative risk of major bleeding is three- to fivefold higher than in patients receiving DAT alone. But this is confounded by the fact that patients receiving triple therapy are typically older and have multiple comorbidities, which might increase bleeding potential. Short-term use of triple therapy (for one month) is associated with at least a two-fold lower risk of major bleeding compared with prolonged use (more than six months). But patients receiving DAT only after PCI (prolonged warfarin interruption) have a three-fold increase in stroke or thromboembolic events, compared with patients receiving triple therapy or warfarin plus a single antiplatelet agent.[7,43,44]

KEEP ASPIRIN DOSE AND INTERNATIONAL NORMALIZED RATIO (INR) LOW

For patients receiving triple therapy, expert's advice is that the dose of aspirin should be kept as low as possible (75 to 81 mg), clopidogrel should be given at its standard dose of 75 mg/day, and warfarin should be administered under tight control to achieve a slightly lower target INR of 2.0 to 2.5. They also suggest that proton-pump inhibitors (PPIs) should be considered as prophylaxis against gastric bleeds.[7,43,44]

The issue of using PPIs with clopidogrel has been fraught with controversy as it is thought that there may be an interaction between these agents. The latest consensus of experts is that there is no good evidence that events are increased when PPIs are given with clopidogrel. The studies suggesting increased events are confounded. Many physicians do give PPIs as prophylaxis to patients on triple antithrombotic therapy, but they tend to use pantoprazole and esomeprazole, which have the least incriminating data regarding an interaction with clopidogrel.[43,44]

PCI IN PATIENTS TAKING WARFARIN

In patients on warfarin who need PCI, it is suggested that it may be better to choose a BMS and commit the patient to a short course of clopidogrel, rather than to an extended course of triple therapy. It is recommended that BMS should be considered for use in target vessels less likely to benefit from DES (for example, vessels >3 mm in diameter, short lesions <15 mm, and de novo stenoses). Clopidogrel regimens as short as two to four weeks have been reported to offer adequate protection from early stent thrombosis with BMS, but current guidelines recommend approximately three to six months of triple therapy, after which patients may continue on aspirin and warfarin alone. DES use and acceptance therefore the increased risk of bleeding should be reserved for very high-risk lesions. For patients with high bleeding risk treated with a DES, it is advised that triple therapy may be limited to three to six months, with warfarin plus clopidogrel and a prophylactic PPI continued thereafter.[7,26,43,44]

HOW TO COPE WITH BLEEDING

Bleeding on triple therapy is a particularly difficult problem. Severe or life-threatening bleeding usually requires re-

versal of warfarin therapy and, in some cases, platelet transfusions to counteract clopidogrel therapy. If DAT requires urgent discontinuation, the patient should be closely monitored for the risk of stent thrombosis. In patients with mild or moderate bleeding, every effort should be made to maintain the INR as close to 2.0 as possible, and the aspirin dose should be kept at <100 mg. If bleeding persists, it is advised that aspirin be discontinued first, as clopidogrel seems to be more important than aspirin in preventing stent thrombosis after PCI.[7,26,43,44]

NEW DRUGS AND STENT DESIGNS

All these uncertainties will be further compounded by the imminent arrival on the market of new anticoagulant and antiplatelet drugs and new stent designs.

The factor Xa antagonists, rivaroxaban (Xarelto) and apixaban, as well as direct thrombin inhibitors, such as dabigatran (Pradaxa), which might replace warfarin, also dramatically increase bleeding risk when combined with aspirin plus clopidogrel and so may not much help patients requiring triple therapy.

The new antiplatelet drug prasugrel is more potent than clopidogrel and associated with higher bleeding rates and so is not likely to be suitable for use in combination with warfarin. However, the newer compound **AZD 6140** (ticagrelor [Brilinta]) is shorter acting and reversible, which might be advantageous when used in patients who also require warfarin. The new under-investigation protease-activated receptor 1 (PAR-1) antagonist **SCH 530348** has shown promising results in preliminary trials, with no increase in bleeding yet seen. If this drug becomes clinically available, it may replace clopidogrel in patients who require warfarin, giving a modified triple combination that might have an improved safety profile. Finally, the cyclooxygenase inhibitor triflusal is potentially associated with lower bleeding risk and has been demonstrated as safe and effective in combination with warfarin in patients with atrial fibrillation and so could prove useful in patients requiring oral anticoagulation and undergoing PCI, but randomized studies are needed.[21,22,32-39]

In addition, new stents are being introduced with thinner struts and polymer coatings, which are thought to be associated with better endothelialization and less vascular inflammation than previous DESs. And another new generation of stents that employ bioabsorbable polymers or are designed to capture circulating endothelial precursor cells to promote vascular healing is in development, and the hope is that these stents could be less subject to late thrombosis and might require shorter durations of dual antiplatelet therapy.[7,43,44]

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