Dual antiplatelet therapy: optimal timing, management, and duration

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Platelet activation and aggregability play a key role in the genesis of arterial thrombus secondary to plaque rupture. For coronary patients, inhibition of platelet function is crucial to decrease the rate of major adverse cardiac events but may expose them to excess bleeding risk. Switching P2Y12 inhibitors is common, yet the clinical consequences are unknown. The aim of this review is to provide an overview of the evidence from randomized, clinical trials and epidemiological studies, with a focus on the optimal duration of dual antiplatelet therapy (DAPT) and appropriate agent and dose selection. The report discusses the latest evidence regarding switching therapies during DAPT, the potential benefits of a personalized strategy, management of the preoperative period, and other clinical perspectives in this complex and rapidly changing field. Ongoing trials will be useful to answer to some important unresolved questions.

Keywords
Dual antiplatelet therapy • Acute coronary syndrome • Stents • Optimal duration

Introduction

Percutaneous coronary intervention (PCI) with stenting is one of the most common vascular procedures for the treatment of coronary artery disease and its use is increasing worldwide. The main complications following stent implantation are in-stent restenosis and stent thrombosis, which can be fatal.

Placement of a bare-metal stent (BMS) immediately triggers a sequence of pathological changes: thrombus formation, inflammation, smooth muscle cell proliferation and migration, and tissue remodelling, which can progress to restenosis.1 Drug-eluting stents (DES) reduce neointimal proliferation and restenosis though suppression of smooth muscle cell proliferation and migration.1 Drug-eluting stents have lower rates of restenosis and target vessel revascularization than BMS, but they have a slightly higher propensity for very late stent thrombosis (> 1 year), due in part to delayed vessel healing and polymer hypersensitivity.2,3

In view of the evidence demonstrating their greater efficacy in preventing restenosis and recurrent ischaemia, DES are the preferred option in eligible acute coronary syndrome (ACS) patients.4–6 Guidelines recommend dual antiplatelet therapy (DAPT) comprising aspirin plus an oral P2Y12 adenosine diphosphate-receptor blocker following DES implantation, for the prevention of stent thrombosis.4–6 Whereas aspirin treatment should be administered indefinitely,4–6 the optimal duration for DAPT is unknown, and remains the subject of intense debate. We review here the published evidence for DAPT following coronary stenting and look to future trials that we hope will, in time, inform clinical practice.

Randomized trial evidence on antiplatelet therapies

Dual antiplatelet therapy with P2Y12 inhibitors plus aspirin after coronary stenting

The benefits of extended treatment with DAPT vs. aspirin after coronary stenting are clear. In the CREDO trial,7 patients with stable angina pectoris or non-ST-elevation myocardial infarction (NSTEMI) were randomized to receive clopidogrel or placebo after stenting, in addition to aspirin. At 1 year, clopidogrel was associated with a 26.9% (P = 0.02) relative reduction in death, myocardial infarction, or stroke, with a trend towards a higher risk of major bleeding (P = 0.07). In the CURE trial,8 patients with NSTE-ACS were randomized to clopidogrel or placebo for 3–12 months, on
top of aspirin therapy. Clopidogrel reduced the incidence of cardiovascular death or non-fatal myocardial infarction (9.3 vs. 11.4%, P < 0.001), but increased the risk of major bleeding (P = 0.001). In the subgroup of ACS patients who underwent PCI, long-term administration of clopidogrel in addition to aspirin was associated with lower rates of cardiovascular death, myocardial infarction, or any revascularization (P = 0.03).9

Later trials compared more potent P2Y12 inhibitor therapies. In the TRITON-TIMI 38 trial,10 moderate-to-high-risk ACS patients undergoing PCI were randomized to prasugrel or clopidogrel for 6–15 months in addition to aspirin. While the incidence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke was lower with prasugrel (P < 0.001), the risk of bleeding was greater (P = 0.03).

In the PLATO trial, > 18 000 ACS patients were randomized to ticagrelor or clopidogrel on top of aspirin for 6–12 months.11 The incidence of cardiovascular death, myocardial infarction, or stroke at 12 months was lower with ticagrelor vs. clopidogrel (9.0 vs. 10.7%, P = 0.0025), with no difference in the rates of total (P = 0.88) or severe (P = 0.38) bleeding according to the PLATO definitions, but with an excess of TIMI major bleeding complications.12

**Optimal duration of dual antiplatelet therapy**

**American and European guidelines: is there consensus?**

Patients with an ACS are recommended to receive DAPT for 6–12 months after the event and for up to 12 months after DES placement according to European guidelines,4,5 and for 12 months or longer according to US guidelines18,31 (Table 1). European guidelines recommend aspirin plus either prasugrel or ticagrelor over aspirin plus clopidogrel in ACS patients undergoing stenting,3 whereas US guidelines offer no preference for the type of thienopyridine.6

In the revascularized population, the risk of stent thrombosis following BMS implantation is greatest during the first 30 days. Consequently, both European and US guidelines recommend DAPT for ≥1 month following BMS implantation in stable coronary artery disease, but for longer in an ACS (Table 1).13

Recommendations regarding DAPT duration following DES implantation are less consistent. The US guidelines currently recommend a minimum duration of 12 months of DAPT (on the basis of limited data),7 whereas European guidelines recommend 6–12 months of DAPT.4,5

New-generation DES have improved safety profiles relative to their earlier counterparts and may not require extension of DAPT up to 12 months (Table 2).14–21 Consequently, the optimal duration of DAPT after stenting continues to be investigated. It may also be device specific,22 potentially further complicating the issue.

**Short duration of dual antiplatelet therapy: lessons from randomized trials**

The results from trials investigating shorter durations of DAPT were consistent, showing that a shorter duration may be sufficient to prevent ischaemic events after DES implantation.14–17 The studies are, however, inconsistent in terms of the types of stents used and the durations of DAPT examined, and were underpowered for low-frequency endpoints such as stent thrombosis. Consequently, the findings require confirmation in meta-analyses or other large-scale, all-comer randomized trials with long clinical follow-up.

**Extended duration of dual antiplatelet therapy: lessons from randomized trials**

The results from a pooled analysis from the REAL-LATE and ZEST-LATE24 trials suggest that > 12 months of DAPT is no more effective than aspirin alone in reducing the rate of myocardial infarction or cardiac death patients with a DES. This finding was confirmed by a recent publication from the DES-LATE trial,19 which involved patients who had received 12 months of DAPT without complications. A further 24 months of DAPT vs. aspirin did not reduce the risk of cardiac death, myocardial infarction, or stroke 24 months after randomization, with no difference major bleeding (Table 2).

To date, the largest amount of data on DAPT after coronary stenting comes from the DAPT trial, which was powered to determine whether prolonged DAPT (2.5 vs. 1 year) improves late outcomes by reducing stent-related and non-stent-related cardiovascular events.20 A total of 9961 patients with a DES who had received DAPT for 1 year and were without ischaemic or bleeding complications were randomized to a further 18 months of DAPT or placebo. Extended duration of DAPT reduced the rates of stent thrombosis (P < 0.001) and major adverse cardiovascular and cerebrovascular events (P < 0.001) up to 30 months vs. placebo. The rate of moderate or severe bleeding was, however, increased with extended DAPT (P = 0.001) (Table 2). The data from this trial are limited to patients without an ischaemic or bleeding event during the 12 months after DES implantation and who were fully compliant with the DAPT regimen, thus limiting the generalizability of the findings. Whether these results will help to define clinical practice remains to be determined.

Results were published recently for the double-blind PEGASUS-TIMI 54 study, in which > 21 000 stable patients were randomized 1–3 years after an initial myocardial infarction to ticagrelor 60 or 90 mg twice daily or placebo on a background of low-dose aspirin.25 Both ticagrelor doses reduced, vs. placebo, the rate of the primary efficacy endpoint, with Kaplan–Meier rates at 3 years of 7.85% (ticagrelor 90 mg), 7.77% (ticagrelor 60 mg), and 9.04% (placebo group) (hazard ratio for 90 mg of ticagrelor vs. placebo, 0.85; 95% confidence interval [CI], 0.75–0.96; P = 0.008; hazard ratio for 60 mg of ticagrelor vs. placebo, 0.84; 95% CI, 0.74–0.95; P = 0.004). These benefits were partially counterbalanced by an increase in TIMI major bleeding with ticagrelor (2.60% with 90 mg, 2.30% with 60 mg) vs. placebo (1.06%) (both P < 0.001), with similar rates of intracranial haemorrhage or fatal bleeding. Full evaluation of the data is ongoing to determine which high-risk ischaemic subgroups have a significant net clinical benefit (e.g. diabetes, polyvascular disease), and, conversely, in which subgroups prolonged DAPT is unnecessary, indeed deleterious.

**Lessons from observational studies**

**Risk of late stent thrombosis**

Concerns about the risk of late stent thrombosis were raised in 2006 in an analysis from the SCAAR registry.26 In a recent analysis from the
same registry, involving 7 years of data from 177 448 patients, DES were associated with significantly lower rates of stent thrombosis at 12 months, but with higher rates beyond 12 months, which concur with their earlier findings. However, the adjusted relative risk of stent thrombosis between 1 and 5 years was greater with the older-generation DES relative to BMS (1.81; 95% CI 1.44–2.28, \( P < 0.001 \)), whereas that for new-generation DES was not different. These contemporary observational data indicate that new-generation DES have very low rates of stent thrombosis, which appear to be maintained over the long term.

**Duration of dual antiplatelet therapy**

Landmark analyses from the Duke Heart Registry suggested that extended treatment with clopidogrel was associated with a lower risk of death, or death/myocardial infarction, in patients with a DES, whereas no such association was present in patients with a BMS.27

The SWEDHEART investigators investigated long-term DAPT in 56 440 ACS patients receiving newer-generation DES.28 Dual antiplatelet therapy taken for > 3 months was associated with a lower risk of all-cause death, reinfarction, or ischaemic/non-ischaemic stroke (\( P = 0.0042 \)), which was also significant in the group that underwent revascularization (\( P < 0.0001 \)). Similar results were observed for the 6-month regimen. While the number of bleeding events was small, the risk of bleeding was increased in the group who received > 3 months of DAPT treatment (\( P = 0.0018 \)) but not in those who underwent revascularization.28 These data suggest that DAPT exceeding 3 months after the index event is associated with a lower risk of death, reinfarction, or stroke.

The North American National Heart, Lung, and Blood Institute Dynamic Registry conducted 1- and 2-year landmark analyses in 3130 patients who received one or more DES and were discharged on DAPT. The results indicated a significant benefit for the combined 4-year rate of death or myocardial infarction associated with continued use of DAPT vs. discontinuation at 12 or 24 months.29 These results are in agreement with CREDO7 and PCI-CURE8, which showed a benefit to 1 year of treatment with clopidogrel following PCI. In contrast, a landmark analysis from the observational \( \gamma \)-Cypher registry, conducted in Japanese patients, did not demonstrate any clinical benefit of DAPT exceeding 6 months after sirolimus-eluting stent implantation.30 However, the authors cautioned that these data may not be applicable outside of Japan.

### Table 1 Guidelines on antiplatelet therapy after coronary stenting

<table>
<thead>
<tr>
<th>Condition</th>
<th>European guidelines4,34</th>
<th>US guidelines6,35</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stable coronary artery disease</strong></td>
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<tr>
<td>DAPT (P2Y12 inhibitor plus aspirin) ≥ 1 month (class IA) 6 months (class IB) with new-generation DES</td>
<td>Clopidogrel 75 mg/day for &gt; 1 month and ideally up to 12 months in patients not at high risk of bleeding (class IB)6</td>
<td>Clopidogrel 75 mg/day for ≥ 12 months in patients not at high risk of bleeding (class IB)6</td>
</tr>
<tr>
<td>Aspirin Lifelong single antiplatelet therapy (usually aspirin 75–100 mg/day) (class IA)</td>
<td></td>
<td>Aspirin 81–325 mg/day indefinitely (class IA)</td>
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<tr>
<td><strong>Non-ST-elevation myocardial infarction</strong></td>
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<tr>
<td>DAPT (P2Y12 inhibitor plus aspirin)</td>
<td></td>
<td>≥ 12 months (prasugrel, ticagrelor, clopidogrel) (class IB)6,35</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Aspirin 75–100 mg/day long term (class IA)3,34</td>
<td>Aspirin 81–325 mg/day indefinitely (class IA)6,35</td>
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<tr>
<td><strong>ST-elevation myocardial infarction</strong></td>
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<tr>
<td>DAPT (P2Y12 inhibitor plus aspirin) 1–12 months (prasugrel or ticagrelor) (class IC)6 6–12 months (prasugrel or ticagrelor) (class IB)6</td>
<td>≥ 12 months (prasugrel, ticagrelor, clopidogrel) (class IB)6</td>
<td></td>
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<tr>
<td>Aspirin Aspirin 75–100 mg/day indefinitely (class IA)6</td>
<td></td>
<td>Aspirin continued indefinitely (class IA)6</td>
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<tr>
<td><strong>Primary PCI in ST-elevation myocardial infarction</strong></td>
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<tr>
<td>DAPT (P2Y12 inhibitor plus aspirin) 12 months (prasugrel, ticagrelor, clopidogrel only when prasugrel or ticagrelor are not available or are contraindicated) (class IA)6</td>
<td>≥ 12 months (prasugrel, ticagrelor, clopidogrel) (class IB)6</td>
<td></td>
</tr>
<tr>
<td>Aspirin Aspirin 75–100 mg/day indefinitely (class IA)6</td>
<td></td>
<td>Aspirin continued indefinitely (class IA)6</td>
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<tr>
<td><strong>Other considerations</strong></td>
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<tr>
<td>DAPT may be used for more than 6 months in patients at high ischaemic risk and low bleeding risk (class IIb, C)4</td>
<td>In patients at bleeding risk, earlier discontinuation is reasonable (class IIa, C)6</td>
<td>Continuation of DAPT beyond 12 months may be considered (class IIb, C)6</td>
</tr>
</tbody>
</table>
Switching during dual antiplatelet therapy with P2Y<sub>12</sub> inhibitors

Switching from prasugrel to clopidogrel is relatively frequent within the recommended 1-year duration of treatment, even during the in-hospital phase. In a large registry, switching from clopidogrel to prasugrel was associated with high-risk angiographic characteristics, reinfarction in-hospital, and private health insurance coverage. Conversely, older age, previous cerebrovascular event, in-hospital coronary artery bypass grafting, in-hospital bleeding, and warfarin use at discharge were associated with switching from prasugrel to clopidogrel. No data are available on the clinical consequences of switching these therapies. In a recent study, early switching from prasugrel 10 mg to clopidogrel 75 mg in patients with low on-treatment platelet reactivity reduced the risk of minor bleeding events but unmasked a group of non-responders to clopidogrel (from 0% before to 29% after the switch), with unknown consequences in terms of ischaemic events.

Switching from ticagrelor to prasugrel in patients with stable coronary disease was evaluated in the pharmacodynamic SWAP-2 study: compared with continued ticagrelor therapy, switching to prasugrel was associated with an increase in platelet reactivity that was partially mitigated by the administration of a loading dose, with unknown clinical consequences.

The personalized strategy of dosing P2Y<sub>12</sub> inhibitors in dual antiplatelet therapy

The optimal dose of aspirin (75–100 mg daily) is well established and recommended in all international guidelines. There is, however, a grey zone regarding the optimal dose of P2Y<sub>12</sub> inhibitors, and the ‘one size fits all’ approach has been challenged. In the FEATHER trial, low-dose prasugrel (5 mg) provided a similar level of platelet inhibition in low-body-weight patients as prasugrel 10 mg in higher body weight patients. In the PRASFIT trials, low-dose prasugrel (3.75 mg maintenance dose) demonstrated a reduction in ischaemic events vs. clopidogrel (300 mg loading dose/75 mg maintenance dose), with no excess of bleeding. Definitive conclusions cannot be drawn, however, because both studies were underpowered. In the ANTARTIC-trial, the risks and benefits of low-dose prasugrel (5 mg) were evaluated in a fragile elderly population. A low maintenance dose of ticagrelor (60 mg bid) was tested in combination with aspirin in the PEGASUS-TIMI 54 trial, and DAPT with higher dose ticagrelor (90 mg bid) in the PLATO trial.

Lowering the dose of P2Y<sub>12</sub> inhibitors or removing aspirin are new management approaches under evaluation (e.g. GLOBAL LEADERS trial [NCT01813435]), with the aim of reducing bleeding while maintaining optimal protection against ischaemia.

The concept of personalized treatment, based on assessment of platelet reactivity with bedside monitoring assays and genotyping...
with rapid genetic testing platforms, has been the subject of much debate. High platelet reactivity is well established as an independent predictor of increased cardiovascular events. The factors related to variability of response to clopidogrel can be broadly divided into four categories: environmental, cellular, clinical, and genetic. Genetic variability in drug absorption and metabolism is a key factor responsible for the inefficient generation of the active drug metabolite. The two-step hepatic CYP-dependent oxidative metabolism of the prodrug appears to be particularly important. Pharmacogenomic analyses have identified loss-of-function variant alleles of CYP2C19 to be the predominant genetic mediators of the antiplatelet effect of clopidogrel. Several trials have assessed whether this risk factor is modifiable, improving clinical outcome with adjustment of P2Y12 antagonist therapy in patients with a poor metabolic response. The data so far have been neutral: the TRIGGER PCI trial randomized patients with stable coronary artery disease after PCI and with high platelet reactivity to prasugrel 10 mg daily or clopidogrel 75 mg daily; the trial was discontinued due to the low event rate. The GRAVITAS trial followed, and examined the efficacy of double-dose clopidogrel (150 mg daily) in a similar low-risk post-PCI population. This personalized strategy did not affect clinical outcome, which may have been related to the inadequate treatment of high platelet reactivity by double-dose clopidogrel and methodological bias. Finally, the randomized ARCTIC trial included a higher-risk population, tested for both aspirin and clopidogrel resistance, and offered several treatments for high platelet reactivity, with follow-up platelet function testing to ensure adequate response. Despite this trial design, there was no statistical difference in incidence of cardiovascular events between the monitoring vs. conventional treatment arms, but there was a trend towards a lower risk of bleeding events. No benefits of the genotype analysis were observed in the prespecified ARCTIC-gene study. The genetic clopidogrel profile was a good marker of platelet function response but was unrelated to clinical outcome. Genetic information appears to add little to the pharmacodynamic information. However, ongoing studies (RAPID MANAGE [NCT02044146], TAILOR-PCI [NCT01742117]) using genetic testing to adjust antiplatelet therapy are being performed to evaluate the potential benefits of this strategy. In view of these results, platelet function monitoring and genetic testing cannot be recommended routinely in the general PCI population or, at least, patients with stable coronary disease may not benefit from a platelet function test. However, platelet function monitoring may play a role in selected groups (e.g. with stent thrombosis or bleeding events), and further research is needed on platelet function testing, especially in ACS patients. We await the results of the ANTARCTIC trial, which is evaluating the value of a platelet function test in the elderly population with ACS, with a focus on bleeding events.

Preoperative management of dual antiplatelet therapy in clinical practice

One important issue that arises in is how to manage patients on DAPT who are referred for surgical intervention. The approach chosen depends on the urgency of the procedure and the patient’s bleeding and thrombotic risks. Where feasible, elective, non-urgent surgery should be delayed until after completion of the recommended course of DAPT. Aspirin treatment should continue, if possible, during the procedure. If surgery cannot be delayed, a shorter duration of DAPT may be considered. In cardiacl-stable or asymptomatic patients undergoing non-urgent, non-cardiac surgery, a minimum of 1 month (ideally 3 months for BMS and 6 months for new-generation DES) of DAPT may be acceptable for patients in whom surgery cannot be delayed further. In patients undergoing non-emergency major surgery with high-to-very-high bleeding risk, guidelines recommend discontinuation of clopidogrel or ticagrelor 5 days and prasugrel for 7 days before surgery, while continuing treatment with aspirin. In high-risk patients, these guidelines recommend continuation of P2Y12 inhibitor therapy during coronary artery bypass graft surgery, while taking care to minimize the risk of bleeding. In patients at very high bleeding risk, discontinuation of DAPT before surgery and the use of bridging therapies may be appropriate, with resumption of DAPT (including loading doses of thienopyridines) as early as possible after surgery. Low-molecular-weight heparin or unfractionated heparin in place of DAPT is not recommended.

Perspectives

Important questions remain in several fields of cardiovascular disease. What is the best strategy in the case of concomitant ACS and atrial fibrillation? What is the optimal long-term strategy in very high-risk patients (e.g. with multivessel coronary disease, polyarterial disease, or chronic kidney disease)? What is the precise role of non-vitamin K antagonist oral anticoagulant drugs, in addition to the new antiplatelet agents? What are the potential benefits of switching DAPT with P2Y12 inhibitors? The findings of ongoing and future trials will help to answer these questions.

Conclusions

Optimal individualized management of DAPT remains challenging. Ongoing trials will provide useful information about prolonged duration of DAPT in high-risk patients, with evaluation of the net clinical benefit in large subgroups, to optimize the management of antithrombotic drugs and help clinicians’ decisions.

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