Duration of dual antiplatelet therapy after coronary artery stenting: where is the sweet spot between ischaemia and bleeding?

Ronald K. Binder and Thomas F. Lüscher*

Editorial Office, European Heart Journal, Zurich Heart House, Careum Campus, Moussonstreet 4, Zurich 8091, Switzerland

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Permanent or transient intraluminal scaffolding of coronary arteries achieved by currently available stents effectively lowers the rate of acute vessel occlusion, persistent dissection, and restenosis. The latter complication is further reduced by local anti-proliferative drug delivery (drug eluting stent, DES), albeit delaying vascular healing with complete re-endothelialization. Blood exposed to foreign bodies may clot, which in case of coronary stent struts increases the risk of vascular occlusion (i.e. stent thrombosis, ST), myocardial infarction, and death. As ST is associated with high mortality, it is a feared complication of percutaneous coronary intervention (PCI).

Dual antiplatelet therapy

Anti-thrombotic therapy effectively reduces blood clotting and is mandatory during and after PCI. Platelet activation and aggregation on the stent surface is the main mechanism leading to ST. Pharmacological inactivation of the enzyme cyclooxygenase by its acetylation by acetylsalicylic acid (Aspirin) and concomitant blockade of the P2Y12 receptor on the platelet surface by reversible or irreversible receptor antagonists (e.g. clopidogrel, ticagrelor, or prasugrel) effectively reduces platelet aggregation. A combination of these drug classes (i.e. dual antiplatelet therapy, DAPT) has become a cornerstone of post-PCI management and effectively reduces the risk of ST.

Stable coronary artery disease

After the roll-out of the first-generation DES (CYPHER® and TAXUS™), an increased incidence of late and very late ST was observed in comparison with bare metal stents. At the same time, there was no evidence available from randomized controlled trials (RCTs) defining the optimal duration of DAPT after DES implantation. Therefore, an arbitrary recommendation for 12 months DAPT after DES implantation was issued by guideline committees. In the meantime evidence has accumulated suggesting that in stable coronary artery disease (sCAD) the duration of DAPT after DES implantation may be shortened without an increased risk of ischaemic events (Figure 1). Therefore, the European Society of Cardiology’s Guideline on Stable Coronary Disease changed the default recommendation to 6 months DAPT after DES implantation in sCAD.

Acute coronary syndromes

After an acute coronary syndrome (ACS) patients are at increased risk for further ischaemic events in comparison with patients undergoing PCI for sCAD. This is attributed to an increased inflammatory state and higher vulnerable plaque burden prone to rupture. Therefore, mainly based on the CURE trials, the recommended duration of 12 months DAPT after an ACS remained unchanged irrespective of treatment modality (conservative, PCI, or surgical revascularization).

Novel evidence

Recently, the largest RCT in this field—the DAPT-trial—was published and reheated the debate on the optimal duration of DAPT. In this study, more than 9000 patients after coronary stent implantation were randomized to receive either 12 or 30 months of DAPT. The combined primary endpoint of death, myocardial infarction, or stroke was significantly decreased with 30 months in comparison with 12 months DAPT (4.3 vs. 5.9%, P = 0.001). About half of the reduction in the primary endpoint was not attributed to a lower rate of ST (0.4 vs. 1.4%, P < 0.001), but to a reduced incidence of spontaneous myocardial infarction in patients taking 30 months DAPT. This was unrelated to the previous PCI involving the culprit artery, but rather reflected events in other coronary segments and hence the natural history of coronary atherosclerosis. However, moderate or severe bleeding was significantly increased with prolonged DAPT (2.5 vs. 1.6%, P = 0.001) and, surprisingly, all-cause mortality was slightly, but significantly increased with prolonged DAPT (2.3 vs. 1.8%, P = 0.04). However, the latter difference was
mainly attributed to a higher rate of cancer deaths in the 30 months DAPT group. In the light of an absolute bleeding increase of 0.9% compared with an absolute risk reduction in the primary endpoint of 1.6%, the net clinical benefit of 30 months over 12 months DAPT overall seems marginal.

**Stent types and dual antiplatelet therapy**

The trial reminds us that there are distinct phases of DAPT: first the prevention of ST and second the reduction of coronary syndromes unrelated to previous PCIs. The former is important before complete endothelialization of the stent struts, a process that differs substantially between different stent types and possibly also patients. The most benefit from prolonged DAPT was observed in patients receiving a first-generation TAXUS™ stent, while those receiving an everolimus eluting stent do not appear to have advantage from prolonged platelet inhibition. Indeed, during the first years after implantation of a first-generation DES the cumulative incidence of ST does not level off.8 In contrast, most likely due to the improved biocompatibility and decreased thrombogenicity of newer generation DES, ST are a rare event beyond the first year after implantation.22 Although the evidence is not solid yet, the mandatory duration of DAPT for the prevention of ST after stent implantation may be as low as 6, 3, or even 1 month depending on stent generation and procedural and patient factors (Table 1). On the other hand, prolongation of DAPT...
beyond 1 year may be beneficial in patients at increased risk for disease progression or very late ST.

**Rebound after dual antiplatelet therapy cessation?**

Then there appears a third phase after stent implantation: DAPT withdrawal. Particularly in the DAPT trial, a striking rise in events was noted within the first 3 months of DAPT cessation, suggesting a sort of rebound phenomenon. Whether DAPT-cessation unmasks patients with incomplete stent endothelialization or vulnerable plaques or whether there is a true rebound effect with increased platelet aggregability after DAPT withdrawal, remains to be determined.

**Individualized dual antiplatelet therapy management**

The flip-side of anti-thrombotic therapy is an increased bleeding risk. While prolongation of DAPT duration reduces ischaemic events, the rate of bleeding increases with prolonged DAPT, particularly beyond 12 months (Figure 2). Thus, the thousand dollar question is: Where is the sweet spot between ischaemia and bleeding? Every patient has a unique risk of bleeding, ST or disease progression (Table 1 and 2). In the light of current evidence there is no ‘one-size-fits-all’ strategy for DAPT duration after DES placement in sCAD as such an approach does not consider the patient’s individual risk. Currently, there is no validated score for the long-term prediction of bleeding risk and of ischaemic events after DES placement. However, as clinicians, we can estimate this risk based on certain factors (Table 1 and 2). For

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**Table 2** Long-term risk factors for bleeding after percutaneous coronary intervention

<table>
<thead>
<tr>
<th>Procedural factors</th>
<th>Patient characteristics</th>
<th>Pharmacological factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term risk factors</td>
<td>Age</td>
<td>Prolonged dual antiplatelet therapy</td>
</tr>
<tr>
<td>Femoral access, Large sheath size</td>
<td>History of bleeding, Low body weight</td>
<td>Concomitant use of oral anticoagulation</td>
</tr>
<tr>
<td>No vascular closure device</td>
<td>Acute coronary syndrome</td>
<td></td>
</tr>
<tr>
<td>Long-term risk factors</td>
<td>Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>Gastrointestinal disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Impaired kidney function</td>
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<tr>
<td></td>
<td>Liver disease</td>
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<tr>
<td></td>
<td>Cerebrovascular accident</td>
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<td></td>
<td>Malignancy</td>
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**Figure 2** Rates of bleeding are consistently higher for prolonged DAPT, reaching statistical significance in some studies (DAPT, dual antiplatelet therapy).
in those at increased ischaemic risk. An open question is when to decide on the optimal DAPT duration for an individual patient. In current practice, this is mostly done at the time of stent implantation. However, all relevant information on individual ischaemic and bleeding risk may not be available during PCI and it may be more prudent to take the decision of DAPT duration during follow-up when the mandatory first DAPT phase is completed. This would parallel the DAPT trial in which patients were randomized 12 months after PCI, if they had not experienced a major adverse cardiovascular or cerebrovascular event, repeat revascularization, or moderate or severe bleeding while on DAPT. Finally, there may be a patient subgroup which benefits from indefinite DAPT. Although a recent meta-analysis found an increased mortality—driven by non-cardiovascular death—in patients taking more than 12 months DAPT, this may not apply to selected patients at high ischaemic and low bleeding risk. Indeed, in the CHARISMA-trial patients with a history of myocardial infarction had improved outcomes with long-term DAPT compared with Aspirin monotherapy. Moreover, the recently presented PEGASUS-TIMI 54 trial investigating long-term DAPT with ticagrelor on top of Aspirin monotherapy in patients with a history of remote myocardial infarction, found a significant reduction of the composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke with prolonged DAPT. The role of long-term DAPT as well as of Aspirin monotherapy will be further challenged by the ongoing GLOBAL LEADERS trial (NCT 01813435), which investigates ticagrelor monotherapy vs. DAPT.

Meanwhile, the changing landscape of scientific evidence and guideline recommendations encourages anti-thrombotic management based on individual risk assessment and careful clinical judgment.

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