A brief history of dual antiplatelet therapy (DAPT)

DAPT using aspirin and a P2Y\textsubscript{12} platelet ADP receptor blocker has been established since more than 20 years as the pharmacological background of percutaneous coronary intervention (PCI) and post-acute coronary syndrome (ACS) (Table 1). First, the combination of aspirin and ticlopidine given for 30 days has shown superiority over aspirin and anticoagulant therapy in patients undergoing coronary artery stenting (1). Subsequently, in the landmark CURE study, DAPT using aspirin and clopidogrel (the so-called 2\textsuperscript{nd} generation P2Y\textsubscript{12} receptor blocker, devoid of the myelotoxicity of ticlopidine) given for a median duration of 9 months (maximum 12 months) has shown superiority over aspirin alone in patients with non-ST elevation ACS (2). Finally, two “3\textsuperscript{rd} generation” P2Y\textsubscript{12} blockers, prasugrel and ticagrelor, more powerful and predictable in antiplatelet effect as compared to clopidogrel, showed superiority over clopidogrel as adjunct to aspirin across the ACS spectrum. The two trials validating these new agents had a duration of about 12 months (3,4), reinforcing (though not necessarily confirming, due to the missing aspirin-only arm) the CURE study standard. Following these studies, practice Guidelines have recommended, and maintained indefinitely, to start DAPT at the time of index ACS using the 3\textsuperscript{rd} generation P2Y\textsubscript{12} blockers, and to continue this treatment for 12 months. However, the duration of DAPT has become matter of debate for years, and even the subject of specific Guidelines on both sides of the Atlantic (5,6).

Longer or shorter duration of DAPT?

In recent years, several important studies have tackled the CURE-derived concept of 12-month DAPT, many of them testing shorter duration, and some testing longer duration of therapy (6). This trial-based controversy has also been the subject of metanalyses (7,8). Implicit in its mode of action, there is no doubt that, compared to aspirin alone, DAPT significantly increases the risk of bleeding, particularly gastrointestinal, and especially in elderly patients. This increased risk persists indefinitely and unpredictably (9): although some bleeding risk scores have been developed and validated, they have been endorsed with moderate enthusiasm by practice Guidelines, with a grade IIb recommendation (6). Prolonging DAPT has systematically been shown to increase significantly the risk of major nonfatal bleeding (10). On the other hand, due to the well-known protective effect of antiplatelet therapy in secondary prevention of ischemic heart disease (11), prolonging DAPT has actually been shown to reduce the risk of MI and stroke, but had no effect on overall or cardiovascular mortality (10). Therefore, current guidelines...
are very prudent (grade IIb, LoE A) in recommending prolongation of DAPT after the 12-month standard, stating that “P2Y₁₂ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischemic and bleeding risk of the patient” (12). However, for most clinicians, and for many reasons, the real issue has now become “how short can we make DAPT after a PCI-treated ACS?”

The changing landscape of ACS and PCI

Over the last 15 years, the routine coronary interventional approach to ACS, based on timely myocardial reperfusion in STEMI, and early aggressive treatment in NSTEMI, has improved outcomes across the ACS spectrum in both sexes and at all ages, including elderly patients (13,14). The increasing operator expertise in stent-lesion matching, and the continuous improvement in stent technology, raise questions about the current validity of the 15-year old standard of 12-month DAPT. Perhaps, also the ubiquitous use of high-dose statins starting from an ACS episode has also contributed to plaque stabilization and improved post-acute outcomes. A further reason for shortening DAPT duration is the increasing number of elderly patients being treated with PCI during an ACS, and the additional fact that almost 10% of the ACS population has atrial fibrillation (15), with the associated need of long-term oral anticoagulant therapy in adjunct to DAPT (6).

The concept of stage-adapted DAPT

Post-hoc analyses of the classical post-ACS DAPT studies have shown that most of the reduction in ischemic recurrences after an ACS was observed within the first four weeks of treatment (16), but major bleeding events continued to accrue throughout the year (17,18). These observations led to conceive a first phase with an elevated risk of recurrent thrombotic events, followed by a second phase where the risk of bleeding complications outweighs the ischemic risk. The ischemic phase would require a potent platelet inhibition, using 3rd generation P2Y₁₂ blockers, whereas, during the secondary phase, the degree of platelet inhibition could be reduced (by stepping down to clopidogrel) to optimize the balance between ischemic benefit and bleeding risk. A few studies have been completed in the last year (Table 2). It is remarkable that all these studies, focusing the post-acute phase of ACS, had an extremely low ischemic event rate at one year, highlighting the above mentioned current post-ACS landscape.

The TOPIC study

The single center TOPIC study (19) conducted in Marseille, France, investigated the impact of switching from aspirin plus a 3rd generation P2Y₁₂ blocker to a combination of aspirin and clopidogrel one month after ACS. 646 pts were enrolled over 25 months, at the remarkable pace of 26 pts per month, which means an all-comer study. Patients were enrolled across the ACS spectrum, including those with unstable angina and negative troponin. All patients had undergone PCI during index admission, and drug eluting stents were used in 91% of the cases. At discharge, 43% of the patients were on ticagrelor, and 57% on prasugrel. Randomization took place at one month in patients with

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**Table 1 Generations of orally active P2Y₁₂ platelet ADP receptor blockers and pivotal trials in Acute Coronary Syndromes and Percutaneous Coronary Interventions**

<table>
<thead>
<tr>
<th>Generation, drug</th>
<th>Pivotal trials (ref)</th>
<th>Duration</th>
<th>Ischemic events (HR, 95% CI)*</th>
<th>Bleeding events (HR, 95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st generation, ticlopidine</td>
<td>ISAR (1) Ticlopidine + aspirin vs. VKA + aspirin</td>
<td>30 days</td>
<td>0.25, 0.06–0.77</td>
<td>0.00, 0.00–0.19</td>
</tr>
<tr>
<td>2nd generation, clopidogrel</td>
<td>CURE (2) Clopidogrel + aspirin vs. aspirin alone</td>
<td>3–12 months (median 9 months)</td>
<td>0.80, 0.72–0.90</td>
<td>1.38, 1.13–1.67</td>
</tr>
<tr>
<td>3rd generation, prasugrel</td>
<td>TRITON-TIMI 38 (3), Prasugrel + aspirin vs. Clopidogrel + aspirin</td>
<td>6–15 months (median 14.5 months)</td>
<td>0.81, 0.73–0.90</td>
<td>1.32, 1.03–1.68</td>
</tr>
<tr>
<td>3rd generation ticagrelor</td>
<td>PLATO (4) Ticagrelor + aspirin vs. clopidogrel + aspirin</td>
<td>6–15 months (median 9 months)</td>
<td>0.84, 0.77–0.92</td>
<td>1.25, 1.03–1.53</td>
</tr>
</tbody>
</table>

* HR<1 favours experimental group, VKA, vitamin K antagonist.
no events during the first month. At 1 year, the allocated DAPT regimen was still used by 86% of 322 patients in the switched DAPT group and 75% of 323 patients in the unchanged DAPT group (P<0.01): the main reasons for drug change in both groups were ischemic or bleeding events, need for surgery or need for triple therapy, adding an anticoagulant for atrial fibrillation. The primary aggregate endpoint of cardiovascular death, urgent coronary revascularization, stroke, and Bleeding Academic Research Consortium (BARC) episodes \( \geq 2 \) at 12 months occurred in 43 (13.4%) patients in the switched DAPT group and in 85 (26.3%) patients in the unchanged DAPT (HR 0.48, 95% CI, 0.34–0.68, P<0.01). No significant differences were reported in ischemic endpoints, while BARC \( \geq 2 \) bleeding occurred in 13 (4.0%) patients in the switched DAPT and in 48 (14.9%) in the unchanged DAPT group (HR, 0.30, 95% CI, 0.18–0.50, P<0.01). Although the study was not powered to discriminate individual ischemic endpoints, all of them were lower in the switching therapy group, and all relevant subgroups showed the same trend.

### Table 2 Recent trials of “stage-adapted” P2Y\(_{12}\) receptor blockade in ACS-PCI

<table>
<thead>
<tr>
<th>Study (ref)</th>
<th>Initial P2Y(_{12}) blocker</th>
<th>Time of switch</th>
<th>Mode of switch</th>
<th>Ischemic events (HR, 95% CI)*</th>
<th>Bleeding events (HR, 95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOPIC (19)</td>
<td>Prasugrel or ticagrelor</td>
<td>30 days</td>
<td>Random</td>
<td>0.80, 0.50–1.29</td>
<td>0.30, 0.18–0.50</td>
</tr>
<tr>
<td>TROPICAL ACS (20)</td>
<td>Prasugrel</td>
<td>15 days</td>
<td>Based upon PFT results</td>
<td>0.77, 0.50–1.21</td>
<td>0.82, 0.59–2.13</td>
</tr>
<tr>
<td>ANTARCTIC (21)</td>
<td>Prasugrel 5 mg</td>
<td>15 days</td>
<td>Based upon PFT results</td>
<td>1.06, 0.69–1.62</td>
<td>1.04, 0.68–1.40</td>
</tr>
</tbody>
</table>

ANTARCTIC enrolled patients aged \( \geq 75 \) years. *, HR<1 favours switched group. PCI, percutaneous coronary intervention; ACS, acute coronary syndrome; PFT, platelet function testing.

### The TROPICAL ACS study

A more complex approach has been used by the TROPICAL ACS Investigators (20) in a multicenter study enrolling 2,610 patients at 33 Centers in Europe. All patients had biomarker-positive ACS with successful PCI and a planned treatment with DAPT for 12 months. Enrolled patients were randomised to either standard treatment with prasugrel for 12 months or a stepdown regimen (1-week prasugrel followed by 1-week clopidogrel and PFT-guided maintenance therapy with clopidogrel or prasugrel from day 14 after hospital discharge; guided de-escalation group). The Multiplate analyser (Roche Diagnostics, Rotkreuz, Switzerland) was used for testing. A status of high platelet reactivity (HPR) was defined based on the results of previous studies and the consensus documents of the Working Group on HPR as an ADP test aggregation value of 46 units or higher on the Multiplate analyser (22). In the guided de-escalation group, testing results determined the further course of treatment: patients with HPR were immediately switched back to prasugrel (511 out of 1,304 patients, 39% of the intention-to-treat population), while those without HPR continued on clopidogrel. Analysis was intention to treat but, differently from the TOPIC study, de-escalation to clopidogrel actually happened in only 61% of the experimental group. The primary endpoint was the net clinical outcome of cardiovascular death, MI, stroke or bleeding grade \( \geq 2 \) according to BARC criteria at 1 year. This endpoint occurred in 95 patients (7%) in the guided de-escalation group and in 118 patients (9%) in the control group (HR, 0.81; 95% CI, 0.62–1.06; \( P_{\text{non-inferiority}}=0.0004, P_{\text{superiority}}=0.12 \)). Neither the ischemic (3% vs. 3%), nor the bleeding events (5% vs. 6%) were different in the two groups.

### The ANTARCTIC study in patients aged \( \geq 75 \) years

A platelet function testing approach to allow safe downgrading of antiplatelet therapy was also followed in the ANTARCTIC study (21). Elderly patients have been shown to display high on-clopidogrel platelet reactivity (23), but are also at elevated risk of bleeding events. Therefore, fine tuning of antiplatelet therapy would seem ideal. In this study done at 35 Centers in France, 877 patients aged \( \geq 75 \) years, who had undergone coronary stenting for ACS, were randomly assigned to receive prasugrel 5 mg daily with dose or drug adjustment in case of inadequate response (monitoring group), or prasugrel 5 mg daily with no monitoring or treatment adjustment.
(conventional group). Platelet function testing was done 14 days after randomisation and repeated 14 days after treatment adjustment in patients in the monitoring group. In the monitoring group, 45% of the patients had their P2Y₁₂ blocker adjusted based on the results of platelet function test: in those with high platelet reactivity (≥208 P2Y₁₂ reaction units) the prasugrel dose was increased to 10 mg. In patients with low platelet reactivity (≤85 P2Y₁₂ reaction units) prasugrel 5 mg was replaced with clopidogrel 75 mg, with subsequent checks after a further 14 days. The primary endpoint (a composite of cardiovascular death, MI, stroke, stent thrombosis, urgent revascularisation, and BARC-defined bleeding types 2, 3, or 5 at 12 months) occurred in 28% of the patients in the monitoring group, and 28% in the conventional group (HR, 1.003, 95% CI, 0.78–1.29; P=0.98). No trends between groups were observed in the rates of ischemic or bleeding events.

The above mentioned three studies (Table 2) followed different approaches for adapting DAPT intensity to the different stages of ACS follow-up. The TOPIC study followed a lean approach to reducing P2Y₁₂ intensity, simply shifting from a 3rd generation blocker to clopidogrel, and showed clearcut results, at least in terms of reduced bleeding, in favor of downgrading the intensity of platelet inhibition after 1 month of powerful platelet inhibition. On the other hand, the TROPICAL ACS and the ANTARCTIC studies, led by experts in platelet function testing, made a more complicated attempt to adjust P2Y₁₂ therapy guided by the on-treatment platelet reactivity displayed by the patients after the downgrading (TROPICAL ACS) or after two weeks of the initial drug (ANTARCTIC). The results of these studies, if not powered to definitely reduce to one month after ACS the duration of intense platelet inhibition, should at least further discourage the clinician to use platelet function testing for adapting treatment to disease stage or patient risk.

Conclusions

The so far recommended 12-month course of DAPT after an ACS, explicitly using the powerful 3rd generation P2Y₁₂ receptor blockers reflects a time of ACS treatment which is more than 10 years old. As described in the present editorial, a lot has changed in recent years with regard to PCI safety and patient population being treated with PCI in the acute phase. Shorter or stage-adapted DAPT has clearly shown benefit in terms of reduced bleeding. Larger studies powered to clearly establish the safety of early de-escalation in terms of ischemic events would be welcome. It is unlikely that such studies will be funded by the pharmaceutical industry.

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Footnote

Conflicts of Interest: Dr Savonitto reports consultancy fees from Eli Lilly, Daiichi-Sankyo, Astra-Zeneca, Bristol Meyers Squibb, and Bayer. The other authors have no conflicts of interest to declare.

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