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Reflections after TWILIGHT study: a new era in secondary prevention without aspirin?

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Dual antiplatelet therapy (DAPT) is mandatory in patients undergoing percutaneous coronary interventions (PCIs), but carries an increased bleeding risk which must be weighed over the expected antithrombotic benefit. In recent years, DAPT optimization strategy has been enriched by the concept of early withdrawal of aspirin ('aspirin-free' strategy). This strategy is supported by the modern advancements in pharmacological and procedural fields (i.e. the availability of P2Y12 receptor inhibitors with a concomitant 'aspirin-like' effect), the advocated use of pharmacological non-antiplatelet secondary prevention strategies (i.e. angiotensin-converting enzyme inhibitor, statins, beta-blockers), the use of modern stents and the increasingly widespread use of intra-coronary imaging techniques. In the last few years, five clinical trials (GLOBAL LEADERS, TWILIGHT, STOP-DAPT2, SMART CHOICE, TICO) and their own meta-analysis have been followed, aiming to evaluate the efficacy and safety of different 'aspirin-free' strategies. They showed that aspirin withdrawal (1–3 months after PCI), determines a consistent reduction of bleeding risk, without compromising efficacy endpoints. It resulted in a class IIa indication in the 2020 European Society of Cardiology Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation, which suggested the early withdrawal of aspirin in patients undergoing PCI and considered to be at low ischaemic and low bleeding risk, or at high bleeding risk.

Introduction

Dual antiplatelet therapy (DAPT), which consists of aspirin and a P2Y12 receptor inhibitor, is the strategy of choice in patients undergoing percutaneous coronary intervention (PCI). Most recent European guidelines recommend its use for 6 months after PCI in the context of a chronic coronary syndrome (CCS) and for at least 12 months after the diagnosis of an acute coronary syndrome (ACS).[1] However, the optimal duration of DAPT is still debated. Despite indisputable benefits in terms of ischaemic protection, each DAPT regimen is burdened by an increased bleeding risk.[2] The need to balance ischaemic and bleeding risks has therefore raised the idea of tailoring DAPT duration, abandoning the 'one-size-fits-all' principle and embracing the early discontinuation of one of the two antiplatelet drugs strategy. In particular, the first attempt was obtained through the early withdrawal of the P2Y12 receptor inhibitor, aiming to reduce the temporal exposure to DAPT; on the other hand, an early aspirin withdrawal has been proposed. The rationale behind both strategies is based on better medical and procedural background, marked by notable advances in pharmacological and procedural fields (e.g. the introduction of more potent P2Y12 inhibitors, the evolution of non-antiplatelet secondary prevention pharmacological strategies, the introduction of safer stents and the increasingly widespread use of intra-coronary imaging techniques to optimize PCI outcomes and reduce ischaemic risk).

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The concept of short dual antiplatelet therapy

Shortening of DAPT by early withdrawal of P2Y12 inhibitor has been tested in several clinical trials. These studies have generally demonstrated the non-inferiority of this approach when compared with a longer duration of DAPT (i.e. standard DAPT), but their small sample size does not allow firm conclusions on safety and efficacy. A meta-analysis of these studies, which increases the statistical power of comparison, supported the absence of significant adverse effects related to ischaemic outcomes with short DAPT.[3] Therefore, in the context of PCI performed in CCS patients considered at high bleeding risk (defined by the presence of a high bleeding risk score, such as a PRECISE-DAPT score $>$ 25 points) or at very high bleeding risk, current guidelines allow for shortening DAPT regimen to 3 months (indication of class IIa, level of evidence A) or 1 month (indication of class IIb, level of evidence B), respectively.[4] On the other hand, for ACS patients undergoing PCI and considered to be at high or very high bleeding risk, most recent guidelines suggest aspirin discontinuation after 3–6 months, based on a careful balance between ischaemic and bleeding risks (class IIa indication, level of evidence A). In particular, in patients with high bleeding risk (i.e. PRECISE DAPT score $>$ 25 point or the presence of specific risk factors), P2Y12 receptor inhibitor withdrawal should be considered after 3 months from PCI (indication of class IIa, level of evidence B).[5]

The 'aspirin-free' strategy

Since the discovery of its antiplatelet effect, aspirin has represented the cornerstone of antiplatelet therapy and the basis for comparison for other drugs from the same class (i.e. clopidogrel, ticagrelor, prasugrel). However, in last years, the field of antiplatelet therapy has been enriched by the concept, theoretically justified and clinically attractive, of early aspirin withdrawal. This approach has been successfully tested for the first time among patients undergoing PCI and diagnosed with atrial fibrillation requiring oral anticoagulant (OAC), in whom bleeding risk was considered prohibitive with the use of triple antithrombotic therapy (introduction of DAPT in addition to the OAC).[6] Three concepts support an 'aspirin-free' strategy (*Figure 1*): (i) the evidence that aspirin increases the risk of intracranial and extracranial bleedings (mostly gastro-intestinal bleedings), especially when administered in combination with other antiplatelet drugs; (ii) the availability of modern and more potent P2Y12 receptor inhibitors, which may not benefit from aspirin since they already negatively modulates the production of thromboxane-A2 ('aspirin-like' effect); and (iii) the increasing widespread use of beta-blockers, hypoglycaemic, and lipid-lowering therapies, able to decrease the risk of future cardiovascular events, thus reducing the absolute benefit of aspirin in the context of secondary prevention (before the approval of actual well-established secondary prevention therapies, in fact, the effect of aspirin was tested against placebo).[7] Finally, the HOST-EXAM trial, in a head-to-head fashion, compared aspirin with clopidogrel in patients undergoing PCI who had completed a 6–18 month period of DAPT, showing the superiority of clopidogrel over aspirin in terms of efficacy and safety in a long-term secondary prevention setting.[8]

Experimental clinical evidences

In the last years, five randomized clinical trials (*Table 1*) have tested the 'aspirin-free' paradigm in patients who were not candidates to receive oral anticoagulation. The first of these studies (GLOBAL LEADERS) tested, in a cohort of approximately 16 000 patients, aspirin withdrawal after one month of DAPT (aspirin and ticagrelor) and for the following 24 months after PCI, aiming to evaluate the superiority of this strategy over conventional DAPT.[9] The primary outcome, a composite of all-cause death and Q-wave myocardial infarction, was similar in the experimental and control groups [3.81% vs. 4.37%, 95% confidence interval (CI), 0.87 (0.75–1.01), $P = 0.073$]. Class 3 and class 5 bleedings were chosen as the safety endpoint, measured according to the Bleeding Academic Research Consortium (BARC) definition, and have been reported to be similar between the two study arms [2.04% vs. 2.12%, 95% CI, 0.97 (0.78–1.20), $P = 0.77$]. Moreover, the analysis of each components of the primary endpoint did not find statistically significant differences between the two groups. Nevertheless, the *post hoc* analysis showed a benefit for the experimental strategy in ACS patients in terms of numerical reduction of bleedings. Among limitation, the study enrolled patients at relatively low clinical risk, condition that may explain the low event rate and the difficulty in demonstrating differences between experimental and standard strategies. Because of the lack of a central committee for events adjudication, a central event adjudication group was chosen to test, in a small cohort substudy (7585 patients), the non-inferiority first, and the superiority of the experimental strategy over standard DAPT (GLASSY study). Final results showed that the experimental strategy was non-inferior but also not superior in its endpoints (i.e. ischaemic and haemorrhagic). Moreover, the rate of BARC 3 and 5 bleedings was instead identical between the two groups. Although it proved the non-inferiority but not the superiority, the experimental strategy resulted in an overall reduction of ischaemic risk in the first 12 months of treatment in patients undergoing complex PCI, preserving same bleeding risk. As a final consideration, the GLASSY study showed that the group that mostly benefited from experimental strategy in terms of bleeding reduction, was the ACS group, especially during the first 12 months of treatment, as previously emerged in GLOBAL LEADERS.[10]

One year later, the TWILIGHT trial ($n = 7119$) enrolled patients at high ischaemic and bleeding risk assessed on the basis of clinical and angiographic criteria.[11] The study, multicentre and double-blind in its design, aimed to test, over the first year after PCI, the non-inferiority of ticagrelor monotherapy after 3 months of DAPT, compared with 12 months of standard DAPT. Final results showed that the experimental strategy carries a lower bleeding risk [4.0% vs. 7.1%, hazard ratio (HR) 0.56; $P > 0.001$], without

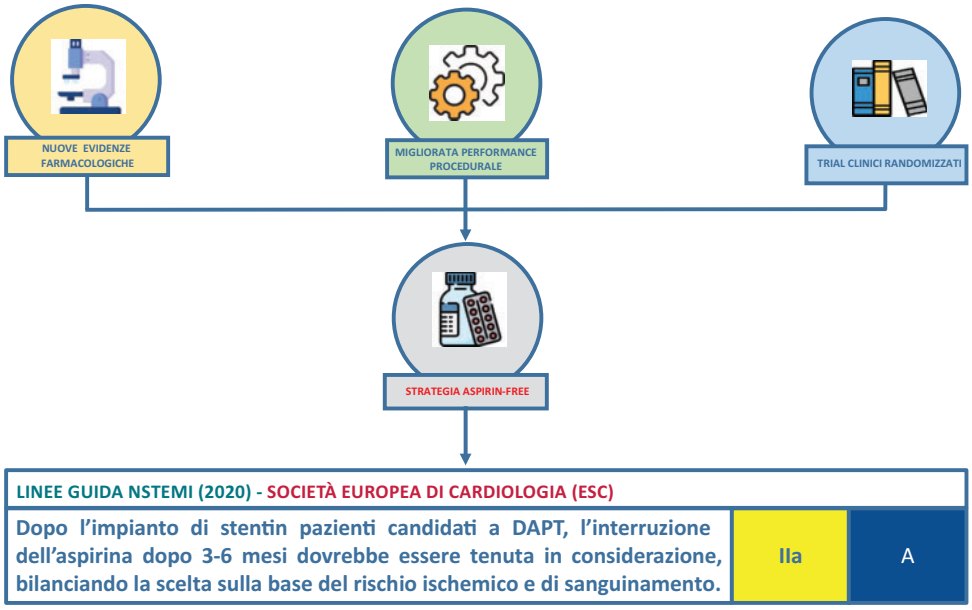

Figure 1 Graphical representation of the rationale behind the 'aspirin-free' strategy. The 'aspirin-free' strategy is based on three key concepts. The first is about the pharmacological evidence that P2Y12 receptor inhibitors have also an aspirin-like effect, acting through the inhibition of thromboxane-A2. The second concept concerns the improvement of procedural performances through the use of improved stent platforms with a reduced thrombogenic microenvironment along with the increased use of intra-coronary imaging techniques. Finally, five clinical randomized trials have evaluated the applicability of specific 'aspirin-free' strategies, and their meta-analysis has shown that discontinuation of aspirin at 1–3 months results in a consistent reduction of bleedings, without affecting efficacy endpoints. To date, a class IIa indication, reserved for a specific group of patients (low ischaemic and bleeding risk or high bleeding risk), has been proposed in the most recent guidelines for the management of acute coronary syndromes without ST-segment elevation, published in 2020 by the European Society of Cardiology (ESC).

significant effects on efficacy endpoints, a composite of death from all causes, myocardial infarction and stroke (3.9% vs. 3.9%, $P < 0.001$ of non-inferiority). Through the enrolment of ACS patients in two-thirds of the cases (64.8%), it was possible to evaluate the impact of the 'aspirin-free' strategy in two different clinical scenarios (i.e. ACS and CCS). In particular, despite a similar risk of ischaemic events, the experimental strategy resulted in a lower rate of bleeding in patients diagnosed with ACS compared to patients with CCS (4.8% vs. 6.4%, HR 0.76).

The most recent trial evaluating the impact of ticagrelor monotherapy was TICO.[12] Similar to TWILIGHT in terms of study design, ticagrelor monotherapy (starting after 3 months of DAPT) was compared to 12 months of standard DAPT in 3056 patients. The results showed that the experimental strategy resulted in a reduction in the incidence of adverse clinical events (3.9% vs. 5.9%, HR 0.66, $P = 0.01$). Importantly, the trial enrolled only ACS patients, and among those, 36% were diagnosed with a ST-segment elevation ACS; the secondary analysis showed a statistically significant reduction in bleedings (1.7% vs. 3.0%, HR 0.56, $P = 0.02$) and a similar incidence of ischaemic events in the two groups (2.3% vs. 3.4%).

It should be noted that all of these trials investigated the discontinuation 1–3 months after PCI. Conversely, ASET—a small pilot trial without a control arm—was designed to investigate the effect of immediate withdrawal of aspirin after PCI, demonstrating an encouraging safety profile, worthy of further large-scale trials.[13]

The interest on testing also clopidogrel monotherapy after aspirin withdrawal led to the design of two randomized clinical trials, conducted in Asia, SMART-CHOICE and STOP-DAPT 2.

The first ($n = 2993$ patients) investigated the impact of clopidogrel monotherapy after 3 months of standard DAPT. The results demonstrated that the experimental strategy was non-inferior to the DAPT in terms of all-cause death, myocardial infarction, and stroke (2.9% vs. 2.5%, $P = 0.007$).[14] Again, the bleeding risk appeared lower (2.0% vs. 3.4%, HR 0.58, $P = 0.02$), with consistent results in various subgroups.

The second, STOPDAPT-2, was designed to demonstrate the non-inferiority of clopidogrel monotherapy after 1 month of DAPT.[15] The experimental strategy appeared not only non-inferior but also superior to the conventional one (2.4% vs. 3.7%, HR, 0.64, $P < 0.01$ for non-inferiority; $P = 0.04$ for superiority), with a reduction in the primary endpoint (cardiovascular death, myocardial infarction, verified stent thrombosis, ischaemic or haemorrhagic stroke, major or minor bleeding) at 12 months. Important limitations of the trial were represented by the intention to test clopidogrel monotherapy in patients with low ischaemic risk (due to clinical, angiographic, and ethnic characteristics) and the partial generalizability of results, due to the routinary use of intra-coronary imaging techniques during PCI, in a higher percentage than other cath-laboratories worldwide.

Recently, in a meta-analysis of the five randomized clinical trials described above, O'Donoghue *et al.*, found that discontinuation of aspirin 1–3 months after PCI carries a consistent reduction in the risk of bleeding, even for BARC 3 and 5 bleedings, when compared to DAPT (HR 0.60, 95%

Table 1 Summary table of the five clinical randomized trials that investigated the efficacy and safety of the 'aspirin-free' strategy in patients undergoing percutaneous coronary intervention

	GLOBAL LEADERS	TWILIGHT	TICO	STOP-DAPT 2	SMART CHOICE
Year	2018	2019	2020	2019	2019
Patients (*n*)	15 968	7119	3056	3045	2993
Age (mean, years)	64.6	65.1	61	68.6	64.5
ACS, *n* (%)	6581 (41.2)	4614 (64.8)	3056 (100)	1148 (38.1)	1741 (58.1)
NSTEMI, *n* (%)	3373 (21.1)	2120 (64.8)	1027 (35)	180 (5.9)	469 (15.7)
STEMI, *n* (%)	2092	–	1103 (36)	561 (18.6)	314 (10.5)
Primary endpoint	Death, AMI-Q	Major or minor bleeding episodes	NACE	MACCE + bleeding episodes	MACCE
Treatment (duration of the treatment)	Standard DAPT for 1 month + ticagrelor the following 23 months vs. standard DAPT for 12 months + 12 months of aspirin; (24 months)	Standard DAPT for 3 months + ticagrelor for the following 9 months vs. standard DAPT for 12 months; (12 months)	Standard DAPT for 3 months + ticagrelor for the following 9 vs. standard DAPT for 12 months; (12 months)	Standard DAPT for 1 month + monotherapy with P2Y12 receptor inhibitor for the following 11 months vs. standard DAPT for 12 months; (12 months)	Standard DAPT for 3 months + monotherapy with P2Y12 receptor inhibitor for the following 9 months vs. standard DAPT for 12 months; (12 months)
MACCE (*n*)	–	135 (3.9) vs. 137 (3.9)	3.5 (2.3) vs. 51 (3.4)	29 (1.96) vs. 37 (2.51)	42 (2.9) vs. 36 (2.5)
Death (*n*)	224 (2.91) vs. 253 (3.17)	34 (1.0) vs. 45 (1.3)	16 (1.1) vs. 23 (1.5)	21 (1.42) vs. 18 (1.21)	21 (1.4) vs. 18 (1.2)
Myocardial infarction (*n*)	248 (3.17) vs. 250 (3.13)	95 (2.7) vs. 95 (2.7)	6 (0.4) vs. 11 (0.7)	13 (0.88) vs. 1 (1.75)	11 (0.8) vs. 17 (1.2)
Stent thrombosis (*n*)	64 (0.8) vs. 64 (0.8)	14 (0.4) vs. 19 (0.6)	6 (0.4) vs 4 (0.3)	4 (0.27) vs. 1 (0.07)	3 (0.2) vs. 2 (0.1)
Ischaemic stroke (*n*)	63 (0.79) vs. 68 (0.85)	16 (0.5) vs. 8 (0.2)	5 (0.3) vs. 9 (0.6)	8 (0.54) vs. 15 (1.03)	11 (0.8) vs. 5 (0.3)
Bleeding (*n*)	–[a]	141 (4.0) vs. 250 (7.1)[a]	53 (3.6) vs. 83 (5.5)[b]	6 (0.41) vs. 23 (1.54)[b]	28 (2.0) vs. 49 (3.4)[a]
Major bleeding (*n*)	163 (2.04) vs. 169 (2.12)	34 (1.0) vs. 69 (2.0)	25 (1.7) vs. 45 (3.0)	3 (0.20) vs. 16 (1.07)	12 (0.8) vs. 14 (1.0)

ACS, acute coronary syndrome; AMI-Q, acute myocardial infarction with Q-waves; MACCE, major adverse cardiac and cerebrovascular event; NACE, net adverse clinical event; NSTEMI, non ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

[a]Bleeding Academic Research Consortium Classification (BARC). Major bleeding defined as class 3 and 5 BARC.

[b]Thrombolysis in Myocardial Infarction Classification (TIMI).

CI 0.45–0.79, $P < 0.001$). With regard to efficacy outcomes, discontinuation of aspirin did not lead to an increase in the risk of major adverse cardiovascular events (MACE), all-cause mortality or stroke. Similar results were also observed when the analysis was focused on ACS patients.[16]

Discussion

Although considered for decades the cornerstone of antiplatelet therapy in the immediate post-PCI and in the long term period, aspirin role is currently debated. The evidence that early aspirin withdrawal reduces the risk of bleeding without a clear increase in ischaemic risk, encouraged the applicability of 'aspirin-free' strategies. Nevertheless, the applicability of this therapeutic regimen in real clinical practice has been questioned. In particular: (i) Which is the most indicated P2Y12 receptor inhibitor to use in monotherapy? (ii) Which patient classes (high risk vs. low risk) and clinical scenarios (ACS vs. non-ACS) may benefit most from this approach? (iii) What is the adequate timing of aspirin withdrawal after PCI (immediately after PCI vs. 1 month vs. 3 months)? and (iv) Which is the most appropriate antiplatelet drug for long-term secondary prevention?

Despite the consolidated evidences on ticagrelor and prasugrel preference over clopidogrel in reducing the risk of MACE in ACS patients undergoing PCI, the lack of direct head-to-head comparisons among different P2Y12 receptor inhibitors in the field of 'aspirin-free' strategies, led the optimal drug choice still undetermined. Moreover, no trials have yet tested the effect of prasugrel monotherapy, although it has already obtained a class IB recommendation for its use in ACS patients undergoing PCI.

Questioning the use of clopidogrel monotherapy in the setting of an 'aspirin-free' strategy, any enthusiasm has been contained by the inter-patients variability in terms of response to the molecule, the possible needing for genotypic evaluation or platelet tests to exclude partial or non-response.

As previously mentioned, great efforts have been conducted to ascertain the optimal duration of any 'aspirin-free' strategy. Since there are no substantial data documenting its effect in the long-term period, the question of continuing the same therapy after the first 12 months post-PCI remains unresolved.

In addition, the controversy has been fuelled by the evidence that the experimental arm of TWILIGHT has shown a numerically higher incidence of stroke. In this regard, the documented inhibitory effect of aspirin on collagen reactive peptide pathway could play a decisive role, since it seems to reduce the incidence of ischaemic phenomena in extra-coronary beds. Furthermore, the recognized systemic anti-inflammatory effect of aspirin negatively correlate to extra-coronary atherosclerotic phenomena. These considerations could limit enthusiasm and increase other concerns about the long-term prevention.

Finally, the innovative aspirin formulation, encapsulated in a lipoid structure, reduces its erosive gastric effect, thus favouring the net balance of efficacy and safety. This, along with the previous explained key points, raises great difficulties in abandoning aspirin therapies.

Shifting the focus to the right timing of aspirin withdrawal, the concept that the greatest ischaemic risk occurs in the first weeks and months after PCI has augmented uncertainty on early DAPT discontinuation. The interruption at different temporal levels, attempted in recent randomized clinical trials, also restricts the decision on the timing of interruption. At this purpose, the recently published meta-analysis by Osman *et al.*, highlighted the positive effects of experimental strategies in terms of reduction of MACE, regardless of the timing of the withdrawal.[16]

Based on previous considerations, the applicability of the 'aspirin-free' strategy should not be generalized, and a tailored approach is now advocated. In particular, the low event rates reported in available trials, suggests that the enrolment was focused primarily on low-risk patients. For this reason, these studies and results should be fully reassessed in an external cohort, to adequately test the applicability of any 'aspirin-free' strategy as a standard of care.

Conclusion

The concept of an early aspirin withdrawal after a short period of DAPT is now a matter of debate, encouraged by data from randomized trials that pave the way for this approach. The 'aspirin-free' strategy is currently recommended, as a class IIa indication, by the European guidelines for the management of ACS without ST-segment elevation, subordinating its application to the balance between safety and efficacy.[5] At the moment, it seems to be intended for patients with low ischaemic and bleeding risk, or those at high risk of bleeding. To date, despite the continuous evolution of secondary prevention pharmacological strategies and the refinement of PCI techniques, it is not possible to generalize its use for patients considered at high ischaemic risk and with low haemorrhagic risk, in whom the intensification of antiplatelet therapy represents the strategy of choice.

Conflict of interest: none declared.

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