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De-escalation therapy after acute coronary syndrome: is it reasonable to switch from prasugrel (or ticagrelor) to clopidogrel early?

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Dual antiplatelet treatment (DAPT) is the treatment of choice to prevent atherothrombotic events in patients with acute coronary syndrome (ACS) treated with percutaneous interventions (PCIs). The availability of different P2Y12 inhibitors set the stage for costum made DAPT, as to achieve the highest profile of safety and efficacy. The *de-escalation therapy* for the newer and more powerful antiplatelet drugs, such as ticagrelor and prasugrel, to clopidogrel, is a strategy for patients with recent ACS, unfit for continuing DAPT for their high risk of bleeding, or side effects, or socio-economic reasons, but without a prohibitive ischaemic risk. There is a need for compelling clinical evidences able to provide the clinical cardiologist with the necessary information to decide the best antiplatelet strategy for each individual patient.

Premise

Dual antiplatelet aggregation therapy (DAPT) with aspirin and a platelet P2Y12 receptor inhibitor is the treatment of choice for the prevention of atherothrombotic events in patients with acute coronary syndrome (ACS) undergoing percutaneous angioplasty (PCI).[1] Clopidogrel, prasugrel, and ticagrelor are the most commonly used oral antagonists of this receptor, whereas the use of ticlopidine has now been abandoned. The current guidelines on antiplatelet therapy in cases of ACS support the use of new and more potent anti-aggregation drugs ticagrelor and, in the presence of a known coronary anatomy, prasugrel for 12 months,[2] to the detriment of a greater risk of bleeding than the use of clopidogrel, which, however, still remains widely used in clinical practice. The availability of different P2Y12 receptor inhibitors has made it possible to switch between molecules based on the particular clinical scenario addressed. In particular, de-escalation therapy is a strategy implemented in patients recently suffering from ACS and at short distance from the PCI, which involves the transition from a platelet antagonist of higher potency, to clopidogrel, a safer molecule in terms of bleeding.[3] Among the many factors that can influence the choice of therapeutic switches, we recognize the high-risk profile of the treated subject, the preferences of both the doctor and the patient himself and socio-economic reasons. Based on the results of the most recent randomized clinical trials (RCTs), the latest guidelines of the European Society of Cardiology (ESC) on myocardial revascularization recognize the possibility of de-escalation therapy in those patients deemed unfit to continue DAPT up to the 12th month from the acute event (recommendation Class IIb, Level of evidence B).[2] We, therefore, propose an overview of the properties of the oral drugs that inhibit the platelet P2Y12 receptor currently available (*Table 1*), providing an account of the clinical evidence concerning de-escalation therapy following SCA and analysing in more detail the scenarios in which this strategy is applicable.

Properties of oral platelet receptor inhibitors P2Y12 drugs and evidence from randomized clinical trials

Clopidogrel is a second-generation thienopyridine which selectively and irreversibly inhibits the platelet P2Y12

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Table 1 Pharmacological properties of oral drugs platelet receptor inhibitors P2Y12

	Clopidogrel	Prasugrel	Ticagrelor
Binding to the receptor	Irreversible	Irreversible	Reversible
Pro-drug	Yes	Yes	No
Half-life of the pre-drug/drug	≈6 h	<5 min	6-12 h
Half-life of the active compound	30 min	2-15 h	30 min
Binding site	ADP binding site	ADP binding site	allosteric site
Frequency of administration	Daily	daily	twice daily
Action on-set	2-8 h	30 min-4 h	30 min-4 h
Action off-set	5-10 days	7-10 days	3-5 days
Pharmacologic interaction	CYP2C19	No	CYP3A
Setting for clinical use	ACS, stable CAD, PCI, PAD, ischaemic stroke	ACS with PCI	ACS

ACS, acute coronary syndrome; PAD, peripheral arterial disease; PCI: percutaneous coronary intervention.

receptor responsible for binding to the powerful ADP platelet activator; is a pro-drug absorbed at the intestinal level and largely hydrolysed by a plasma metabolite in carboxylic acid, metabolically inactive. Only 15% of the pro-drug is oxidized to the active metabolite in the liver through two sequential passages in which the cytochromes belonging to the P450 system are involved. The active thiol derivative of clopidogrel reaches its maximum concentration after about 30 min/h from the administration, while the maximum anti-aggregation effect is obtained at about 6 h from an oral load of 300 mg or after about 2-3 h from a load of 600 mg. Contraindications to the administration of the molecule are hypersensitivity to the active ingredient or the presence of active pathological bleeding. The degree of inhibition of platelet aggregation varies considerably from patient to patient, with an average of about 30% of cases with an inadequate response to the drug ('resistance') and a consequent high platelet reactivity (HPR). Among the multiple causes of resistance to clopidogrel, we can recognize the complex metabolism of the drug that determines different concentrations of metabolite reached, which is influenced by genetic polymorphisms of the enzymes involved in the numerous metabolic steps.[1,4]

Prasugrel is a third generation thienopyridine and is, in turn, a pro-drug that needs, following intestinal absorption and ultra-rapid hydrolysis by a plasma esterase, a single cytochrome-mediated oxidative liver passage to be the active metabolite. This metabolite irreversibly binds the binding site of the platelet receptor P2Y12 causing its inactivation. Compared to clopidogrel, prasugrel is characterized by a higher plasma concentration, a longer half-life, less variability in individual response and lower drug interactions, thus presenting a more rapid, powerful and predictable platelet inhibitory effect.[1,4] In the most important RCT of comparison with clopidogrel, this efficacy translated into a clinical setting of ACS treated with PCI, into a significant reduction of ischaemic events at the expense of a significant increase in major bleedings, prevalent in selected subgroups of patients.[1] The current ESC guidelines on myocardial revascularization in ACS, therefore, recognize prasugrel as a Class I recommendation, level of evidence A, in those patients who have been treated with PCI unless they are more than 75 years old, weigh <60 kg or present active pathological bleeding, previous intracranial haemorrhages, previous strokes or transient ischaemic attacks.[2]

Ticagrelor is a non-tieno-pyridine antiaggregant (cyclopentyl-triazol-pyrimidine) that inhibits the platelet receptor of ADP by binding to an independent site of the P2Y12 subunit and determining a conformational change (non-competitive inhibition). The drug does not require metabolic activation by plasma esterase or hepatic isoenzymes, has a reversible receptor binding and a plasma half-life of 6-12 h. Furthermore, the molecule is able to inhibit the re-uptake of adenosine by erythrocytes, determining the known pleiotropic effects, such as dyspnoea. Compared to clopidogrel, ticagrelor has an increased bioavailability, a more rapid pharmacokinetic action and less individual variability which make it a rapid and powerful inhibitor of platelet aggregation; however, reversible receptor binding and short half-life influence a more rapid disappearance of the antiplatelet effect compared to prasugrel.[1,4] The main RCT of comparison with clopidogrel in patients with ACS demonstrated a significant reduction in the primary ischaemic composite endpoint in the absence of significant differences in major bleeding. However, patients treated with ticagrelor showed a worsening trend of major bleeding unrelated to coronary artery bypass grafting (CABG) and intracranial bleeding, even fatal. The current ESC guidelines on myocardial revascularization in SCA have, therefore, assigned ticagrelor a class I recommendation, Level of evidence A, regardless of the initial treatment strategy, unless active pathological bleeding or previous intracranial haemorrhages are present.[2]

Clinical evidence on de-escalation therapy

Despite an increased risk of major bleeding unrelated to CABG, the major RCTs on prasugrel and ticagrelor established a favourable risk-benefit ratio with a number needed to treat of 46 and 53, respectively compared to the number needed to harm of 167 for both the molecules. The current European guidelines, therefore, recommend a duration of DAPT of 12 months in patients undergoing PCI during ACS, possibly limited to 6 months in the event of a high risk of bleeding defined according to approved risk scores (e.g.

PRECISE-DAPT score $\geq$ 25).[2] On the one hand, in fact, the evidence showed a non-negligible increase in the rate of ischaemic events with reduction in the duration of the DAPT after ACS for <6 months, with a progressive reduction of the same starting from 1 month after acute event.[5] On the other hand, in such clinical setting, the bleeding risk presents a constant increase over time,[6] becoming the potential incentive of a therapeutic switch in those patients with a high haemorrhagic risk profile alongside the doctor's or patient's own preferences, in the presence of side effects and socio-economic reasons mainly related to the higher cost of new anti-aggregation drugs and insurance problems. Registry studies indicate a prevalence of de-escalation therapy of 5–14% in intra-hospital stay and 5–8% following discharge, but identifying an association between this strategy and an increased occurrence of events ischaemic at follow-up in the absence of differences in bleeding events.[7]

These findings were largely attributed to the increased platelet reactivity and the rate of HPR shown by pharmaco-dynamic studies, especially in the case of early clopidogrel switches.[8] Several RCTs have therefore been created to investigate the clinical impact of de-escalation therapy in patients undergoing PCI during ACS (*Table 2*). The randomized TOPIC study showed that this strategy is associated with a reduction in bleeding complications, mainly minor, in the absence of differences in ischaemic events, when applied in patients treated with the new P2Y12 receptor inhibitors and event-free 1 month after acute treatment.[9] This benefit was independent of the platelet inhibition state calculated by the VASP reactivity test in the pre-specified sub-analysis of the study called TOPIC-VASP. The latter also recognized a significant reduction in the net primary composite event, driven both by a lower rate of ischaemic and haemorrhagic events, in those patients suffering from low platelet reactivity subjected to therapeutic switch to clopidogrel compared with patients on standard therapy.[10] Sibbing *et al.*[11] randomized patients after PCI for ACS to a standardized prasugrel treatment for 12 months or a de-escalation regimen 1 week after the acute event in the TROPICAL-ACS trial; patients randomized to clopidogrel maintained treatment only in the absence of recognized HPR to the VERIFY-NOW platelet function test performed after 14 days of discharge, otherwise they underwent a switch-back to prasugrel. The study demonstrated comparable results between the two strategies in terms of net clinical benefit at 1-year follow-up from randomization, without differences in ischaemic risk and with a trend in reduction of predominantly minor bleeding events. The PRAGUE-18 trial compared treatment with prasugrel and ticagrelor in SCA at 1 year of follow-up and in case of switch to clopidogrel justified by economic reasons. In addition to confirming the safety of a de-escalation strategy, Motovska *et al.*,[12] however, pointed out that these patients had a lower ischaemic risk profile than those who maintained standard DAPT therapy. Based on the above results, the most recent ESC guidelines recognize the possibility of de-escalation therapy in those patients deemed unfit to continue DAPT until the 12th month after an ACS (recommendation Class IIb, Level of evidence B) (2). However, several authors have highlighted the numerous criticalities of the RCTs taken into consideration such as the low number, definition of the study endpoints, the high percentage of switch-back from clopidogrel towards the new P2Y12 receptor inhibitors, the choice of the de-escalation strategy guided by platelet function tests and the absence of randomization in the PRAGUE-19 trial.[5,13] To date, moreover, no platelet function test is recommended to guide the choice between a standard strategy or switch.[2] Many observational studies have shown that some tests of platelet function identify (albeit with a very low degree of agreement) patients resistant to clopidogrel and that these patients are not effectively protected from major cardiovascular events.[14] However, the randomized clinical evidence available consists exclusively of pharmaco-dynamic studies (e.g. GRAVITAS study, ARTIC study, ANTARTIC study) of inadequate size to be translated into conclusions of clinical impact. These analyses have shown how, despite laboratory tests (ADP-induced platelet aggregation verified through point-of care testing, such as the VerifyNow P2Y12TM test and the VASP-P test) they predict the thrombotic risk of resistant patients, the improvement of the pharmaco-dynamic response induced by high doses of clopidogrel is not associated with a reduction in the incidence of cardiovascular events.[2,15,16]

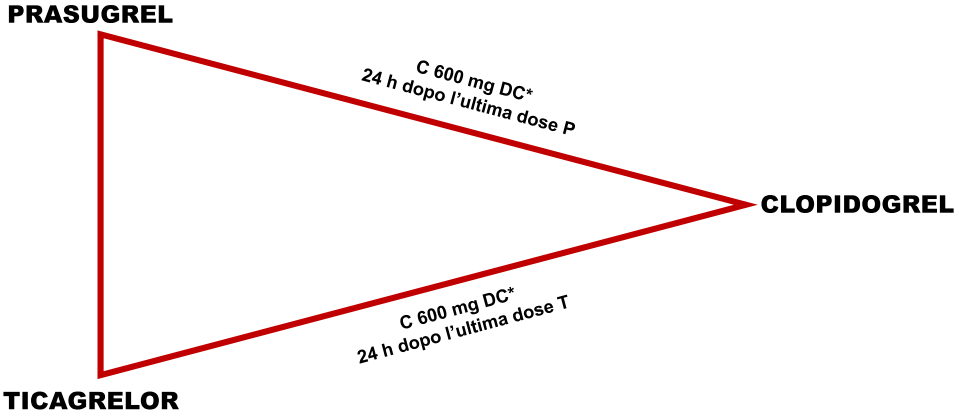
De-escalation therapy: when and how?

In consideration of the non-exhaustive evidence present to date regarding de-escalation therapy, the recommendations of the experts on the subject are limited to advice expressed through consensus documents. Following what is specified in the ESC guidelines, this strategy cannot currently be applied routinely but must be guided by the patient's clinical and angiographic features. It seems reasonable to implement it in those patients deemed unfit to continue DAPT until the twelfth month after ACS (or 6 months if otherwise indicated) characterized by a high haemorrhagic risk profile (e.g. elderly, underweight patients, suffering from previous stroke/TIA or from diseases of the gastro-enteric system or in treatment with oral anticoagulants) or socio-economic reasons but in the absence of a prohibitive ischaemic risk (mostly related to angiographic findings).[3] In the case of bleeding, it is also reasonable to maintain the single antiplatelet therapy with aspirin, especially where the bleeding source has not been identified or has not been removed, as the risk of maintaining the DAPT may be to incur in premature suspension of aspirin. In practice, given the long set of action and the high rate of receptor occupancy by the prasugrel, experts consider the switch to be reasonable with a maintenance dose of clopidogrel, especially in the presence of a high risk of bleeding. At the earliest stage after an ACS, it may also be indicated to resort to a dose of 600 mg of load in light of the high platelet turn-over[3] (*Figure 1*). Regarding ticagrelor, considered the fast off-set of the molecule, the experts recommend a de-escalation therapy through a loading dose of clopidogrel 24 h after the last administration[3] (*Figure 1*).

Table 2 Randomized clinical evidence available on de-escalation therapy in patients with recent acute coronary syndrome

	TOPIC	Tropical-ACS	PRAGUE-19	TOPIC-VASP
Population	New P2Y12i vs. clop	Prasugrel vs. No HPR clop	New P2Y12i vs. clop	LPR vs. No LPR
Randomization	Month from ACS	After 7 days from ACS	NA (switch due to economic reasons)	After 1 month from ACS
Numbers	323 vs. 322	1304 vs. 1306	571 vs. 659	306 vs. 340
Switch-back	14%	40%	—	—
STEMI	42% vs. 44%	55% vs. 56%	93% vs. 92%	40% vs. 40%
NACE	26% vs. 13% ($P < 0.01$)	9% vs. 7% ($P_{non\text{-}inf} < 0.001$)	—	12% vs. 15% ($P = 0.45$)[a]
MACE	12% vs. 9% ($P = 0.36$)	3% vs. 3% ($P_{non\text{-}inf} = 0.01$)	8.5% vs. 2.5% ($P = 0.02$)	7% vs. 12% ($P = 0.11$)[a]
BARC ≥2	15% vs. 4% ($P < 0.01$)	6% vs. 5% ($P = 0.23$)	13.4% vs. 7.3% ($P = 0.001$)	5% vs. 3% ($P = 0.29$)[a]
Follow-up	1 year	1 year	1 year	1 year

ACS, acute coronary syndrome; BARC, bleeding episodes according to Bleeding Academic Research Consortium criteria; HPR, high platelet reactivity; LPR, low platelet reactivity; MACE, combined ischaemic event; NA, non-applicable; NACE, combined haemorrhagic and ischaemic event; P2Y12i, inhibitors of P2Y12 receptor; STEMI, ST-segment elevation acute coronary syndrome.
[a]Sub-analysis nel of patients undergoing de-escalation.



C: clopidogrel; P: prasugrel; T: ticagrelor; DC: dose di carico.
*De-escalation con assunzione di C 75 mg a 24 ore dall'ultima dose di P/T in caso di sanguinamento o elevato rischio emorragico.

Figure 1 Depiction of the strategy of early de-escalation therapy post-acute coronary syndrome. C, clopidogrel; DC: dose di carico; P, prasugrel; T, ticagrelor. [A]De-escalation with C 75 mg intake 24 h after the last P/T dose in case of bleeding or high bleeding risk.

Conclusions

The availability of different P2Y12 receptor inhibitors has made it possible to choose an anti-aggregating platelet therapy tailored to the patient undergoing PCI during ACS, in order to guarantee the highest safety and efficacy profile. De-escalation therapy is currently applicable in those patients deemed unfit to continue DAPT because they are burdened with a high risk of bleeding or socio-economic reasons but in the absence of a prohibitive ischaemic risk. Adequate clinical evidence is needed to provide the clinician with the tools for a less arbitrary choice of anti-aggregation strategy.

Conflict of interest: None declared.

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