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De-escalation of anti-platelet therapy in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a narrative review

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Abstract

Objective: Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor inhibitor is the cornerstone of treatment in patients with acute coronary syndromes (ACS) and in those undergoing percutaneous coronary intervention (PCI). In current clinical situation, availability of different oral $P2Y_{12}$ inhibitors (clopidogrel, prasugrel, and ticagrelor) has enabled physicians to switch among therapies owing to specific clinical scenarios. Although optimum time, loading dose and interval of transition between $P2Y_{12}$ inhibitors is still controversial and needs further evidence, switching between oral inhibitors frequently occurs in clinical practice for several reasons.

Data sources: This review was based on data in articles published in PubMed up to June 2018, with the following keywords "antiplatelet therapy", "ACS", "PCI", "ticagrelor" and "clopidogrel".

Study selection: Original articles and critical reviews on de-escalation strategy in ACS patients after PCI were selected. References of the retrieved articles were also screened to search for potentially relevant papers.

Results: Safety concerns associated with switching between antiplatelet agents, has prompted the use of clopidogrel for patients with ACS especially after PCI as a de-escalation strategy. Practical considerations for de-escalating therapies in patients with ACS such as reducing dose of $P2Y_{12}$ inhibitors or shortening duration of DAPT (followed by aspirin or $P2Y_{12}$ receptor inhibitor monotherapy) as potential options are yet to be standardized and validated.

Conclusions: Current review will provide an overview of the pharmacology of common $P2Y_{12}$ inhibitors, definitions of de-escalation and different de-escalating strategies and its outcomes, along with possible direction to be explored in de-escalation.

Keywords: Acute coronary syndrome; Antiplatelet therapy; Clopidogrel; De-escalation; Ticagrelor

Introduction

Cardiovascular disorders, particularly development of acute coronary syndrome (ACS) is the leading cause of morbidity and mortality across world.[1] The well laid pathophysiological mechanism leading to an ACS is acknowledged to thrombus formation in the coronary artery followed by an erosion or rupture of an atherosclerotic plaque.[2] This is followed by a cascade of intracellular signaling events driven by platelets and plasma components leading to thrombus formation. Final outcome of thrombus formation in the coronary artery is complete or partial vessel occlusion contributing to the constellation of signs and symptoms that characterize patients presenting with an ACS.[2-4] These pathophysiological considerations underscore how inhibition of both platelets and coagulation factors are essential for the treatment and secondary prevention of ACS patients. Therefore, treatment with dual antiplatelet therapy (DAPT), which combines aspirin with a platelet $P2Y_{12}$ receptor antagonist ($P2Y_{12}$ inhibitor) is the most preferred choice to prevent atherothrombotic events in patients with ACS and for those undergoing percutaneous coronary intervention (PCI).[5,6] Clopidogrel, prasugrel, and ticagrelor are commonly used oral platelet inhibitors.[7] Although clopidogrel is a classical $P2Y_{12}$ inhibitor indicated for ACS and is widely prescribed,[8,9] current guidelines support the preferential use of prasugrel and ticagrelor over clopidogrel owing to their superior net clinical benefits by reducing the risk of thrombosis.[5,6,8,10-15] Due to the availability of different oral $P2Y_{12}$ inhibitors demonstrating various benefits and risks, physicians are now able to switch among therapies based on the patient's clinical condition.[16]

However, safety concerns regarding switching between these agents have emerged wherein due to increased risk of

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bleeding, dyspnea, or/and cost (the use of ticagrelor, during the maintenance phase in patients has led to premature discontinuation).[10,11] Thus, early stage potent $P2Y_{12}$ receptor inhibitor monotherapy, reduction of P2Y12 receptor inhibitor dose, shortening duration of DAPT and switching from novel $P2Y_{12}$ inhibitors (ticagrelor or prasugrel to clopidogrel) are now favored to limit the adverse outcomes. Nonetheless, standard de-escalation protocol along with optimal strategy is still not well realized due to contradictory results.

In this overview of the literature pertaining to pharmacotherapy of antiplatelet agent, various de-escalating strategies including the conventional switching to clopidogrel will be presented. Additionally, the practical challenges of how to achieve a balanced platelet inhibition and reduce incidence of bleeding or other adverse events will be discussed.

Properties of $P2Y_{12}$ Receptor Inhibitors

Two principal classes of $P2Y_{12}$ inhibitors exist namely irreversibly and reversibly binding agents.[4,12] Thienopyridines (clopidogrel, prasugrel, and ticlopidine) are irreversibly binding inhibitors,[17] their inactive prodrugs requiring hepatic activation in order to bind covalently to the adenosine diphosphate (ADP)-binding site on the $P2Y_{12}$ receptor.[12,17] Clopidogrel is a second-generation thienopyridine which requires a two-step oxidation process by the cytochrome P450 (CYP) system to produce its active metabolite,[12,17] is widely prescribed. Prasugrel is a third-generation thienopyridine with a potent pharmacokinetic profile than clopidogrel, because it is not hydrolyzed to the same extent by esterases, and requires only a single step of hepatic oxidation. However, the half-life of the active metabolites derived from thienopyridines are very unstable leading to their rapid elimination on failing to bind to the $P2Y_{12}$ receptor.[17]

Reversibly binding inhibitors include cangrelor and ticagrelor.[18,19] Ticagrelor, an oral agent belongs to the cyclopentyl-triazolopyrimidine class.[20] Unlike thienopyridines, ticagrelor is directly active after oral administration and does not require hepatic activation. It is rapidly absorbed with a half-life of 7 to 12 h and consequently requires dosing bid. However, ticagrelor does not directly block the ADP-binding site; instead, the drug reversibly binds to a distinct site on the $P2Y_{12}$ receptor and prevents ADP from activating the $P2Y_{12}$ pathway noncompetitively.[20] Owing to its rapid absorption and direct activity, ticagrelor is considered to be more prompt, potent, and possesses predictable pharmacodynamic effects than clopidogrel.[12,17]

Interactions between $P2Y_{12}$ Inhibitors

ADP which contributes to platelet activation during thrombosis,[3,21] is released from dense granules of platelets and binds to $P2Y_1$ and $P2Y_{12}$ receptors on the platelet membrane.[21] This initiates the activation of $P2Y_{12}$ receptor inducing a cascade of signaling events resulting in platelet aggregation. Owing to this role in platelet activation and thrombus formation, $P2Y_{12}$ receptor has been an important target in the management and prevention of ACS.[3,4,12,18,21,22]

Safety concerns in switching between $P2Y_{12}$ inhibitors could be attributed to the potential drug-drug interactions (DDIs). A DDI is defined as any modification in the effect of a drug when administered concomitantly with another drug, which exist with switching between antiplatelet agents, particularly when switching from ticagrelor to clopidogrel.[16,23] Effects of a $P2Y_{12}$ inhibitor can be hindered, causing inadequate platelet inhibition and thereby, increasing the risk for thrombotic complications (such as stent thrombosis[24,25]) because of a DDI. On the other hand, there may be a potential chance for overdosing too; leading to excessive platelet inhibition and predisposing bleeding complications. Although hitherto few studies have shown a clinical impact of DDIs as a result of switching, robust evidence associating different grades of platelet reactivity with adverse clinical outcomes does exist.[24,26] Possible DDIs when switching $P2Y_{12}$ inhibitors relies mainly on differences in their pharmacological properties. Key pharmacological properties include drug's half-life, the site of action, mechanism of $P2Y_{12}$ receptor binding, and the rate of onset and offset of pharmacodynamic effects which are summarized in Table 1.[4,12]

Table 1: Pharmacological characteristics of $P2Y_{12}$ inhibitors

Characteristics	Clopidogrel	Prasugrel	Ticagrelor
Chemical class	Thienopyridine	Thienopyridine	Cyclopentyl-triazolopyrimidine
Receptor blockade	Irreversible	Irreversible	Reversible
Prodrug	Yes	Yes	No
Oral administration	Yes	Yes	Yes
Loading dose (mg)	300	60	180
Maintenance dose (mg)	75	10	90
Frequency of administration	Once daily	Once daily	Twice daily
Onset of action (h)	2–8	0.5–4	0.5–4
Offset of action	Delayed	Delayed	Rapid
Individual variability	Large	Small	Small
Relative potency	Low	High	High
Mean platelet inhibition	~50%	~70%	~95%
Time to peak inhibition (h)	~12	2	2

Common DAPT

DAPT and their benefits following an ACS is well established by various trials viz., CURE,[26] COMMIT/CCS-2[27] and, CLARITY-TIMI 28[28] trials. When combined with aspirin, clopidogrel showed reduction in 1-year incidence of cardiovascular events when compared with aspirin alone.

This observation was further substantiated by other studies (PLATO[10] and TRITON[11]) wherein $P2Y_{12}$ receptor inhibition was potent and efficient with either ticagrelor or prasugrel as combination therapy with aspirin. DAPT trial (ClinicalTrials.gov number NCT00977938) showed that continued thienopyridine and aspirin therapy beyond 1 year after placement of a drug-eluting stent (DES), when compared to aspirin monotherapy, significantly reduced the risks of stent thrombosis and major adverse cardiovascular and cerebrovascular events.[29] Although, the former arm was associated with an increased risk of bleeding, severe or fatal bleeding was uncommon.[29] In subsequent PEGASUS-TIMI 54 trial,[30] combination of aspirin and ticagrelor against aspirin alone was evaluated in patients with a previous myocardial infarction (MI). As per the findings from this trial, ticagrelor (60 mg) reduced the incidence of cardiovascular death, MI or stroke, but increased the rate of thrombolysis in myocardial infarction (TIMI) major bleeding as compared to aspirin alone.[30]

Based on these data, European[31] and North American[32] guidelines do not recommend DAPT in patients with stable atherothrombotic disease but suggest that with careful consideration, combined antiplatelet therapy may be beneficial in some high risk patients such as early stage of ACS. In consideration of the pathological process of ACS (from instability to stability) and the intensity of the antiplatelet treatment need to be synchronized, a series of de-escalation studies have been carried out which aimed at assessing the optimum dose, duration and clinical beneficial of various antiplatelet therapies, especially $P2Y_{12}$ receptor inhibitors.

De-escalation Background and Definitions

There are several reasons for the exploration of de-escalation. Firstly, occurrence of major bleeding events – which correlated with increased mortality as seen in both PLATO and TRITON-TIMI 38 trials.[10,11] This gradual and increased risk of bleeding events with reduced risk of ischemia forms the foremost reason for de-escalation calling for management of anti-platelet therapy to reduce the occurrence of bleeding [Figure 1]. Secondly, ambiguity about dose requirements for lower body weight and elderly patients using prasugrel, the mandated twice daily dosing of ticagrelor, along with the frequently observed dyspnea as a side effect, limits the general use of these newer inhibitors.[33] Thirdly, major drug costs incurred by use of both ticagrelor and prasugrel when compared to generic clopidogrel demotivates the patients. In brief, de-escalation is considered in case of relevant adverse effects [Figure 1] or the need for concomitant oral anticoagulation or even to cut down cost issues.

De-escalation include any reduction of intensity in antiplatelet treatment in ACS patients, aims at synchronizing with pathological status of ACS, such as switching $P2Y_{12}$ receptor inhibitors or reducing their dose or shortening their duration or early stage (1–3 months after ACS) $P2Y_{12}$ receptor inhibitor monotherapy. De-escalation modalities from clinical practice are summarized in Table 2.

De-escalating Studies and Outcomes

Early stage potent $P2Y_{12}$ receptor inhibitor monotherapy

Current medical guidelines recommend that patients with coronary stent should receive DAPT with both aspirin and

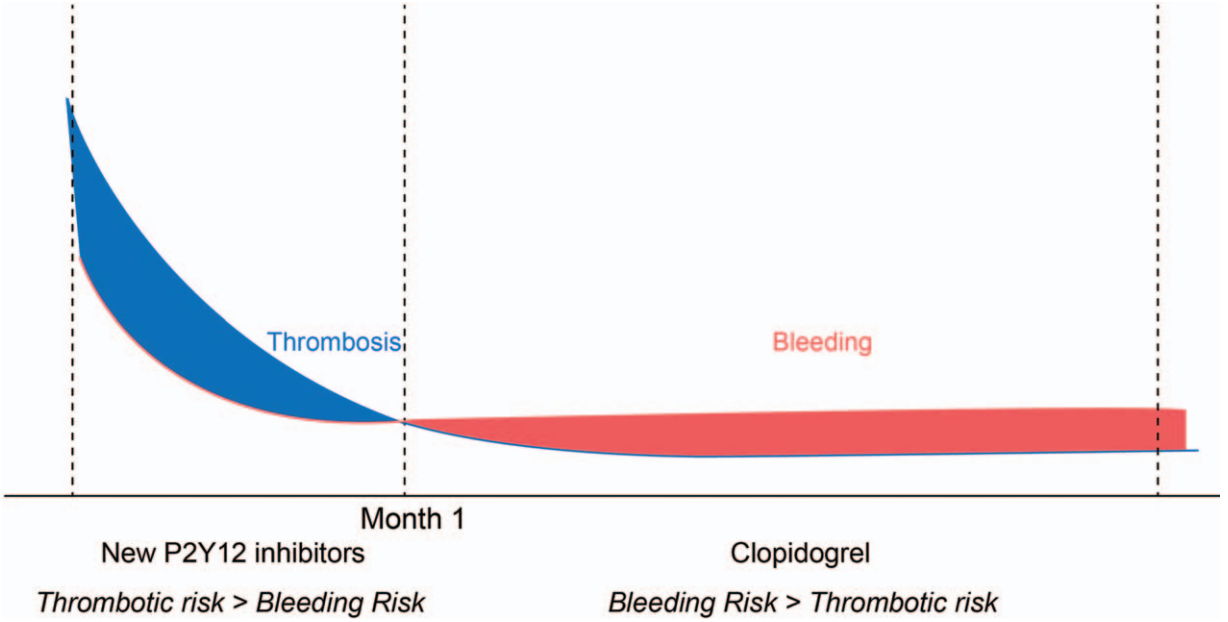

Figure 1: Need for de-escalation.

Table 2: De-escalation modalities in patients with ACS

De-escalation	When?	How?
Early stage potent $P2Y_{12}$ receptor inhibitor monotherapy	- Increased atherothrombotic risk - Increased bleeding risk	1 to 3 months DAPT followed by $P2Y_{12}$ receptor inhibitor monotherapy
Reducing the dose of $P2Y_{12}$ receptor inhibitors	- Stable period after myocardial infarction, with at least one additional atherothrombotic risk factor	Ticagrelor 90 mg bid 1 year then 60 mg bid*
Shortening the duration of dual antiplatelet therapy	- Stable CAD or low-risk ACS (unstable angina) patients with newer generation DES	3 or 6 months of DAPT then aspirin or $P2Y_{12}$ receptor inhibitor monotherapy
Switching From ticagrelor to clopidogrel	- Major bleeding events - Adverse reactions (such as dyspnea) - Need for oral anticoagulation	Clopidogrel 600 mg LD then 75 mg/d* Or clopidogrel 75 mg/d directly*
From prasugrel to clopidogrel	- Major bleeding events - Need for oral anticoagulation	Clopidogrel 600 mg LD then 75 mg/d*

* Combined with aspirin. ACS: acute coronary syndrome; CAD: coronary artery disease; DES: drug-eluting stent; DAPT: dual antiplatelet therapy; LD: loading dose.

potent $P2Y_{12}$ inhibitors (especially ticagrelor).[32] The residual atherothrombotic risk in such patients is more pronounced, thereby providing a rationale for a strategy involving single and more potent $P2Y_{12}$ inhibitor ticagrelor.[34] One such study is the ongoing multinational, randomized double-blinded TWILIGHT (Ticagrelor with aspirin or alone in high-risk patients after coronary intervention; ClinicalTrials.gov identifier: NCT02270242) trial.[35] It aims at testing the hypothesis of ticagrelor monotherapy being superior to DAPT (ticagrelor plus aspirin) in reducing bleeding in high-risk ACS patients who received DAPT (aspirin plus ticagrelor) 3 months after PCI. Adult patients (≥65 years) who present acute ACS along with at least one high-risk factor (such as diabetes mellitus or chronic kidney disease) and at least 1 angiographic risk factor will be included. Post screening, patients will be randomized to either ticagrelor plus aspirin or ticagrelor plus placebo groups and followed-up at 3, 9, and 15 months. Findings from TWILIGHT are expected to provide key relevant insights that may change clinical practice with respect to long-term antiplatelet pharmacotherapy after PCI.

Another recently concluded trial, GLOBAL LEADERS (ClinicalTrials.gov Identifier: NCT01813435) also assessed the benefits and risks of ticagrelor combined with acetylsalicylic acid (ASA) and ticagrelor monotherapy, compared to conventional DAPT in patients undergoing DES implantation.[36] This multicenter, multinational, open-label, randomized clinical trial randomized patients with any clinical indication for PCI to either (i) ticagrelor combined with ASA (≤100 mg) for 1 month followed by monotherapy for 23 months or (ii) standard DAPT with clopidogrel for 12 months plus ASA up to 100 mg, or (iii) ticagrelor standard treatment for 12 months plus ASA ≤100 mg (ACS patients) followed by ASA monotherapy. All-cause death or non-fatal, new Q-wave MI was the primary outcome whereas investigator reported BARC class 4 or 5 bleeding events were the secondary outcome measures. It was seen that at 2 years, in the experimental group, 304 (3.81%) patients had died or had a non-fatal centrally adjudicated new Q-wave myocardial infarction when compared with the control group (349 [4.37%] patients, rate ratio 0.87, 95% confidence interval [CI] 0.75–1.01, $P=0.073$). The incidence of grade 3 or 5 bleeding events did not differ significantly between groups (rate ratio 0.97, 95% CI 0.78–1.20, $P=0.77$). In conclusion, these results do not support or suggest any change in current clinical practices.

Reducing the dose of $P2Y_{12}$ receptor inhibitors

Ticagrelor, a potent, direct-acting $P2Y_{12}$ receptor antagonist is recommended over clopidogrel in both the European and American ACS guidelines.[8,15,37,38] PLATO study shown that platelet inhibition with ticagrelor leads to reduction of atherothrombotic events in patients with ACS,[10] substantially contributing making this agent widely adopted in current practice.[39] Nonetheless, the intensity and time course of platelet inhibition using ticagrelor can vary during the acute phase and the following stable period after MI.[40] In PEGASUS-TIMI 54 trial, patients with 1 to 3 years after a MI, and at least one additional atherothrombotic risk factor, were randomized to 3 arms (all with low-dose aspirin): ticagrelor 90 mg bid, ticagrelor 60 mg bid, or placebo.[41] Ticagrelor 60 mg bid was designed to achieve a slightly lower degree of platelet inhibition compared with 90 mg, but still greater than Clopidogrel 75 mg.[41] Both doses of ticagrelor, as compared with placebo, significantly reduced the primary endpoint of CV death, MI, or stroke, with a relative risk reduction of 15% with 90 mg and 16% with 60 mg (hazard ratio [HR] 0.85, 95% CI 0.75–0.96; $P=0.008$ for 90 mg, and HR 0.84, 95% CI 0.74–0.95; $P=0.004$ for 60 mg). Rates of TIMI major bleeding were higher with ticagrelor (2.60% with 90 mg and 2.30% with 60 mg) than with placebo (1.06%) ($P<0.001$ for each dose *vs.* placebo); the rates of intracranial hemorrhage or fatal bleeding in the three groups were 0.63%, 0.71%, and 0.60%, respectively.[30] The similar efficacy and numerically lower rates of adverse events with the ticagrelor 60 mg bid make it appear to be the more attractive long-term option.

A sub-study of the PEGASUS-TIMI 54 trial also showed that in patients receiving standard or lower dose of ticagrelor, platelet $P2Y_{12}$ receptor inhibition did not differ significantly between the groups despite lowering plasma concentrations of ticagrelor and its active metabolite (AR-C124910XX) by 62%–65% and 54%, respectively.[42] Prevalence of high platelet reactivity (HPR) among patients with ticagrelor 60 mg bid was rare (3.5%).[42] Similar results were seen in diabetics where ticagrelor 60 mg bid was shown to be equally effective to the 90 mg dose in reducing platelet reactivity.[43]

However, ticagrelor discontinuation was more frequent in the PEGASUS-TIMI 54 study compared with the PLATO study.[44] The discontinuation rate during the first year in patients treated with ticagrelor 90 mg bid was higher than in patients receiving 60 mg of ticagrelor bid.[45] It was seen that patients with previous acute myocardial infarction (AMI) were prone to discontinue ticagrelor as a component of their DAPT, usually soon after the beginning of treatment and most often due to non-serious bleeding.[30] On the other hand, improved tolerability with similar efficacy associated to the 60 mg dose as shown in the PEGASUS-TIMI 54 trial, resulted in lower discontinuation rates, plausibly supporting the use of lower dose in stable patients. Although 90 mg ticagrelor dose might achieve higher degree of platelet inhibition in the acute phase of AMI, prevalence of major adverse CV events, including cardiovascular death, MI and stroke is highest immediately after the initial intervention and they gradually decrease reaching a stable level after 1 month.[10,11,46,47] Platelet activation is closely associated with inflammation, explaining why these results observed a parallel decrease in plasma concentrations of inflammatory markers, as well as a decrease in platelet count to stable, lower level observed 1 month after MI.[48-51]

The ongoing ELECTRA pilot (ClinicalTrials.gov Identifier: NCT03251859)[52] study is a randomized, open-label, pharmacokinetic and pharmacodynamic trial designed to evaluate the effect of ticagrelor maintenance dose (MD) reduction on platelet inhibition in stable patients who recently underwent AMI and were treated with PCI. It will evaluate the 45 d platelet reactivity in patients after AMI who randomized into 2 groups: ticagrelor 90 mg bid for the first 45 d after MI treated with PCI; ticagrelor 90 mg bid for the first 30 d after MI treated with PCI, then reduction of the MD to ticagrelor 60 mg bid for the next 15 d. The investigator assumes that a de-escalation strategy with reduced dose of ticagrelor (60 mg bid) following an initial standard dose (90 mg bid) during the first month after AMI may provide equally effective platelet inhibition as compared to maintenance with the standard ticagrelor dose. If this hypothesis is valid, reducing the dose of ticagrelor could be earlier.

Shortening the duration of DAPT

Current European[14] and North American[32] guidelines advise continuing DAPT for 1 year in ACS patients, which are based on findings from previous studies.[10,11,53,54] This strategy was appropriate for patients with sustained increased risk of thrombotic complications, including stent thrombosis and spontaneous cardiovascular events, beyond 6 months. But observations have raised concerns such as long term use of DAPT owing to more bleeding events, increasing rates of all-cause death, thereby offsetting the benefits of reducing cardiac death and nonfatal ischemic events.[55-58]

In recent trials of patients with newer generation DES, shorter durations of DAPT (3–6 months) were non-inferior to 12[59-64] months or 24[65] months either in terms composite of cardiovascular events or major bleeding. Of course, these studies included mostly low-risk patients.[59,60,62-64] Although there was predominantly unstable angina/low risk in ACS patients, they are associated with increased ischemic risk.[66]

In addition to these findings, a sub study from the prospective randomized sub study of the larger Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization (I-LOVE-IT 2) trial,[67] investigated the clinical implications of short-term (6 months) *vs.* standard long-term (12 months) DAPT in patients undergoing PCI with the novel biodegradable polymer drug-eluting stent (BP-DES) device. The study enrolled patients with stable coronary artery disease (CAD) or ACS undergoing PCI. Patients who were randomized to the BP-SES group, were additionally randomized (1:1 ratio) to follow a 6-month DAPT or 12-month DAPT duration before the index PCI. All patients were discharged with a prescription for 100 mg of aspirin indefinitely, and 75 mg clopidogrel for 6 or 12 months after index procedure. The 12-month target lesion failure (TLF) was the primary end point, difference in 1-year TLF rates between the 6-month DAPT (6.8%) and the 12-month DAPT (5.9%) groups were 0.87% (95% CI 1.37%–3.11%), demonstrating non-inferiority of 6-month DAPT to 12-month.

The latest SMART-DATE (6-month *vs.* 12-month or longer DAPT after PCI in patients with ACS: a randomized, open-label, non-inferiority trial) also investigate whether a 6-month duration of DAPT would be non-inferior to the conventional 12-month or longer duration of DAPT after implantation of DES in ACS patients.[68] Clopidogrel was used as a $P2Y_{12}$ inhibitor for DAPT in 79.7% patients in the 6-month DAPT group and in 81.8% patients in the 12-month or longer DAPT group. The primary endpoint (a composite of all-cause death, myocardial infarction, or stroke at 18 months) in the 6-month DAPT group not inferior to in the 12-month or longer DAPT group (4.7% *vs.* 4.2%; absolute risk difference 0.5%; upper limit of one-sided 95% CI 1.8%; P non-inferiority = 0.03 with a predefined non-inferiority margin of 2.0%). However, MI occurred more frequently in the 6-month DAPT group than in the 12-month or longer DAPT group (1.8% *vs.* 0.8%; 2.41, 95% CI 1.15–5.05; $P = 0.02$).

Another ongoing OPT-PEACE trial (ClinicalTrials.gov Identifier: NCT03198741) also aims at evaluating the optimum DAPT duration which can be strategized to reduce gastrointestinal mucosal injury. This randomized study will evaluate ANKON® magnetically controlled

capsule endoscopy (AMCE) as a tool to assess gastrointestinal mucosal injury and bleeding in patients on DAPT. Adult patients (18–80 years) with stable angina or NSTEMI ACS, who have undergone PCI only with implantation of current generation will be recruited. Essentially, these patients should be on DAPT (aspirin + clopidogrel) after DES for at least 6 months. However, patients presented with STEMI or prior implantation with first-generation DES (of >4 stents) and those unable to take DAPT for 12 months will be excluded. Patients will be randomized into 3 arms: aspirin + clopidogrel, clopidogrel and aspirin monotherapy. Gastrointestinal mucosal injury, after 6 months of randomization, is the primary outcome of interest. Severity of gastro-intestinal lesions, bleeding and adverse events are the secondary outcome measures. Findings from this trial will evaluate the relative rates of gastrointestinal injury in patients on three different antiplatelet regimens; and aid in establishing a scoring system which may prove useful in guiding optimal antiplatelet agent usage after PCI.

In summary, data from the aforementioned studies suggest that a minimum duration of 6 or even 3 months is effective in low-risk patients with stable CAD after second-generation DES implantation, whereas in ACS patients, extension of DAPT beyond 12 months appears to be beneficial in high-risk patients, most notably patients with prior MI.

Switching potent $P2Y_{12}$ inhibitors to clopidogrel

International guidelines recommend potent platelet inhibition with prasugrel or ticagrelor in the first year after an ACS.[14,32] Despite these recommendations, an early de-escalation from potent antiplatelet agents to clopidogrel is appealing both from medical and economic perspective.[69] Reasons for de-escalation most predominantly include adverse events and issues with reimbursement or availability of potent platelet inhibitors.[69] For example, the potential clinical reasons for switching from ticagrelor to clopidogrel have been summarized as prior intracranial hemorrhage, dyspnea, bradycardia, active bleeding or increased bleeding risk, and cost considerations.[70,71]

Clinical data indicate that the prevalence of in-hospital de-escalation is 5% to 14% [Tables 3 and 4].[69,70,72-79] These patients are less likely to be privately insured and have risk factors associated with increased bleeding risk such as older age, lower body weight, previous transient

Table 3: Switching to clopidogrel (after PCI): findings from registries and RCT

Study	Population	$P2Y_{12}$ receptor inhibitors	Clinical outcomes
Bagai *et al*[70] (ACTION Registry GWTG and CathPCI)	NSTEMI and STEMI undergone PCI (n=47,040)	P to C: 11.5% T to C: n/a	n/a
Zettler *et al*[77] (TRANSLATE-ACS)	NSTEMI, STEMI undergoing PCI (n=8672)	P to C: 97.4% T to C: 87.5%	• Before switching: MACE: 18.5% in the C group, 2.1% in the P group, 1.5% in the T group. Moderate/severe Bleeding: 0.9% in the C group, 0.3% in the P group, 0% in the T group. • After switching: MACE: 1.9% in the group who switched from C, 0.8% in the group who switched from P, 0 in the group who switched from T. No bleeding events were observed.
De Luca *et al*[78] (SCOPE)	ACS undergone PCI (n=1363)	In cath-lab switch: n/a At discharge switch: P to C: 0.8% T to C: 1% After discharge switch: P to C: 0.7% T to C: 0.8% From admission to follow-up switch: P to C: 1.3% T to C: 1.8%	In-hospital outcomes: NACE: 22.7% in patients who switched from P/T to C, 0% in patients who switched from C to P/T and between P and T. MACE: 20.4% in patients who switched from P/T to C, 0% in patients who switched from C to P/T and between P and T. Bleeding: 3.8% in patients who switched from P/T to C, 0% in patients who switched from C to P/T and between P and T.
Cuisset *et al*[79] (TOPIC)	ACS undergone PCI (n=646)	P/T to C: 50%	Outcomes at 1 year: Net clinical benefit: 13.4% in patients who switched, 26.3% in patients who did not switch.
Sibbing *et al*[69] (TROPICAL-ACS)	Biomarker positive ACS with a successful PCI (n=2610)	P to C: 50%	Outcomes at 1 year: Net clinical benefit: 7% in patients who switched (guided de-escalation group), 9% in patients who did not switch.

Modified from Rollini *et al*.[16] ACS: acute coronary syndrome; C: clopidogrel; MACE: major adverse cardiac events; NACE: net adverse clinical events; NSTEMI: non-ST-elevation myocardial infarction; P: prasugrel; PCI: percutaneous coronary intervention; RCT: randomized controlled trial; STEMI: ST-elevation myocardial infarction; T: ticagrelor; n/a: not applicable.

Table 4: Switching to clopidogrel (non PCI): findings from registries and RCT

Study	Population	$P2Y_{12}$ receptor inhibitors	Clinical outcomes
Clemmensen *et al*[73] (MULTIPRAC)	STEMI ($n=2053$)	P to C: 8.3% T to C: n/a	In-hospital outcomes: no differences in MACE and non-CABG related bleeding in patients switched from C (6.1%) to P *vs.* patients on P (4.1%) only.
Bagai *et al*[74] (TRANSLATE-ACS)	NSTEMI, STEMI ($n=11,999$)	P to C: 11.5% T to C: 2.1%	Outcomes at 6 months: no significant differences in MACE and bleeding in any switched patients (2.7% bleeding rate) *vs.* non switched (3.3% bleeding rate).
Schiele *et al*[75] (FAST-MI)	NSTEMI, STEMI ($n=4101$)	P to C: 4.6% T to C: n/a	n/a
De Luca *et al*[76] (EYESHOT)	NSTE-ACS, STEMI ($n=2585$)	In cath-lab switch: P/T to C: 0.3% At discharge switch: P/T to C: 3.2% Switch in medically managed patients: P/T to C: 3.4%	n/a

Modified from Rollini *et al*.[16] ACS: acute coronary syndrome; C: clopidogrel; CABG: coronary artery bypass graft; MACE: major adverse cardiac events; NSTEMI: non-ST-elevation myocardial infarction; P: prasugrel; PCI: percutaneous coronary intervention; RCT: randomized controlled trial; STEMI: ST-elevation myocardial infarction; T: ticagrelor; n/a: not applicable.

ischemic stroke, in-hospital treatment with coronary artery bypass graft (CABG) surgery, atrial fibrillation/flutter, and use of oral anticoagulants (OACs).[70,72-76] Switching between $P2Y_{12}$ inhibitors after hospital discharge occurs in 5% to 8% of patients, most of them are de-escalation cases.[77]

A recent meta-analysis of observational studies and registries reported a higher de-escalation rate from ticagrelor to clopidogrel in 19% in ACS patients when compared to the data mentioned above.[80] The rate of switching was highest for in-hospital treatment (22%) followed by at discharge (20%). De-escalation to clopidogrel occurred in 17% of patients[80] post discharge followed up to 1 year. Clinical outcomes associated with de-escalation to clopidogrel were also assessed and the rate of major adverse cardiac and cerebrovascular event (MACCE) was 2.1% (95% CI 0.9–3.3). Cardiovascular mortality rate was 1.4% (95% CI 0–2.9) and 2.0% (95% CI 0.3–3.8) for myocardial infarction. Rate of all-cause mortality was 3.1% (95% CI 0.4–5.9) and the prevalence of bleeding events was 3.3% (95% CI 1.7–4.9) for all bleeding (major and minor) and 1.1% (95% CI −0.3–2.5) for major bleeding.[81]

The TOPIC (Timing of Optimal Platelet Inhibition After ACS) study showed that in patients who have been event free for the first month after an ACS on a combination of aspirin plus a new-generation $P2Y_{12}$ inhibitor, de-escalation to aspirin plus clopidogrel was associated with reduced bleeding complications, mostly minor.[79] Although this study did not show any differences in ischemic events between groups, play of chance cannot be ruled out given the limited sample size of the trial. The TROPICAL-ACS (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for ACS) study showed that a guided de-escalation (to clopidogrel) of antiplatelet treatment by platelet function testing (PFT) was non-inferior to standard treatment with prasugrel at 1 year in terms of net clinical benefit.[69] The TROPICAL-ACS study did not show any increase in ischemic events, although there was a trend though not a statistically significant reduction in bleeding. However, it is noteworthy to mention that 40% of patients in de-escalation group required escalation back to prasugrel, in the de-escalation group, thereby nullifying any bleeding advantage. Thus far, TROPICAL-ACS is the only randomized trial using results of PFT to adjust antiplatelet therapy (de-escalation) apart from few other studies.[82-84]

Moreover, due to different site of action and affinity of the active metabolites of $P2Y_{12}$ receptor inhibitors, the probability of a drug-to-drug interaction is highly anticipated. There is a paucity of studies [Table 5] assessing the pharmacodynamic effects associated with de-escalation to clopidogrel therapy that have consistently shown an increase in platelet reactivity and HPR rates, with some reporting lower bleeding events.[85,86] It is important to note that although switching from prasugrel or ticagrelor to clopidogrel is intuitively associated with an increase in platelet reactivity and HPR rates, the different speed of offset of the drugs may have important therapeutic implications, particularly with regard to the timing of clopidogrel administration and whether it should be given as a loading dose (LD). Related pharmacodynamic studies are enumerated in Table 5.

Switching from ticagrelor to clopidogrel

Data on the optimum switching from novel $P2Y_{12}$ receptor inhibitor ticagrelor to clopidogrel are very limited. Pharmacodynamic data indicate that due to its rapid offset of action (3–5 days),[87] ticagrelor does not allow clopidogrel to achieve its full antiplatelet effects if administered at a 75 mg daily MD regimen. Moreover, clopidogrel has an unpredictable and variable pharmacodynamic profile even if given at a 600 mg LD.[88] Based on these considerations, a 600 mg LD of clopidogrel should preferably be given when switching from ticagrelor therapy.

Table 5: Switching to clopidogrel: pharmacodynamic studies

Study	Study design	Population	Key findings due to switching
Wiviott *et al* (PRINCIPAL TIMI 44)[11]	Multicentre, randomized, double-blind, double-dummy, active-comparator-controlled, crossover	Planned PCI	IPA: after 15 days 61.9% with 10 mg P to 46.8% of 150 mg C PRI: after 15 days 21.7% with 10 mg P to 48% of 150 mg C
Pourdjabbar *et al* (CAPITAL OPTI-CROSS)[23]	Prospective, randomized, open-label	ACS	PRU: at 48 h ~40 when receiving T (180 mg followed by 90 mg MD bid) to 114.0±73.1 after 600 mg C ~40 when receiving T (180 mg followed by 90 mg MD bid) to 165.1±70.5 after 75 mg C PRU: at 72 h ~40 when receiving T (180 mg followed by 90 mg MD bid) to 165.8±71 after 600 mg C ~40 when receiving T (180 mg followed by 90 mg MD bid) to 184.1±68 after 75 mg C
Kerneis *et al*[85]	Prospective, observational, registry	ACS	MPA: after 15 days 21.0±10.4% with 10 mg P to 43.8±15.1% of 75 mg C PRU: after 15 days 14.2±27.9 with 10 mg P to 155±87.2 of 75 mg C PRI: after 15 days 12.5±11.9% with 10 mg P to 43.6±21.8% of 75 mg C
Deharo *et al* (POBA)[86]	Prospective, observational	ACS	PRI: 7.0±2% with P (10 mg) to 37.8±15.6% with C (75 mg)
Franchi *et al* (SWAP-4)[90]	Randomized, open-label	ACS	PRU: Similar between the C 600 mg and C 75 mg ($P=0.29$) at 24 h and 48 h No differences over time between C 600 mg-24 h and C-600 mg-12 h ($P=0.26$) MPA: Lower in C 600 mg-24 h ($P=0.041$) and C 600 mg-12 h ($P=0.028$) compared with C 75 mg-24 h No differences between C 600 mg-24 h and C 600 mg-12 h ($P=0.92$) PRI: Lower in C 600 mg-24 h compared with C75 mg-24 h ($P=0.025$)
Gurbel *et al* (RESPOND)[87]	Randomized, double-blind, double-dummy, crossover	Stable CAD	Non-responder cohort: MPA: 36±14% with T (14 days of 75 mg daily MD followed by 14 days of 90 mg bid MD) to 56±9% after 600 mg C Responder cohort: MPA: 25±11% with T (180 mg LD load followed by 14 days of 90 mg bid MD) to 45±8% after 600 mg C
Sardella *et al* (RESET GENE)[99]	Open-label, crossover, randomized	Stable CAD with HPR undergoing PCI	HPR defined as AUC>450; AUC 180.5 after 15 days of 10 mg P to 330 after 15 days of 150 mg C

ACS: acute coronary syndromes; AUC: area under the curve; C: clopidogrel; CAD: coronary artery disease; HPR: high on-treatment platelet reactivity; IPA: inhibition of platelet aggregation; LD: loading dose; MD: maintenance dose; MPA: maximal platelet aggregation; P: prasugrel; PCI: percutaneous coronary intervention; PRI: platelet reactivity index; PRU: $P2Y_{12}$reaction units; T: ticagrelor.

Although the optimal timing to switch after the last dose of ticagrelor is unknown, a pharmacodynamic study showed drug interaction in patients who switched to Prasugrel 12 h after the last MD of ticagrelor, suggesting the existence of a residual effect of ticagrelor on the $P2Y_{12}$ receptor.[89] Therefore, at least 12 h after the last MD of ticagrelor, administration of 600 mg LD of clopidogrel should be considered, because this would thus allow sufficient time for ticagrelor and its metabolite to be eliminated (half-life ~8–12 h).

The recent SWAP-4 study (ClinicalTrials.gov Identifier: NCT02287909)[90] evaluated the optimal strategy for de-escalation from ticagrelor to clopidogrel on the basis of

pharmacodynamic effects. This prospective, randomized, open-label study was conducted in patients on MD of aspirin (81 mg/d) and clopidogrel (75 mg/d). After a 7-day regime with ticagrelor (180 mg LD followed by 90 mg bid MD), patients ($n=80$) were randomized into 1 of 4 groups: group A, clopidogrel 600 mg LD 24 h after the last MD of ticagrelor (clopidogrel 600 mg-24 h); group B, clopidogrel 600 mg LD 12 h after the last MD of ticagrelor (clopidogrel 600 mg-12 h); group C, clopidogrel 75 mg/d MD 24 h after the last MD of ticagrelor (clopidogrel 75 mg-24 h); and group D, ticagrelor 90 mg bid MD (ticagrelor 90 mg bid). Ticagrelor 90 mg bid led to lower platelet reactivity than clopidogrel regimen. $P2Y_{12}$ reaction unit (PRU) levels were similar between the clopidogrel 600 mg-24 h (group A) and the clopidogrel 75 mg-24 h (group C) ($P=0.29$), including at 48 h (primary endpoint; least mean difference, −6.9; 95% confidence interval, −38.1 to 24.3; $P=0.66$). PRU levels were lower with clopidogrel 600 mg-12 h (group B) than with clopidogrel 75 mg-24 h (group C; $P=0.024$). Maximal platelet aggregation (MPA) over time was lower in both clopidogrel 600 mg-24 h (group A; $P=0.041$) and C-600 mg-12 h (group B; $P=0.028$) compared with clopidogrel 75 mg-24 h (group C). Platelet reactivity index profiles paralleled those observed with $P2Y_{12}$ reaction units. There were no pharmacodynamic differences between clopidogrel 600 mg-24 h (group A) and clopidogrel 600 mg-12 h (group B). These findings suggest that de-escalation from ticagrelor to clopidogrel therapy is associated with an increase in platelet reactivity and use of an LD before the initiation of an MD regimen of clopidogrel is thought to mitigate these observations.

Existing consensus and recommendations on switching to clopidogrel

The 2017 ESC DAPT guideline[91] recommended clopidogrel LD (600 mg) 24 h after last ticagrelor dose in either acute or chronic setting for de-escalation, and recommended clopidogrel LD (600 mg) 24 h after last prasugrel dose in acute setting while clopidogrel MD (75 mg) 24 h after last prasugrel dose in chronic setting. As declaration in guideline, these switching algorithms are all based on pharmacodynamics.[6] And the "International Expert Consensus on Switching Platelet $P2Y_{12}$ Receptor-Inhibiting Therapies" which recently released included same recommendations.[92]

Practical Problems to be Solved

Period of de-escalation

Currently, there are variations in regional DAPT practices and also with regards to their switching protocols. A great deal of uncertainty prevails among clinicians and healthcare providers regarding the default time of de-escalating strategy for most patients with ACS. Current guidelines are largely based on evidence that predates potentially important technological advances, including second-generation DES, while in recent trials, only a minority of patients presented with an ACS and many of these studies were underpowered to detect differences due to low event rates.[32] Existing evidence to date has been extrapolated to a broader population with a higher risk of both atherothrombotic events and bleeding, this has left uncertainty regarding the relative benefits and risks of one period of treatment *vs.* another in real-world patients with ACS.[33]

As thrombotic risks vary from weeks/months following an ACS or PCI, the timing of switching since the initiating event may be defined as acute (<24 h), early (1–30 days), late (>30 days–1 year), or very late (>1 year).[93] In spite of evidence from single centre[94] and pharmacodynamic studies[85] suggest that acute or early switching might be safe and could reduce bleeding events, a lack of persuasion limits any meaningful recommendations. Nevertheless, results from TROPICAL-ACS[69] and SWAP-4[90] have supplement new insights in defining the best strategy for de-escalation between $P2Y_{12}$ antagonists, and also complement the evidence supporting to recommendations in guidelines.

After the TOPIC study[79] was published, a possible and ideal de-escalation was proposed [Figure 2]. ACS patients who usually carry an increased risk of thrombosis can be efficiently combated by newer $P2Y_{12}$ inhibitors. Nonetheless, this risk is gradually taken over by an increased risk of bleeding events, when bleeding risk is more pronounced than the thrombotic risk, would call for a late de-escalation or switching.

Regardless of recommendations from international guidelines, mounting evidences suggest that the best strategy to optimize a fine balance between reducing the ischemic risk and avoiding bleeding risk could be to stratify patients using simple risk scores.[95,96] This would thereby help establish the ideal intensity and duration of antithrombotic therapy in individual patients and also guide de-escalating the anti-platelet therapy.

Personalized medicine

The critical clinical question therefore arises: how can individuals who are more or less likely to benefit from de-escalation/switching protocol of treatment be identified? Recommendations offered to switch $P2Y_{12}$ receptor inhibitors is critically and technically based on time and type of patients.[97] Type of patients, in particular is a key factor deciding this switch, as it will either expose some patients to an excessive duration of treatment or disadvantage other patients by withdrawing therapy that protects them from MI caused due to excessive bleeding. A tailored antiplatelet strategy looks promising, only if a physician is capable of selecting the best $P2Y_{12}$ inhibitor for an individual patient.

From a practical perspective, a PFT-guided de-escalation therapy shows hope for patients unsuitable for prolonged therapy with potent $P2Y_{12}$ inhibitors, such as those at increased risk of bleeding or with limited access to extended treatment with Prasugrel.[69] However, multiple large trials have failed to show a benefit for a platelet function based tailoring strategy.[82,98] Future studies to observe and guide de-escalation of anti-platelets treatment are still required. Additionally, though easy-to-use PFT is widely available, implementation of PFT could be a major challenge if patients cannot easily access hospitals that conduct PFT.

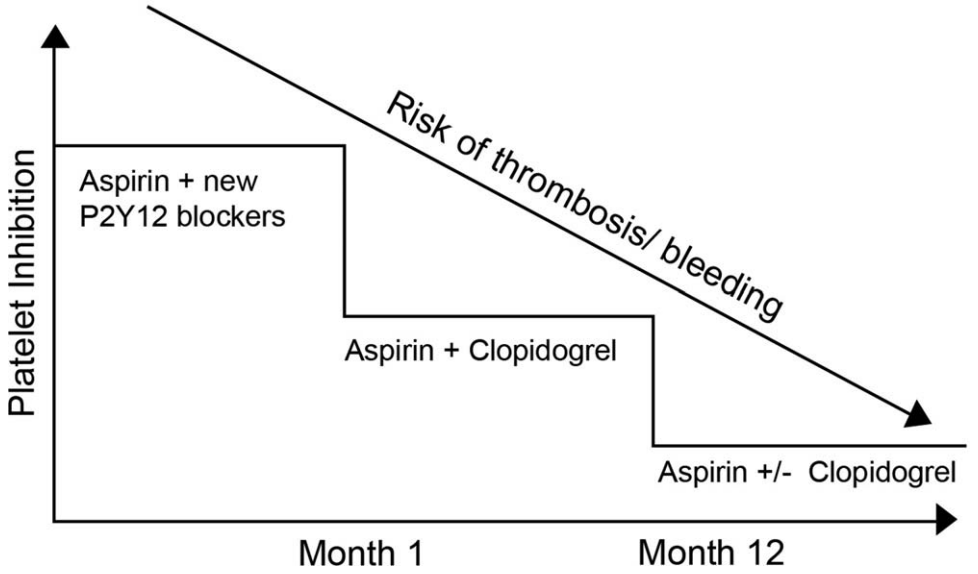

Figure 2: Possibly optimal de-escalation or switching.

Post hoc analysis from PLATO has suggested that the risk of atherothrombosis in non-carriers of a cytochrome P450 (CYP) 2C19 [CYP2C19] loss-of-function (LoF) allele treated with clopidogrel is similar with the risk of those treated with ticagrelor.[99] With this laid background and decreasing costs per sample, the introduction of fast and easy to use point-of-care genotyping devices, genotyping is now achievable and more affordable for use in daily clinical practice.[100] Although PFT and CYP2C19 genotype based tailoring strategy offers promising answers, lack of comprehensive data from studies limits its clinical application. In general, further research is needed to define prediction tools with high discriminatory value in real-world settings, and the potential for net clinical benefit according to the switching protocol of antiplatelet therapy.

Conclusion

Switching between $P2Y_{12}$-inhibiting therapies is very common in clinical practice. Significant and important drug interactions during the switching protocol could be possibly observed, which is mainly driven by differences in the pharmacology properties of $P2Y_{12}$-receptor inhibitors, their binding sites, half-life, and the rate of onset and offset of action. However, the clinical effect of most switching strategies is not fully determined, given the lack of trials adequately powered or designed to test for safety and efficacy of these strategies. Apart from the PEGASUS-TIMI 54 trial, other available data on the effects of de-escalation are derived from very few clinical trials and from registries or pharmacodynamic studies. Findings from specifically designed pharmacodynamic studies which used surrogate markers of platelet reactivity have made a great contribution in optimizing switching approaches. More clinical studies to substantiate long-term benefits of de-escalation protocols are needed in future. Furthermore, de-escalating the dose and duration or switching the type of $P2Y_{12}$ receptor inhibitors and also as a single anti-platelet therapy have been emerging as effective strategies by controlling the risk of bleeding and occurrence of ischemic events. As briefed in "De-escalating studies and outcomes" section: (i) the dose of $P2Y_{12}$ receptor inhibitors might be reduced in stable patients after MI with at least one additional atherothrombotic risk factor; (ii) duration of DAPT, may perhaps be shortened to 3 or 6 months in stable CAD or low-risk ACS (unstable angina) patients with newer generation DES; (iii) and patients with DAPT including potent $P2Y_{12}$ receptor inhibitors reporting major bleeding or other adverse reactions (such as dyspnea) or requiring oral anticoagulation, could be switched from ticagrelor/prasugrel to clopidogrel. Although the results of studies on ticagrelor monotherapy have not been published, and more mechanistic studies substantiating these protocols, both quantitatively and qualitatively are needed.

Previous research data have shown that de-escalation in low ischemic risk patients offers comparable antiplatelet efficacy along with lowering bleeding events. However, whether or not this result can be validated in routine clinical practice remains to be tested. Physicians' ability to weigh out the benefits and risks of higher or lower platelet inhibition in their patients may lead to individualized prescriptions. They will constantly need to make difficult decisions drawing a fair balance between reducing individual ischemic events and bleeding risks, since the condition of the patient is always changing.

Conflicts of interest

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Author contributions

The author is responsible for all content and editorial decisions.

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