De-Escalation of P2Y₁₂ Receptor Inhibitor Therapy after Acute Coronary Syndromes in Patients Undergoing Percutaneous Coronary Intervention

Danny Kupka, MD and Dirk Sibbing, MD

ABSTRACT

Dual antiplatelet therapy (DAPT) — a combination of a P2Y₁₂ receptor inhibitor and aspirin — has revolutionized antithrombotic treatment. Potent P2Y₁₂ inhibitors such as prasugrel and ticagrelor exhibit a strong and more consistent platelet inhibition when compared to clopidogrel. Therefore, ticagrelor and prasugrel significantly reduce ischemic events, but at an expense of an increased bleeding risk in acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI). These observations have engaged intensive clinical research in alternative DAPT regimens to achieve sufficient platelet inhibition with an acceptable bleeding risk. Our review focusses on P2Y₁₂ receptor therapy de-escalation defined as a switch from a potent antiplatelet agent (ticagrelor or prasugrel) to clopidogrel. Recently, both unguided (platelet function testing independent) and guided (platelet function testing dependent) DAPT de-escalation strategies have been investigated in different clinical studies and both switching strategies could be possible options to prevent bleeding complications without increasing ischemic risk. In light of the still limited data currently available, future large-scale trials should accumulate more data on various DAPT de-escalation regimens with both ticagrelor and prasugrel in unguided and guided de-escalation approaches. In the current review we aim at summarizing and discussing the current evidence on this still emerging topic in the field of antiplatelet treatment.

Keywords: Acute coronary syndrome; P2Y₁₂ Inhibitors; DAPT de-escalation

INTRODUCTION

Dual antiplatelet therapy (DAPT) — a combination of a P2Y₁₂ receptor inhibitor and aspirin — has revolutionized antithrombotic treatment options in an acute coronary syndrome (ACS) patients with and without invasive management. The accessibility of a variety of P2Y₁₂ inhibitors enabled physicians to switch these drugs in reflection of individual patient features including their bleeding and thrombotic risk after stent implantation. The potent P2Y₁₂ inhibitors prasugrel and ticagrelor exhibit a strong and more consistent platelet inhibition when compared to clopidogrel. These pharmacologic properties resulted in a significant reduction in ischemic events, albeit at the expense of an increased bleeding risk in ACS.
patients undergoing percutaneous coronary intervention (PCI).\(^3\) The challenge of preventing ischemic events with an acceptable bleeding risk of ACS patients by adapting P2Y\(_{12}\) receptor inhibitor therapy is a field of intensive research.\(^9\) Switching between oral P2Y\(_{12}\) inhibitors can either result in a stronger P2Y\(_{12}\) receptor inhibition (e.g. clopidogrel to prasugrel or ticagrelor) or reduced P2Y\(_{12}\) receptor inhibition (e.g. ticagrelor or prasugrel to clopidogrel). Those strategies are defined as DAPT escalation and de-escalation, respectively.\(^7\) In the pivotal phase III trials (PLATO, TRITON-TIMI 38) ticagrelor and prasugrel significantly reduced ischemic events especially in the early period after PCI when compared to clopidogrel.\(^3\)\(^4\) However, bleeding complications are an omnipresent issue during the entire maintenance phase of DAPT (Figure 1). In addition, switching to clopidogrel may have an economic advantage given the high treatment costs of ticagrelor and prasugrel.\(^7\) An unguided DAPT de-escalation approach is already adopted by many physicians when treating ACS patients after PCI\(^7\) but the limited data that is available is still conflicting.\(^3\)\(^9\)\(^10\) Moreover, the current clinical practice guidelines offer no clear recommendations on de-escalation of P2Y\(_{12}\) inhibitors, leaving clinicians uninformed on how to manage these patients.\(^3\)\(^11\)\(^12\) Our review summarizes and explains the rationale as well as the current evidence on de-escalating P2Y\(_{12}\) receptor inhibitor treatment, including both un-guided and guided treatment approaches.

**GENERAL ASPECTS OF P2Y\(_{12}\) RECEPTOR THERAPY DE-ESCALATION**

Oral P2Y\(_{12}\) receptor inhibitor treatment is a key element for secondary prevention of thrombotic events in ACS patients and especially for those patients with invasive management by means of PCI.\(^2\) For ACS patients the current clinical practice guidelines recommend a one-year treatment period with a potent P2Y\(_{12}\) inhibitors combined with aspirin.\(^13\)\(^14\) Prasugrel and ticagrelor are superior to clopidogrel in preventing ischemic events\(^9\) due to a more immediate and intense platelet inhibition. In general, escalated DAPT is accompanied by a higher risk for bleeding events and those bleeds are very prominent during the maintenance phase of treatment (Figure 1).\(^3\)\(^4\)\(^15\)\(^16\) Therefore, identification of appropriate patients for DAPT de-escalation may prove useful for an optimized and more

![Figure 1](https://e-kcj.org)
personalized P2Y_12 receptor treatment after PCI. As outlined in Figure 2 there are factors that favor and there are factors against a DAPT de-escalation approach. In clinical practice, there is a variety of possibilities to downgrade the potency of antiplatelet treatment over time and this may include a dose reduction of potent P2Y_12 receptor blockers, a discontinuation of aspirin, and a possible shortening of the DAPT duration. Our review focuses on a true DAPT de-escalation defined as a switch from a potent P2Y_12 blocker such as prasugrel or ticagrelor to clopidogrel. Indeed, many physicians already shorten the treatment duration with the potent drugs to the early weeks or months after the ACS event. The main reasons for de-escalation in this setting are reduced costs and concerns of bleeding during prasugrel and ticagrelor treatment, respectively. In case of ticagrelor, side effects such as dyspnea represent an additional possibility for modifying the ongoing treatment. Although there is general paucity of randomized data on de-escalating P2Y_12 blocker therapy (Table 1), 2 randomized controlled trials have provided first and promising results on the efficacy and safety of such a biologically plausible treatment regimen. Whereas the timing of optimal platelet inhibition after acute coronary syndrome (TOPIC) trial investigated an unguided DAPT strategy that included both ticagrelor and prasugrel, Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndrome (TROPICAL-ACS) used platelet function testing to guide DAPT de-escalation from the potent P2Y_12 inhibitor prasugrel to clopidogrel.

**UNGUIDED DUAL ANTIPLATELET THERAPY DE-ESCALATION**

Observational data suggests an in-hospital de-escalation rate of 5–14% and a post-hospital switching rate of 5–8%. For instance, Treatment With Adenosine Diphosphate (ADP) Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome (TRANSLATE ACS), a large multicenter, longitudinal registry in 12,365 ACS patients captured data on post discharge switching in patients with acute myocardial infarction. Among patients discharged on prasugrel or ticagrelor a switch to clopidogrel was very common and strongly associated with having a government medication insurance.
Studies addressing issues of P2Y₁₂ inhibitor switching are described by approach, study design and key results. TROPICAL-ACS and TOPIC are randomized controlled trials, whereas SCOPE and TRANSLATE ACS are observational studies on outcomes after switching. PRAGUE-18 was not intended to address P2Y₁₂ inhibitor switching. This post-hoc analysis analyzes DAPT switching one year after randomization.

ACS = acute coronary syndrome; ADP = adenosine diphosphate; BARC = bleeding academic research consortium; CABG = coronary artery bypass grafting; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MACE = major adverse cardiac events; MI = myocardial infarction; NACE = net adverse cerebrovascular events (combination of MACE and bleeding events); NNT = number needed to treat; PCI = percutaneous coronary intervention; PFT = platelet function testing; PRAGUE-18 = Comparison of Prasugrel and Ticagrelor in the Treatment of Acute Myocardial Infarction; RCT = randomized controlled trial; SCOPE = Switching From Clopidogrel to New Oral Antiplatelet Agents During Percutaneous Coronary Intervention; TIMI = thrombolysis in myocardial infarction; TROPICAL-ACS = Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndrome.

Table 1. Studies on P2Y₁₂ receptor inhibitor de-escalation

| Study (acronym) | Approach | P2Y₁₂ receptor inhibitors | No. of patients and study design | Key results | Ref. |
|-----------------|----------|----------------------------|---------------------------------|-------------|-----|
| TROPICAL-ACS    | Effect of PFT-guided de-escalation in PCI-treated patients | Prasugrel | Clopidogrel | RCT | Primary endpoint (control vs. PFT-guided de-escalation): Net clinical benefit of CV death, MI, stroke, BARC bleeding;2 (9% vs. 7%; HR, 0.81; 95% CI, 0.62–1.06; p=0.0004) Subgroup analysis (escalation vs. de-escalation) - CV death, MI, stroke (3% vs. 3%; p=0.0115) - BARC bleeding events:2 (6% vs. 5%; HR, 0.82; 95% CI, 0.59–1.33; p=0.23) | (10,20,43) |
| TOPIC           | Effect of unguided de-escalation in PCI-treated patients | Ticagrelor | Prasugrel | Clopidogrel | RCT | Primary endpoint: (control vs. unguided de-escalation): CV death, urgent revascularization, stroke, BARC bleeding:2 (26.3% vs. 13.7%; HR, 0.48; 95% CI, 0.34–0.68; p=0.001) | (7,14) |
| SCOPE           | Investigate the incidence of switching P2Y₁₂ blocker and its safety in ACS patients with PCI | Ticagrelor | Prasugrel | Clopidogrel | Observational study | Primary endpoint: MACE (1.6%) and NACE (5.6%) Switching rate: cath lab (2.3%), discharge (3.3%), follow-up (5.2%) Subgroup analysis (escalation vs. de-escalation) - Patients with escalation: no NACE occurred among patients receiving an escalation (escalation vs. de-escalation: OR, 25.2; 95% CI, 1.4–242.9; p=0.02) - Patients with de-escalation: NACE increased (OR, 5.3; CI, 2.1–18.2; p=0.04) | (32) |
| TRANSLATE ACS   | Investigation of post-discharge P2Y₁₂ receptor blocker switching | Ticagrelor | Prasugrel | Clopidogrel | Observational study | Primary endpoint: MACE, factors for ADP receptor inhibitor choice Switching rate: overall 7.6% Switch in P2Y₁₂ inhibitor groups: ticagrelor (28.3%), prasugrel (15.4%), clopidogrel (3.6%) Main reasons for switching: costs (40.3%), physicians decision (60.7%) | (9,10) |
| PRAGUE-18       | Evaluate treatment of ticagrelor versus prasugrel in patients with STEMI undergoing PCI | Prasugrel | Ticagrelor | RCT | Primary endpoint (prasugrel vs. ticagrelor): CV death, MI, stroke, all-cause mortality, definite stent thrombosis (HR, 1.167; 95% CI, 0.742–1.835; p=0.503), all bleeding (10.9% vs. 11.1%; p=0.999), TIMI major bleeding (6.6% vs. 5.7%; p=0.754) Switching rate: economic (39%), antiagulation (3.2%), adverse events (4.5%), other 6.8% | (10,44) |

Studies on P2Y₁₂ receptor inhibitor switching suggest that factors such as costs, physician decision, and patient education can influence the decision to switch. Financial hardship and the cost of medication are additional factors that may impact the decision to switch. The results from these studies highlight the importance of considering both clinical and cost-related factors when making decisions about DAPT de-escalation.
Non-economically switch was accompanied by a higher ischemic event rate. Overall, patients who de-escalated to clopidogrel due to economic reasons had reduced risk compared with those who continued on ticagrelor or prasugrel. However, it must be emphasized that PRAGUE-18 investigators reported those outcome measures in relation to switch of treatment, while the trial was not specifically designed to address those questions.29

Non-randomized registry data from the Switching From Clopidogrel to New Oral Antiplatelet Agents During Percutaneous Coronary Intervention (SCOPE) registry in 1,363 patients revealed that ischemic events were substantially increased in patients undergoing a de-escalation approach after PCI for ACS.30 Such findings should raise a note of caution to an unguided de-escalation approach, although randomized data from a smaller single-center trial is promising. Indeed, the TOPIC trial evaluated the clinical benefit of an unguided DAPT de-escalation by switching from prasugrel or ticagrelor to clopidogrel one month after PCI for ACS (Figure 3). This smaller single-center study enrolled 646 patients and the primary end point — a net clinical benefit endpoint consisting of cardiovascular death, urgent revascularization, stroke and bleeding as defined by the Bleeding Academic Research Consortium (BARC) classification — occurred in 13.4% in the switched versus 26.3% in the unswitched group (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.34–0.68; p<0.01). This net benefit favoring DAPT de-escalation was driven by a reduction in overall bleeding events but it must be emphasized that ischemic events like stent thrombosis or myocardial infarctions were not reported in a detailed manner at all. Interestingly, in a platelet function testing (PFT) sub-study of the TOPIC trial (TOPIC-VASP) de-escalated DAPT was superior regardless of initial platelet reactivity, but the benefit was greater in low on-treatment platelet reactivity patients.31 Considering all the available evidence on an unguided DAPT de-escalation approach it must be emphasized that the data

---

**Figure 3.** Trials and possible strategies for un-guided and guided DAPT de-escalation. The figure shows studies and strategies on DAPT de-escalation approaches for P2Y<sub>12</sub> receptor therapy. (A) Guided de-escalation of DAPT investigated in the TROPICAL-ACS trial. Patients were enrolled if they had biomarker-positive acute coronary syndrome with successful PCI and randomly assign to a PFT-based DAPT de-escalation arm or uniform prasugrel treatment. (B) Unguided DAPT de-escalation investigated in the TOPIC trial. Patients with ACS and undergoing coronary intervention, on aspirin and a potent P2Y<sub>12</sub> blocker were randomly assigned to switch to aspirin and clopidogrel or continuation of their drug regimen with a potent P2Y<sub>12</sub> inhibitor.

**ACS** = acute coronary syndrome, **DAPT** = dual antiplatelet therapy, **PFT** = platelet function testing; **TOPIC** = timing of optimal platelet inhibition after acute coronary syndrome; **TROPICAL-ACS** = Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndrome.
available is conflicting and that further studies in larger cohorts of patients are urgently needed to lend more support to such an unguided approach of de-escalating DAPT (early or late) in ACS patients after PCI.

GUIDED DAPT DE-ESCALATION

The pro-drug clopidogrel is characterized by a significant response variability and a substantial proportion of patients exhibit a status of high on-treatment platelet reactivity (HPR). This and other circumstances triggered the development of ex-vivo PFT assays.\(^{34-37}\) Indeed, DAPT de-escalation from a potent P2Y\(_{12}\) inhibitor to the less potent clopidogrel should account for the large response variability of the latter\(^{38}\) and the consequential issue of HPR, which exists in a relevant number of ACS patients.\(^{39}\) HPR patients exhibit a higher risk for ischaemic events including myocardial infarction and stent thrombosis.\(^{40}\) Hence, PFT could serve to safeguard a DAPT de-escalation by identifying HPR patients on clopidogrel, as those patients may be exposed to a higher risk of thrombotic events due to insufficient P2Y\(_{12}\) inhibition and they should therefore continue with potent P2Y\(_{12}\) inhibitors. Taking all these relevant aspects into consideration, the objective of the randomized, multicenter investigator-initiated TROPICAL-ACS trial\(^{29}\) (n=2,610 patients) was to investigate the safety and efficacy of a PFT-guided early de-escalation of antiplatelet treatment compared to standard prasugrel therapy in ACS patients undergoing PCI. The trial met its primary endpoint and demonstrated non-inferiority for a net clinical benefit endpoint in patients scheduled for PFT guided de-escalation vs. conventional prasugrel treatment.\(^{29}\) Importantly, the rates of ischemic events including CV death, MI or stroke were similar in the guided de-escalation study group vs. control group and a trend towards less bleeding during guided treatment was reported. Therefore, a strategy of guided DAPT de-escalation can be considered in selected ACS patients (NSTEMI and STEMI) as an alternative to 12 months treatment with ticagrelor or prasugrel. It must be acknowledged that such a guided de-escalation strategy results in clopidogrel treatment in most but not in all patients, as some patients would have to be escalated back to prasugrel. The TROPICAL-ACS trial was powered for demonstrating non-inferiority for the primary endpoint (net clinical benefit) and was not powered for ischemic events alone. Thus, large-scale trials would be helpful to corroborate the safety of such a concept with respect to ischemic risk of ACS patients after treatment de-escalation. For the time being and based on the reported results a selective use of a guided DAPT de-escalation strategy seems reasonable and this strategy may be a good alternative for DAPT in selected patients and especially for those who cannot go for 1-year potent platelet inhibition.

Elderly ACS patients have a unique risk profile for both ischemic and bleeding events. The ANTARCTIC trial (Adjust Antiplatelet Therapy in Elderly Patients Stented for an Acute Coronary Syndrome) aimed to assess the safety and efficacy of PFT in 877 ACS patients ≥75 years.\(^{40}\) The study compared a reduced dose of prasugrel (5 mg/d, as recommended for elderly patients) vs. PFT-guided escalation (10 mg prasugrel) or de-escalation (75 mg clopidogrel) in the intervention arm. Study results were neutral, with similar ischemic and bleeding rates in both groups (28% vs. 28%; HR, 1.003; 95% CI, 0.78–1.29; p=0.98). When interpreting ANTARCTIC results it should be noted that superiority of low-dose prasugrel over standard clopidogrel treatment in terms of clinical outcomes has not been demonstrated, independent of whether or not PFT was included.\(^{41}\) A subgroup analysis of TROPICAL-ACS also addressed the impact of age on clinical outcomes after guided
de-escalation. In patients younger than 70 years the incidence of the primary endpoint (cardiovascular death, myocardial infarction, stroke, BARC bleeding) was significantly lower in the guided de-escalation versus the control group (5.9% vs. 8.3%; HR, 0.70; 95% CI, 0.51–0.96; p=0.03; NNT=42) mainly driven by reduced bleeding events. In patients older than 70 years the primary endpoint occurred more frequent but was indistinguishable between both groups (15.5% vs. 13.6%). Thus, the age-dependent results from TROPICAL-ACS confirmed ANTARCTIC study results and a possible benefit of PFT with individualized treatment may be confined to younger patients while effects are neutral in the elderly.

THE EAST-ASIAN PARADOX OF PLATELET INHIBITION

Specific considerations must be reflected for the large population of East Asian patients, who carry a different and very specific risk profile for both ischemic and bleeding complications when compared to the Caucasian population. Related to this, a different and specific genetic profile (higher prevalence for the CYP2C19*2 and *3 Loss-of-Function [LoF] alleles) is associated with a significantly higher rate of HPR in East Asian patients. Despite this difference and very surprisingly, East Asians do not show an elevated risk for thrombotic complications. In contrast, a significantly lower risk of ischemic events was described leading to a phenomenon further referred to as the ‘East Asian paradox.’ Thus, based on these specific clinical observations, a right-shifted therapeutic window of on-treatment P2Y₁₂-directed platelet reactivity with higher cut-offs for HPR may apply to East Asian patients in contrast to Caucasians and this may have an impact on drugs and drug dosing for those patients. Moreover, with respect to a lower body mass index reduced doses of prasugrel and ticagrelor may be a good choice for East Asian patients specifically.

CONCLUSION AND OUTLOOK

In conclusion and based on the results of the pivotal phase III trials a 12 months DAPT that includes prasugrel or ticagrelor for ACS patients after PCI is standard of care in 2018 and beyond. However, a DAPT de-escalation must be considered as an attractive alternative treatment concept and may be considered in specific clinical scenarios (bleeding events, high bleeding risk, socio-economic indications) as an alternative to DAPT with potent P2Y₁₂ receptor inhibitors (Figures 1 and 2). Based upon the current evidence any DAPT de-escalation should be guided and an unguided de-escalation may carry a substantial risk for the patient. Alternative treatment regimens of single antiplatelet therapy after stopping aspirin early after PCI and with continued treatment with a potent P2Y₁₂ receptor inhibitor (ticagrelor) are under clinical investigation in the GLOBAL LEADERS (ClinicalTrials.gov, NCT01813435) and TWILIGHT (ClinicalTrials.gov, NCT02270242) trials. Those trials may have the potential to reduce bleeding risk without influencing antithrombotic efficacy. In contrast to a PFT guided adjustment of antiplatelet therapy, the TAILOR PCI (ClinicalTrials.gov, NCT01742117) and POPular Genetics trial (ClinicalTrials.gov, NCT01761786) use a genetic approach of individualized DAPT. As clopidogrel response is dependent on CYP2C19 polymorphisms, these trials investigate the usefulness of selective genotyping (CYP2C19) during P2Y₁₂ receptor inhibitor treatment. All the published and ongoing trials in concert are important as attempts to move forward and to pave the way for a contemporary concept of a more personalized P2Y₁₂ receptor inhibitor therapy that includes both escalation and de-escalation strategies for selected patients.
REFERENCES

1. Schömig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med* 1996;334:1084-9.

2. Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. *Nat Rev Cardiol* 2015;12:30-47.

3. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045-57.

4. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357:2001-15.

5. Sibbing D, Angiolillo DJ, Huber K. Antithrombotic therapy for acute coronary syndrome: past, present and future. *Thromb Haemost* 2017;117:1240-8.

6. Rollini F, Franchi F, Angiolillo DJ. Switching P2Y12-receptor inhibitors in patients with coronary artery disease. *Nat Rev Cardiol* 2016;13:11-27.

7. Angiolillo DJ, Rollini F, Storey RF, et al. International expert consensus on switching platelet P2Y12 receptor-inhibiting therapies. *Circulation* 2017;136:1955-75.

8. Velders MA, Abtan J, Angiolillo DJ, et al. Safety and efficacy of ticagrelor and clopidogrel in primary percutaneous coronary intervention. *Heart* 2016;102:617-25.

9. Bagai A, Peterson ED, Honeycutt E, et al. In-hospital switching between adenosine diphosphate receptor inhibitors in patients with acute myocardial infarction treated with percutaneous coronary intervention: Insights into contemporary practice from the TRANSLATE-ACS study. *Eur Heart J Acute Cardiovasc Care* 2015;4:499-508.

10. Motovska Z, Hlinomaz O, Kala P, et al. 1-year outcomes of patients undergoing primary angioplasty for myocardial infarction treated with prasugrel versus ticagrelor. *J Am Coll Cardiol* 2018;71:371-81.

11. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;64:e139-228.

12. Valgimigli M, Bueno H, Byrne RA, et al. ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for Dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2017;2017:26.

13. Ibanez B, James S, Agewall S, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2017;2017:26.

14. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;37:267-315.

15. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet* 2009;373:723-31.

16. Wiviott SD, Braunwald E, Angiolillo DJ, et al. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic...
outcomes by optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial Infarction 38. Circulation 2008;118:1626-36.

17. Antman EM, Wiviott SD, Murphy SA, et al. Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitionN with Prasugrel-Thrombolysis In Myocardial Infarction) analysis. J Am Coll Cardiol 2008;51:2028-33.

18. Becker RC, Bassand JP, Budaj A, et al. Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J 2011;32:2933-44.

19. Saito S, Ishihiki T, Kimura T, et al. Efficacy and safety of adjusted-dose prasugrel compared with clopidogrel in Japanese patients with acute coronary syndrome: the PRASFIT-ACS study. Circ J 2014;78:1684-92.

20. Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Engl J Med 2017;377:1513-24.

21. Alexopoulos D, Xanthopoulou I, Deftereos S, et al. In-hospital switching of oral P2Y12 inhibitor treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention: prevalence, predictors and short-term outcome. Am Heart J 2014;167:58-76.e2.

22. Clemmensen P, Greico N, Ince H, et al. MULTInational non-interventional study of patients with ST-segment elevation myocardial infarction treated with PRimary Angioplasty and Concomitant use of upstream antiplatelet therapy with prasugrel or clopidogrel--the European MULTIPRAC Registry. Eur Heart J Acute Cardiovasc Care 2015;4:220-9.

23. De Luca L, Leonardi S, Cavallini C, et al. Contemporary antithrombotic strategies in patients with acute coronary syndrome admitted to cardiac care units in Italy: The EYESHOT Study. Eur Heart J Acute Cardiovasc Care 2015;4:441-52.

24. Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015;372:1791-800.

25. Alexopoulos D, Xanthopoulou I, Perperis A, et al. Dyspnea in patients treated with P2Y12 receptor antagonists: insights from the GReek AntiPlatElet (GRAPE) registry. Platelets 2017;28:691-7.

26. Bonaca MP, Bhatt DL, Oude Ophuis T, et al. Long-term tolerability of ticagrelor for the secondary prevention of major adverse cardiovascular events: a secondary analysis of the PEGASUS-TIMI 54 trial. JAMA Cardiol 2016;1:4-25-32.

27. Cuisset T, Deharo P, Quilici J, et al. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. Eur Heart J 2017;38:3070-8.

28. Sibbing D, Aradi D, Jacobshagen C, et al. A randomised trial on platelet function-guided de-escalation of antiplatelet treatment in ACS patients undergoing PCI. Rationale and design of the Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes (TROPICAL-ACS) Trial. Thromb Haemost 2017;117:188-95.

29. Sibbing D, Aradi D, Jacobshagen C, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. Lancet 2017;390:1747-57.
31. Motovska Z, Hlinomaz O, Miklik R, et al. Prasugrel versus ticagrelor in patients with acute myocardial infarction treated with primary percutaneous coronary intervention: multicenter randomized PRAGUE-18 Study. *Circulation* 2016;134:1603-12.

32. De Luca L, D’Ascenzo F, Musumeci G, et al. Incidence and outcome of switching of oral platelet P2Y12 receptor inhibitors in patients with acute coronary syndromes undergoing percutaneous coronary intervention: the SCOPE registry. *EuroIntervention* 2017;13:459-66.

33. Deharo P, Quilici J, Camoin-Jau L, et al. Benefit of switching dual antiplatelet therapy after acute coronary syndrome according to on-treatment platelet reactivity: the TOPIC-VASP pre-specified analysis of the TOPIC randomized study. *JACC Cardiovasc Interv* 2017;10:2560-70.

34. Gurbel PA, Bliden KP, Hiatt BL, O’Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation* 2003;107:2908-13.

35. Tantry US, Bonello L, Aradi D, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. *J Am Coll Cardiol* 2013;62:2261-73.

36. Gurbel PA, Bliden KP, Samara W, et al. Clopidogrel effect on platelet reactivity in patients with stent thrombosis: results of the CREST Study. *J Am Coll Cardiol* 2005;46:1827-32.

37. Sibbing D, Braun S, Morath T, et al. Platelet reactivity after clopidogrel treatment assessed with point-of-care analysis and early drug-eluting stent thrombosis. *J Am Coll Cardiol* 2009;53:849-56.

38. Aradi D, Kirtane A, Bonello L, et al. Bleeding and stent thrombosis on P2Y12-inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. *Eur Heart J* 2015;36:1762-71.

39. Stone GW, Witzenbichler B, Weisz G, et al. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *Lancet* 2013;382:614-23.

40. Cayla G, Cuisset T, Silvain J, et al. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. *Lancet* 2016;388:2015-22.

41. Levine GN, Jeong YH, Goto S, et al. Expert consensus document: World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. *Nat Rev Cardiol* 2014;11:597-606.

42. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med* 2009;360:354-62.

43. Mega JL, Close SL, Wiviott SD, et al. Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. *Lancet* 2010;376:1312-9.

44. Mega JL, Simon T, Collet JP, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA* 2010;304:1821-30.

45. Wallentin L, James S, Storey RF, et al. PLATO investigators. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. *Lancet* 2010;376:1320-8.