EuroIntervention 2023;18:e1304-e1306 published online e-edition April 2023

Aspirin: should it be stopped directly after PCI?

Paul A. Gurbel[1]*, MD; Udaya S. Tantry[1], PhD; Patricia O. Guimarães[2], MD, PhD; Pedro A. Lemos[2,3]**, MD, PhD

1. Sinai Center for Thrombosis Research and Drug Development, Sinai Hospital of Baltimore, Baltimore, MD, USA; 2. Hospital Israelita Albert Einstein, São Paulo, Brazil; 3. Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil

Introduction

Aspirin has long been a cornerstone of secondary prevention in patients undergoing percutaneous coronary intervention (PCI). However, advances reducing the thrombogenicity of coronary stents and the introduction of potent $P2Y_{12}$ receptor inhibitors prompted a series of randomised trials of $P2Y_{12}$ receptor inhibitor monotherapy that questioned the role of aspirin, even immediately after PCI. In this perspective article, we asked experts in the field to provide their opinions on aspirin-free strategies and the optimal duration of aspirin after PCI.

Perspective of Paul A. Gurbel, MD; Udaya S. Tantry, MD

Aspirin remains the bedrock of antiplatelet therapy for reducing recurrent arterial thrombotic complications. The current guideline recommendation for all patients undergoing percutaneous coronary intervention (PCI) without contraindications is treatment with an aspirin loading dose followed by a daily maintenance dose of 75-100 mg (Class I, Level A)[1]. The maintenance dose is largely based on a 2002 meta-analysis of randomised trials of an antiplatelet regimen in high vascular risk patients[2]. In that meta-analysis, aspirin therapy at a 75-150 mg daily dosing was associated with a 32% proportional reduction in vascular events and a 50% proportional increase in major extracranial bleeding. Overall mortality was also significantly reduced with aspirin. A lot has happened since then: potent $P2Y_{12}$ inhibitors have come to the fore to treat high-risk PCI patients on top of aspirin. Post-PCI bleeding in the setting of dual antiplatelet therapy (DAPT) has been clearly shown to carry an elevated mortality risk that may exceed the risk associated with coronary thrombosis[3]. This latter sobering evidence has stimulated a reassessment of the utility of aspirin after PCI to curtail bleeding, particularly in the presence of effective $P2Y_{12}$-receptor blockade. There is now overwhelming evidence that the synchronous blockade of 2 platelet activation pathways (COX-1 and $P2Y_{12}$) causes more bleeding than the blockade of either pathway alone.

Continuous downstream signalling from the $P2Y_{12}$ receptor is critical for the activation of the glycoprotein (GP)IIb/IIIa receptors and subsequent stable platelet aggregation. Therefore, in the

**Corresponding author: Sinai Center for Thrombosis Research and Drug Development, Sinai Hospital of Baltimore, 2401 West Belvedere Avenue, Baltimore, MD 21215, USA. Email: pgurbel@lifebridgehealth.org*

***Corresponding author: Hospital Israelita Albert Einstein, Av. Albert Einstein, 627/701 - Morumbi, São Paulo - SP, 05652-900, Brazil. Email: pedro.lemos@einstein.br*

DOI: 10.4244/EIJ-E-23-00001

presence of effective $P2Y_{12}$-receptor inhibition, aspirin may not provide greater overall platelet inhibitory and resultant anti-ischaemic effects to outweigh the increased bleeding risk. In line with this, a therapeutic window for $P2Y_{12}$ inhibition has been revealed, where inhibition above a certain threshold does not confer further anti-ischaemic benefits[4].

There are pharmacodynamic and clinical data to support potent (effective) $P2Y_{12}$-inhibitor monotherapy. In a healthy volunteer *ex vivo* study (n=9), the addition of 75 mg or 300 mg of daily aspirin on top of prasugrel was associated with only modestly enhanced platelet inhibition in response to various agonists[5]. The TWILIGHT Trial demonstrated a lower rate of clinically relevant bleeding (any overt, actionable sign of haemorrhage) and a similar rate of ischaemic events among high-risk PCI patients who were treated with ticagrelor monotherapy as compared to ticagrelor plus aspirin after 3 months of DAPT. In a mechanistic substudy of TWILIGHT (n=51), similar *ex vivo*-measured thrombus size under dynamic flow conditions and similar adenosine diphosphate-induced and thrombin receptor-activating peptide-induced platelet aggregation were demonstrated with DAPT versus ticagrelor monotherapy[3]. Randomised trials comparing DAPT with $P2Y_{12}$-blocker monotherapy in 32,181 stented patients and meta-analyses reported an overall 50-60% reduction in major bleeding with monotherapy, with no ischaemic penalty[6].

Further data to support effective $P2Y_{12}$-inhibitor monotherapy immediately after stenting were explored in a multicentre pilot trial of patients with low bleeding and ischaemic risk (SYNergy Between PCI With Taxus and Cardiac Surgery [SYNTAX] scores <23) (n=201). Elective everolimus-eluting stenting was performed in patients on aspirin and clopidogrel therapy. Prasugrel monotherapy was then administered immediately following stenting to all patients for 3 months. The rates of the primary ischaemic (n=1) and bleeding endpoints (n=1) were low, with no stent thrombosis[7].

Taken together, the emerging pharmacodynamic and clinical data suggest that aspirin therapy in the presence of effective $P2Y_{12}$-receptor inhibition may not be associated with an incremental antiplatelet/anti-ischaemic effect that outweighs the increase in bleeding risk. Moreover, the current use of newer-generation thin-strut drug-eluting stents may further tip the bleeding-ischaemia scale in favour of $P2Y_{12}$-receptor inhibitor monotherapy. Furthermore, in the current era of rigorous secondary prevention strategies targeting hypertension, diabetes mellitus, lipids, and inflammation, the addition of aspirin to effective $P2Y_{12}$-receptor inhibition may not provide the additional anti-ischaemic benefits seen in the "old era". However, we need to be careful about our exuberance for an aspirin-free era of PCI. There are reasons why incremental bleeding occurs when COX-1 blockade is added to $P2Y_{12}$-receptor blockade that extend beyond the mechanistic studies reported above. These reasons include the effects of aspirin on coagulation, inflammation, and the physical characteristics of the clot − properties that may be important in the high-risk prothrombotic patient, particularly early on in the stenting time period.

Perspective of Pedro A. Lemos, MD, PhD; Patricia O. Guimarães, MD, PhD

Right from the start of coronary stenting in clinical practice, more than 35 years ago, the occurrence of thrombotic events has been perceived as the most feared complication. The subsequent introduction of high-pressure stent implantation coupled with an antiplatelet scheme comprising the association of aspirin (ASA) and a $P2Y_{12}$ inhibitor, the so-called dual antiplatelet therapy (DAPT), brought the risk of stent thrombosis down to acceptable levels, revolutionising interventional cardiology. Since then, coronary stents have been rapidly catapulted into the domain of dominant devices utilised worldwide, and DAPT has been established as the standard of care after percutaneous coronary intervention (PCI)[8].

However, over the years, expressive improvements have been gradually added to the interventional armamentarium, ultimately reshaping the landscape of the field. To name a few, current thin-strut low-dose drug-eluting stents, as well as sophisticated implantation techniques make today's PCI less thrombogenic than historical procedures[9]. Moreover, the evolution of antiplatelet drugs, from ticlopidine to clopidogrel, and later, to ticagrelor and prasugrel, has provided very predictable and potent antiplatelet possibilities at the present day[10]. Also, contemporary knowledge has evolved, and nowadays it is well known that the summed effects of two antiplatelet agents increase the risk of haemorrhagic complications and that post-PCI bleeding has a strong association with poor outcomes, even greater than that of post-discharge myocardial infarction[11].

Taking all these points into consideration, current PCI tends to be less thrombogenic, antiplatelet drugs are more efficacious and predictable, and avoidance of haemorrhage is an important learned fact. One may therefore hypothesise that monotherapy with a $P2Y_{12}$ inhibitor – without ASA – would be sufficient to provide similar degrees of ischaemic protection, with the potential advantage of decreasing the risk of bleeding complications, compared with DAPT[10].

A strategy of omitting ASA after a short period of DAPT has already been tested in several randomised trials with overall favourable results, leading guidelines to endorse the discontinuation of ASA, instead of the $P2Y_{12}$-inhibitor, when DAPT is de-escalated to single antiplatelet therapy[3]. Presently, several other ongoing clinical trials are investigating $P2Y_{12}$-inhibitor monotherapy to better understand the clinical value of this strategy[10].

To date, in all completed randomised clinical trials, $P2Y_{12}$-inhibitor monotherapy was instituted only after an initial period of ASA plus $P2Y_{12}$-inhibitors (i.e., DAPT) of 1-3 months[10]. However, the latest pharmacodynamic investigations suggest that the presence of ASA provides little additional benefit to the platelet inhibition promoted by potent $P2Y_{12}$ blockers and, in fact, may increase the haemorrhagic propensity[10]. Those recent mechanistic insights, therefore, raise the question on whether ASA in the early phase after PCI is truly essential to prevent thrombotic complications or whether its use only contributes to inducing bleeds, including in-hospital ones.

The impact of ASA withdrawal at day 0 after PCI was assessed in the Acetyl Salicylic Elimination Trial: The ASET Pilot Study (ASET), which recorded null ischaemic events among 201 chronic stable angina patients who were treated with aspirin-free prasugrel monotherapy initiated immediately after the procedure[7]. The ongoing PercutaNEOus Coronary Intervention Followed by Monotherapy INstead of Dual Antiplatelet Therapy in the SETting of Acute Coronary Syndromes: The NEO-MINDSET Trial (NEOMINDSET) (ClinicalTrials.gov: NCT04360720) is designed to compare monotherapy with a potent $P2Y_{12}$ inhibitor versus DAPT in 3,400 participants with acute coronary syndromes; they will be followed for 12 months. The final results of this trial will be available in 2024.

In light of what we currently know, should aspirin be stopped at day 0 after PCI? Unfortunately, a definitive answer to this question is not available yet. However, both mechanistic and initial clinical data signal that this may be a promising approach for many, if not most, patients, pending scientific results which are soon to be released. Until then, we should keep our mindset fluid and adaptable to an eventual time when sufficient data are (perhaps) available to let go of our strong attachment to ASA.

Conflict of interest statement

P.A. Gurbel has received consulting fees and/or honoraria from Bayer, Otitopic, Janssen, UpToDate, Cleveland Clinic, Adeno, Wolters Kluwer Pharma, Web MD Medscape, Baron and Budd, the North American Thrombosis Forum, and Innovative Sciences; and institutional research grants from the Haemonetics, Janssen, Bayer, Instrumentation Laboratories, Amgen, Idorsia, Otitopic, Hikari Dx, Novartis, Precision Biologic, Nirmidas Biotech, and R-Pharma International; in addition, P.A. Gurbel has two patents issued: Detection of restenosis risk in patients and Assessment of cardiac health and thrombotic risk in a patient. P.A. Gurbel was an expert witness in a lawsuit associated with Plavix. S. Tantry has received an honorarium from UpToDate. P.A. Lemos declares institutional research funding from and/or being an unpaid advisory board member for Abbott, Corindus Inc., Scitech, Boston Scientific, and Flouit but has not received personal payments by pharmaceutical companies or device manufacturers; being part of Argonauts, an innovation facilitator; and being partially supported by a grant from The National Council for Scientific and Technological Development (CNPq) – Brazil (grant number 306677/2019-9). P.O. Guimarães has no conflicts of interest to declare.

References

1. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferović PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO. 2018 ESC/EACTS Guidelines on myocardial revascularization. *EuroIntervention.* 2019;14:1435-534.

2. Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet.* 2009;373:1849-60.

3. Baber U, Zafar MU, Dangas G, Escolar G, Angiolillo DJ, Sharma SK, Kini AS, Sartori S, Joyce L, Vogel B, Farhan S, Gurbel P, Gibson CM, Fuster V, Mehran R, Badimon JJ. Ticagrelor With or Without Aspirin After PCI: The TWILIGHT Platelet Substudy. *J Am Coll Cardiol.* 2020;75:578-86.

4. Tantry US, Bonello L, Aradi D, Price MJ, Jeong YH, Angiolillo DJ, Stone GW, Curzen N, Geisler T, Ten Berg J, Kirtane A, Siller-Matula J, Mahla E, Becker RC, Bhatt DL, Waksman R, Rao SV, Alexopoulos D, Marcucci R, Reny JL, Trenk D, Sibbing D, Gurbel PA; Working Group on On-Treatment Platelet Reactivity. 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.

5. Leadbeater PD, Kirkby NS, Thomas S, Dhanji AR, Tucker AT, Milne GL, Mitchell JA, Warner TD. Aspirin has little additional anti-platelet effect in healthy volunteers receiving prasugrel. *J Thromb Haemost.* 2011;9:2050-6.

6. Verheugt FWA, Damman P, Damen SAJ, Wykrzykowska JJ, Woelders ECI, van Geuns R-M. $P2Y_{12}$ blocker monotherapy after percutaneous coronary intervention. *Neth Heart J.* 2021;29:566-76.

7. Kogame N, Guimarães PO, Modolo R, De Martino F, Tinoco J, Ribeiro EE, Kawashima H, Ono M, Hara H, Wang R, Cavalcante R, Moulin B, Falcão BAA, Leite RS, de Almeida Sampaio FB, Morais GR, Meireles GC, Campos CM, Onuma Y, Serruys PW, Lemos PA. Aspirin-Free Prasugrel Monotherapy Following Coronary Artery Stenting in Patients With Stable CAD: The ASET Pilot Study. *JACC Cardiovasc Interv.* 2020;13:2251-62.

8. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, Bittl JA, Cohen MG, DiMaio JM, Don CW, Fremes SE, Gaudino MF, Goldberger ZD, Grant MC, Jaswal JB, Kurlansky PA, Mehran R, Metkus TS Jr, Nnacheta LC, Rao SV, Sellke FW, Sharma G, Yong CM, Zwischenberger BA. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2022;145:e18-e114.

9. Piccolo R, Pilgrim T, Heg D, Franzone A, Rat-Wirtzler J, Räber L, Silber S, Serruys PW, Jüni P, Windecker S. Comparative Effectiveness and Safety of New-Generation Versus Early-Generation Drug-Eluting Stents According to Complexity of Coronary Artery Disease: A Patient-Level Pooled Analysis of 6,081 Patients. *JACC Cardiovasc Interv.* 2015;8:1657-66.

10. Capodanno D, Baber U, Bhatt DL, Collet JP, Dangas G, Franchi F, Gibson CM, Gwon HC, Kastrati A, Kimura T, Lemos PA, Lopes RD, Mehran R, O'Donoghue ML, Rao SV, Rollini F, Serruys PW, Steg PG, Storey RF, Valgimigli M, Vranckx P, Watanabe H, Windecker S, Angiolillo DJ. P2Y12 inhibitor monotherapy in patients undergoing percutaneous coronary intervention. *Nat Rev Cardiol*, 2022;19:829-44.

11. Généreux P, Giustino G, Witzenbichler B, Weisz G, Stuckey TD, Rinaldi MJ, Neumann FJ, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferri E, Yadav M, Francese DP, Palmerini T, Kirtane AJ, Litherland C, Mehran R, Stone GW. Incidence, Predictors, and Impact of Post-Discharge Bleeding After Percutaneous Coronary Intervention. *J Am Coll Cardiol.* 2015;66:1036-45.