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Letter to the Editor

Early de-escalation of DAPT after PCI: implications of the latest randomized trials in the COVID era

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Dear Sir,

Coronavirus disease 2019 (COVID-19) has changed the way we practice cardiology. All of a sudden, the focus of a cardiologist's practice has shifted from primary percutaneous coronary intervention (PCI) to thrombolysis, from myocardial infarction to COVID-19 associated myocarditis, from looking for ST-T changes on an electrocardiogram to the measurement of QTc, and from routine heavy OPDs to teleconsultations. COVID-19 has changed us all. Next, we might have to change our practice pattern of dual antiplatelet therapy (DAPT) in post PCI patients. This change seems pivotal in the view of the latest data from the recently published randomized controlled trials (RCTs) on the use of DAPT in post PCI patients[1–5] in conjunction with the heightened risk of thrombocytopenia and bleeding associated with COVID-19 [6,7]

Studies have shown that thrombocytopenia frequently occurs in patients with COVID-19.[6] Furthermore, the autopsy studies have shown the frequent occurrence of diffuse alveolar hemorrhage in coronavirus induced lung damage. Such observations suggest a high bleeding tendency associated with COVID-19.[7,8]

DAPT remains the cornerstone therapy in the prevention of ischemic events following PCI. Despite numerous clinical trials, controversy exists regarding the optimal duration of DAPT after PCI with drug-eluting stent (DES).[9,10] All major cardiology society guidelines recommend at least six months of DAPT (aspirin and a P2Y12 inhibitor) following PCI for stable coronary artery disease and 12 months of DAPT in the setting of an acute coronary syndrome (ACS).[1,2] However, in the last 1–2 years, multiple RCTs viz. TICO, TWILIGHT, SMART-CHOICE, and STOPDAPT-2, have demonstrated that early de-escalation of DAPT (1–3 months) to P2Y12 inhibitor monotherapy instead of aspirin is associated with a lower risk of total bleeding events compared with 12 months of DAPT.[1–4] This benefit is achieved without increasing the risk of ischemic outcomes or mortality (See Table 1). Reduced bleeding with no increase in ischemic end-points favors 1–3 months DAPT followed by P2Y12 inhibitor monotherapy in patients with PCI and DES. This approach appears much more appealing in the current context of the COVID-19 pandemic, which is frequently associated with thrombocytopenia and bleeding complications.

Regarding the choice of agent for P2Y12 inhibitor monotherapy, ticagrelor appears to have the edge since most of these recent DAPT trials have used ticagrelor as the P2Y12 inhibitor monotherapy.[1,2,5] Additionally, ticagrelor possesses the most potent anti-inflammatory properties out of all P2Y12 inhibitors,[8,9] which might offer additional advantage against the inflammation-mediated organ damage in the setting of COVID-19. Furthermore, the subgroup analysis of the PLATO trial revealed that, compared to clopidogrel, ticagrelor was associated with a lower incidence of subsequent pulmonary events, sepsis, and the associated mortality.[10] Ticagrelor further showed beneficial effects in the setting of pneumonia in the XANTHIPPE trial, where its use led to reduced incidence of lung injury and sepsis.[11] Ticagrelor might also offer another advantage by protecting against the superadded bacterial infections in COVID-19 patients since a recent experimental study demonstrated good antibacterial activity of ticagrelor against antibiotic-resistant gram-positive bacteria with the standard antiplatelet dosages.[12] However, there exist a few concerns too. Some of the investigational therapies for COVID-19 like lopinavir, and ritonavir through their inhibitory effects on the CYP3A4 metabolism, have the potential to increase the blood levels of ticagrelor and its associated bleeding risk.[13] Inhibition of CYP3A4 may also result in decreased conversion of prodrug clopidogrel into its active form, and thereby may decrease its antiplatelet efficacy.[14] Prasugrel is not prone to these interactions and is, therefore, a reasonable choice, in the absence of contraindications, for use with lopinavir and ritonavir. However, the use of prasugrel as the agent for P2Y12 inhibitor monotherapy 1–3 months post PCI is less well studied compared to ticagrelor and clopidogrel.[1–5]

Data from the national interventional council suggests that approximately 4 lac PCIs are performed in India every year.[15] Since the patients with cardiovascular diseases are more prone to get infected with COVID-19[16] and keeping in mind the upsurge of COVID-19 cases in India in the past two weeks despite the gross under-testing, it is highly likely that many post PCI patients might get affected by this unprecedented pandemic and might develop an elevated bleeding risk. In such exceptional circumstances, it would be apt for us not to wait for the guidelines to change; instead,

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Table 1
Recent trials evaluating the short duration DAPT (dual antiplatelet therapy) in post PCI (Percutaneous intervention) patients.

Trial Name (Year of publication)	Methods	Results	Interpretation
TICO(March 2020)[1]	1. Randomized, open label trial involving 3056 patients. 2. ACS treated with the ultrathin bioresorbable polymer sirolimus-eluting stent (Orsiro). 3. Ticagrelor monotherapy after 3 months of DAPT ($n = 1527$) was compared with 12 months of Ticagrelor based DAPT ($n = 1529$) after PCI for ACS	1. Primary outcome (composite of death, MI, stent thrombosis, stroke, TVR, TIMI major bleeding) at 12 months occurred in 3.9% in monotherapy group versus 5.9% in standard DAPT group ($p = 0.01$). 2. Secondary outcome of major bleeding occurred in 1.7% of monotherapy group compared with 3% of standard therapy ($p = 0.02$).	The TICO trial showed that ticagrelor monotherapy after 3 months of DAPT was superior at preventing ischemia and bleeding after PCI for ACS.
TWILIGHT (November 2019)[2]	1. Randomized. Double blind, placebo controlled trial involving 7119 patients 3 months post PCI (for stable angina in 29%). 2. Short duration DAPT (3 months) followed by ticagrelor monotherapy was compared with longer duration DAPT (12 months) among patients undergoing PCI with a DES and with ≥1 high risk feature of ischemia or bleeding.	1. The primary end point of BARC type 2, 3, or 5 bleeding, between randomization at 3 months post PCI and 12 months, occurred in 4.0% among patients randomly assigned to receive ticagrelor plus placebo and 7.1% among patients assigned to receive ticagrelor plus aspirin ($p < 0.001$). 2. The incidence of death from any cause, nonfatal myocardial infarction, or nonfatal stroke was 3.9% in both groups ($p < 0.001$ for noninferiority)	The TWILIGHT trial showed that Ticagrelor monotherapy after 3 months of DAPT was superior at preventing bleeding compared with longer-duration DAPT (additional 12 months) among patients undergoing PCI with a DES and at high ischemic or bleeding risk. Ischemic rates met criteria for noninferiority. These results were maintained among the subgroup of patients presenting with Non ST-elevation ACS, Diabetes mellitus, and those undergoing complex PCI.
STOPDAPT-2 (June 2019)[3]	1. Randomized, open label trial, involving 3045 patients undergoing PCI (for stable angina in 62%). 2. Patients were randomized either to 1 month of DAPT followed by clopidogrel monotherapy ($n = 1523$) or to 12 months of DAPT with aspirin and clopidogrel ($n = 1522$). 3. In the initial 1 month 62% of patients received clopidogrel in addition to aspirin, while 38% received Prasugrel in addition to aspirin as part of DAPT. After 1 month, those who received prasugrel initially were switched to clopidogrel.	1. The primary end point defined as the composite of cardiovascular death, MI, ischemic or hemorrhagic stroke, definite stent thrombosis, or major or minor bleeding at 12 months occurred in 2.36% of patients with 1-month DAPT compared to 3.70% of patients with 12-month DAPT, meeting the criteria for non-inferiority ($p < 0.001$) and for superiority ($p = 0.04$). 2. Composite of death, MI, stent thrombosis, or stroke at 1 year occurred in 2.0% of patients in the 1-month DAPT group compared with 2.5% of patients in the 12-months DAPT group (p for noninferiority = 0.005) 3. TIMI major/minor bleeding at 1 year occurred in 0.4% of patients in the 1-month DAPT group compared with 1.5% of patients in the 12-months DAPT group (p for superiority = 0.004)	One-month DAPT was noninferior to 12-month DAPT at preventing major adverse ischemic events and superior to 12-months DAPT at preventing TIMI major/minor bleeding.
SMART-CHOICE (June 2019)[4]	1. Randomized, open label trial, involving 3045 patients undergoing PCI (for stable angina in 42%). 2. Short-duration DAPT (3 months) followed by P2Y12 inhibitor monotherapy ($n = 1495$) was compared with longer duration DAPT for 12 months ($n = 1498$) among patients undergoing PCI. 3. Clopidogrel was used in 77% of patients, while prasugrel/ticagrelor were used in remaining 23% of patients.	1. The primary outcome, MACCE (all-cause death, MI, or stroke) at 12 months, for 3 months vs. 12 months of DAPT, was 2.9% vs. 2.5%, p for noninferiority = 0.007; p for superiority = 0.46. 2. Secondary outcomes of stent thrombosis occurred in 0.2% vs. 0.1% ($p = 0.65$) in the 3 months vs. 12 months DAPT groups respectively, while the BARC 2–5 grade bleeding was 2.0% vs. 3.4% ($p = 0.02$) respectively.	Short-duration DAPT (3 months) followed by P2Y12 inhibitor monotherapy was noninferior to longer-duration DAPT (12 months) among unselected patients undergoing PCI with a DES.
GLOBAL LEADERS (September 2018)[5]	1. Randomized, open label trial. 2. Patients undergoing PCI with a biolimus A9-eluting stent for Stable coronary artery disease or ACS were randomly assigned (1:1) to 75–100 mg aspirin daily plus 90 mg ticagrelor twice daily for 1 month, followed by 23 months of ticagrelor monotherapy ($n = 7980$), or standard dual antiplatelet therapy with 75–100 mg aspirin daily plus either 75 mg clopidogrel daily (for patients with stable coronary artery disease) or 90 mg ticagrelor twice daily (for patients with acute coronary syndromes) for 12 months, followed by aspirin monotherapy for 12 months ($n = 7988$).	1. The primary outcome, all-cause mortality or nonfatal myocardial infarction, occurred in 3.8% of the ticagrelor monotherapy group compared with 4.4% of the control group ($p = 0.073$). The findings were the same in multiple tested subgroups. 2. Secondary outcomes of all-cause mortality occurred in 2.8% of the ticagrelor monotherapy group vs. 3.2% of the control group ($p = 0.18$). Myocardial infarction 1.0% vs. 1.3%, $p = 0.14$) and grade 3 or 5 bleeding (2.0% vs. 2.1%, $p = 0.77$) were also similar between the two groups.	Among patients who underwent PCI with a biolimus-eluting stent, 1 month of DAPT followed by ticagrelor monotherapy for 23 months was noninferior, but not superior to 12 months of DAPT followed by aspirin monotherapy for 12 months. The GLASSY substudy revealed that 1 month of DAPT was noninferior to 12 months of DAPT at preventing death, myocardial infarction, stroke, or urgent target vessel revascularization. One month of DAPT also failed to reduce major bleeding events compared with 12 months of DAPT.

Abbreviations: ACS = Acute Coronary Syndrome; MI = Myocardial Infarction; TVR = Target Vessel Revascularization; TIMI = Thrombolysis In Myocardial Infarction; DES = Drug Eluting Stent; BARC=Bleeding Academic Research Consortium; MACCE = Major Adverse Cardiac And Cerebrovascular Events; GLASSY = GLOBAL LEADERS Adjudication SubStudY.

imbibe on the current evidence-based data and start early de-escalation of DAPT (1–3 months) to P2Y12 monotherapy, preferably with ticagrelor, in our post PCI patients.

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Author's contribution

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Both the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Disclosures

None.

Declaration of competing interest

The authors have no conflict of interest to declare.

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