JACC: CARDIOVASCULAR INTERVENTIONS VOL. 11, NO. 18, 2018

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Chronic Thrombocytopenia and Percutaneous Coronary Intervention

The Virtue of Prudence*

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This Daemon always forbids me to do something which I am going to do, but never commands me to do anything.

—Socrates (1)

In Plato's *Apology of Socrates*, Socrates claimed to have an inner "daimonion" (literally, a "divine thing") that frequently warned him against mistakes, but never told him what to do (1). Similar to Socrates daemon, treatment of coronary artery disease in patients with chronic thrombocytopenia (cTCP) should raise a red flag because we clearly do not know what is right, and the probability of making mistakes is rather high (2,3). In adults, cTCP could be due to platelets' increased destruction (e.g., chronic immune thrombocytopenia, drug-induced thrombocytopenia), reduced production (e.g., hematologic malignancies, including myelodysplastic syndromes or bone marrow infiltration, chemotherapy/radiotherapy, viral infections), or altered distribution (e.g., splenic sequestration in chronic liver disease). Given the higher bleeding risk and the multiple comorbidities in patients with cTCP (4,5), treatment strategies are limited. These patients have almost invariably been excluded from randomized clinical trials of percutaneous coronary intervention (PCI) or secondary prevention antithrombotic therapies. Hence, the real impact of cTCP in patients undergoing PCI is largely unknown.

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In this issue of *JACC: Cardiovascular Interventions,* Ayoub et al. (6) evaluated the clinical impact of cTCP on in-hospital events after PCI. The authors used the NIS (National Inpatient Sample) database, an all-payer inpatient database, to select patients with cTCP from a cohort of more than 1.4 million patients undergoing PCI from 2012 to 2014. A total of 35,180 patients (2.5%) had a diagnosis of cTCP at the time of PCI. cTCP was present for at least 1 year before PCI, and its definition was based on the International Classification of Disease-9th Edition-Clinical Modification coding at discharge. Patients with acute or periprocedural thrombocytopenia were excluded. cTCP patients were compared to a propensity-matched cohort without cTCP, leading to 32,565 patients per group.

Patients undergoing PCI with cTCP had a more than doubled risk of post-procedural bleeding (odds ratio [OR]: 2.4; 95% confidence interval [CI]: 2.05 to 2.72; $p < 0.0001$). Patients with as compared to those without cTCP experienced a higher risk of post-procedural vascular complications (OR: 1.94; 95% CI: 1.43 to 2.63; $p < 0.0001$), red-blood cell (OR: 2.1; 95% CI: 1.8 to 2.24; $p < 0.0001$) or platelet transfusion (OR: 11.7, 95% CI: 6.0 to 22.6; $p < 0.0001$), and post-procedural ischemic (OR: 1.6; 95% CI: 1.2 to 2.1; $p = 0.01$), but not of hemorrhagic stroke. Ultimately, in-hospital mortality after PCI was significantly higher in patients with cTCP. Interestingly, the higher mortality could not be entirely justified by the excess of bleeding.

This study teaches us 3 important lessons. First, patients undergoing PCI with cTCP are complex medical patients with multiple comorbidities: in such

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

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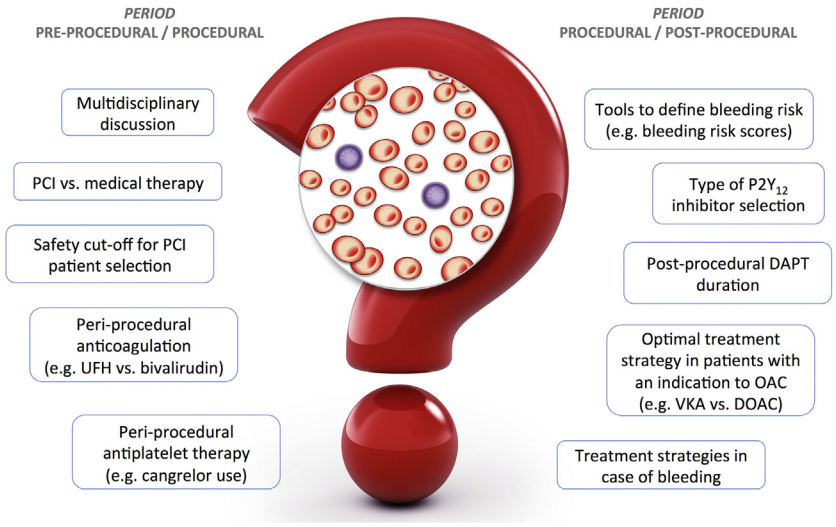
ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2018.06.051

FIGURE 1 Unanswered Questions for the Treatment of Patients With cTCP Undergoing PCI



cTCP = chronic thrombocytopenia; DAPT = dual antiplatelet therapy; DOAC = direct oral anticoagulant; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; UFH = unfractionated heparin; VKA = vitamin-K antagonist.

a scenario, all available measures to identify/correct reversible causes for thrombocytopenia should be implemented with a multidisciplinary approach. Second, patients with cTCP are at higher risk of bleeding and vascular access site complications. Special attention should be paid to prevent bleeding complications, including favoring the radial access (7), careful dosing of antithrombotic agents (8), use of low-dose aspirin, short duration of dual antiplatelet therapy, and routine use of proton pump inhibitors (3). Third, among patients undergoing PCI, cTCP is a readily available marker of higher overall clinical risk and frailty (9). Although bleeding accounts for a significant proportion of the in-hospital complications in patients with cTCP, plausible explanations for the increased risk of non-bleeding-related adverse events and mortality observed in this study might be ischemic rebound due to suboptimal antithrombotic therapy, the abrupt cessation of treatment in case of a higher perceived risk (e.g., further decrease of platelet count during hospital stay), or need for transfusion; yet cTCP might simply qualify as a marker of comorbidity, associating with a higher mortality and ischemic risk irrespective of bleeding (5).

This study has limitations, which should be put into perspective (6). The data used were from an administrative claims-based database with a relatively poor level of granularity (10). Thrombocytopenia definition in this study came from administrative coding at discharge, which should represent a rough estimate of a platelet count <150,000 U/μl, but was not validated by single patients' blood counts. This does not allow stratification on the basis of severity of thrombocytopenia, which would have been extremely valuable because the clinical risk changes dramatically between mild and severe thrombocytopenia (2,4). The study could exclusively evaluate in-hospital events. Longer-term follow-up during the first 1 to 6 months after PCI is of paramount importance to evaluate the impact of the mandatory antithrombotic treatment after coronary stenting (3). Better understanding of the impact of thrombocytopenia etiology will be important to drive accurate decision making (2). In the current study, immune-mediated thrombocytopenia showed a mortality risk, which was roughly one-half that of other cTCP causes, whereas it was similar to that of patients without cTCP (6). Immune-mediated thrombocytopenia can be often controlled with corticosteroids, and allows more treatment options during and after PCI. On the other hand, other causes of cTCP, such as malignancy or chronic liver disease, could be associated with poorer outcomes (2).

Finally, despite the non-parsimonious logistic regression-based propensity-matching approach, there remain imbalances between patients with or without cTCP with respect to existing comorbidities or prior cerebrovascular history. cTCP patients are inherently different as compared with those without

cTCP, and prospective randomized studies are needed to provide controlled outcome data.

Many questions remain unanswered at this stage (**Figure 1**). PCI is generally discouraged in patients with severe thrombocytopenia, yet a precise cutoff at which PCI poses excessive safety concerns outweighing treatment benefits is unknown (2). Procedural anticoagulation with the use of bivalirudin rather than unfractionated heparin in patients with cTCP has never been explored. Nonrandomized data among patients with prior heparin-induced thrombocytopenia provides reassuring information, with no novel episodes of post-procedural severe thrombocytopenia (11). Glycoprotein IIb/IIIa inhibitors are contraindicated in patients with thrombocytopenia as these drugs are associated with a higher risk of acquired thrombocytopenia and bleeding, especially with abciximab or generic formulations of tirofiban (9,12). At variance with some glycoprotein IIb/IIIa inhibitors, cangrelor is not associated with acquired thrombocytopenia, and its clinical efficacy and safety were shown to be consistent irrespective of thrombocytopenia occurrence (13). The optimal post-procedural antiplatelet therapy type and duration are also unknown. Generally, a treatment with clopidogrel is preferred over ticagrelor and prasugrel (2,3). Ticagrelor should be used with caution because its reversible platelet inhibition might pose problems in case of need for platelet transfusion (14). As a general rule, dual antiplatelet therapy duration should remain short, and triple therapy in patients with indication to oral anticoagulation might be avoided because of the excessive bleeding risk (3). Mechanical strategies to avoid chronic anticoagulation (e.g., left atrial appendage occlusion in patients with atrial fibrillation) may be considered.

While waiting for more robust, evidence-based, treatment strategies for patients with cTCP, the virtue of prudence, as that defended by Socrates and his inner daemon, appears yet to be the best approach.

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KEY WORDS acute coronary syndrome(s), dual antiplatelet therapy, percutaneous coronary intervention, thrombocytopenia