

Hobson's choice; platelet inhibition and thrombocytopenia

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Thomas Hobson was a livery stable owner in Cambridge, England, in the 17th century who had an extensive stable of over 40 horses and ran a thriving horse rental business. His customers believed that, upon entry, they would be given their choice of mounts, when in fact he offered them no choice: Hobson required that all his customers choose the horse in the stall closest to the door or have no horse at all. Quite literally, they had no choice but 'Hobson's choice'. Similarly, in percutaneous coronary intervention (PCI), adjunctive pharmacotherapy with platelet inhibitors and anticoagulant regimes have improved clinical outcomes through a reduction in ischemic events including stent thrombosis¹⁻³, albeit at the expense of increased bleeding complications⁴. Whilst the delivery of antiplatelet agents and anticoagulant regimes can be personalized at an individual patient level in an attempt to balance the reduction in ischemic risk whilst minimizing the increased risk of major bleeding, like Hobson's choice in the 17th century, there is currently no option to avoid these agents altogether in PCI in high bleeding risk patients. Thus, in general, it is either 'antiplatelet inhibition or no PCI', a 21st century interventional cardiologist's manifestation of Hobson's choice.

Thrombocytopenia is not uncommon in patients undergoing PCI with a reported prevalence of around 6% in a pooled analysis of the ACUTY and HORIZONS-AMI trials,⁵ with up to 7% of elective patients⁶ and 13% of patients with acute coronary syndrome (ACS) developing new thrombocytopenia during their hospitalization.⁷ Patients with thrombocytopenia tend to be older^{5,7,8}, have more extensive coronary disease⁵ and a greater prevalence of adverse clinical characteristics including renal failure⁹, diabetes mellitus^{5,7,8} and prior PCI or CABG^{5,8}. Furthermore, thrombocytopenia is a recognised side effect of treatment with glycoprotein IIb/IIIa inhibitors (GP IIb/IIIa)¹⁰ or heparin¹¹ through immune-mediated mechanisms^{8,12}.

In this current issue of *Circulation: Cardiovascular Interventions*, using a pooled, patient-level analysis derived from over 23,000 participants from the CHAMPION trials, Groves et al.¹³ report that 0.8% of patients undergoing PCI develop thrombocytopenia. GpIIb/IIIa use, age, diabetes, hyperlipidemia, and prior CABG were all independently associated with acquired thrombocytopenia; with GPIIb/IIIa use the strongest predictor (OR 2.85, 95% CI 2.07 to 3.94; P<0.001). Importantly, Cangrelor treatment itself had no effect on the incidence of thrombocytopenia irrespective of whether a GPIIb/IIIa was used.

In line with previous work that has reported adverse clinical outcomes associated with acquired thrombocytopenia following PCI^{6, 8, 14, 15}, the current study reports that patients who developed thrombocytopenia after PCI had a 13-fold independent increased risk of GUSTO severe bleeding and a 3-fold increased risk of stent thrombosis at 48 hours. Further, there was a 3- and 5-fold increased adjusted risk of 30-day MACE and mortality, respectively in the thrombocytopenia group. Even in the patients who did not sustain a major bleeding complication within 48 hours, thrombocytopenia remained independently associated with increased risk of MACE at 30 days. The latter is almost certainly under-appreciated and of considerable clinical relevance.

Whilst such increased risks associated with thrombocytopenia are, in general, well known, less is known about the optimal management of patients who either have prevalent thrombocytopenia or develop it following treatment. Patients with thrombocytopenia are routinely excluded from landmark antiplatelet trials such as TRITON-TIMI 38¹⁶, PLATO¹⁷ and consequently the safety of contemporary antiplatelet therapies used in ACS patients is not well defined. Specifically, there are currently no guideline recommendations or consensus reports to guide interventionists on the management of PCI patients with thrombocytopenia.

The authors have previously published an opinion piece regarding the management of PCI patients with thrombocytopenia, and have included management recommendations made according to the clinical setting (elective and ACS) and the severity of thrombocytopenia.¹⁸ These recommendations include identification and correction of any reversible causes of thrombocytopenia, and minimization of bleeding risk including avoidance of non-steroidal anti-inflammatory drugs, GPIIb/IIIa inhibitors and utilization of proton pump inhibitors.

In ACS patients who are not undergoing PCI, the authors recommend that clopidogrel monotherapy should be considered if platelet count is $<100 \times 10^9/L$ but $>50 \times 10^9/L$, in the absence of bleeding. In contrast, in those patients with a platelet count $<50 \times 10^9/L$ or in the setting of active bleeding, the authors advise stopping all antiplatelet therapy and avoiding PCI altogether. In ACS patients with a platelet count $>50 \times 10^9/L$ undergoing PCI, recommendations include adopting a transradial approach, restricting DAPT therapy to 1-month post-stent and using second generation DES rather than BMS. Finally, in patients with stable coronary artery disease, the authors suggest stopping antiplatelet therapy and avoiding PCI in patients

with a platelet count $<50 \times 10^9/L$ whilst in those patients with a platelet count $>50 \times 10^9/L$ and $<100 \times 10^9/L$, clopidogrel monotherapy and a proton pump inhibitor is recommended. If a patient's symptoms persist despite optimal medical therapy, the risks should be weighed against the benefits of proceeding with an invasive strategy on an individual basis.

The data presented remind operators regarding the importance of the challenge we face, on behalf of our patients, in the management of thrombocytopenia. Specifically, we face 2 very different clinical scenarios: firstly, the thrombocytopenic patient in front of us in whom PCI is otherwise the optimal revascularization strategy, and second, the post PCI patient who develops thrombocytopenia. In the first scenario, our choices include avoiding PCI altogether, and modification of the intensity and duration of antiplatelet therapy, although it is common to ignore a degree of thrombocytopenia completely. In post PCI acquired thrombocytopenia, our management depends upon the level of the drop, whether the low platelet count is accompanied by dysfunction of those platelets that are present, and, of course, the actual or theoretical bleeding risk. Little, above and beyond common sense and experience-based judgement, helps to inform our management decisions in such circumstances, although modification of the intensity and duration of antiplatelet therapy is foremost in our armory. There are currently no risk scores to predict the development of thrombocytopenia post PCI, and the non-modifiable independent predictors of developing thrombocytopenia identified in the current study such as age, prior CABG and diabetes are non-specific and feature in most risk scores for adverse outcomes for both ischemic and bleeding risk. As such, they offer little value as the basis for thrombocytopenia avoidance strategies.

There is one exception. In the current study use of GpIIb/IIIa inhibitors was reported to be the strongest predictor of post PCI thrombocytopenia and this represents an important modifiable risk factor. The use of GPIIb/IIIa inhibitors in PCI has fallen dramatically since peak period in the 1990s and early 2000s following randomized trials such as EPILOG and EPISTENT, in which such agents were routinely used for large patient subgroups. Their use in contemporary practice has declined due to a number of factors including improved PCI technique, stent technology and more potent oral P2Y₁₂ inhibitors. Nevertheless, they are still used in cases where there is perceived to be high ischemic risk, significant thrombotic burden or in bailout for cases of slow flow / no reflow. Data derived from the CHAMPION

trials have shown that Cangrelor reduces the requirement for bail out GpIIb/IIIa inhibitors in PCI ¹⁹ and so may reduce the requirement for GpIIb/IIIa inhibitors further in contemporary practice.

Groves et al have provided interventionalists with a timely reminder of the outcome risks associated with the acquisition of thrombocytopenia after PCI. The important observation that this risk of adverse outcome extends beyond the index admission is particularly valuable. Avoiding GPIIb/IIIa inhibitors wherever possible emerges as a clear-cut message. Our response to the development of thrombocytopenia post PCI in our patients should be based upon common sense and experience. Specifically, we should seek factors that may be causing or exacerbating the low platelet count, detect evidence of actual bleeding and estimate theoretical bleeding risk, and then make a bespoke and considered judgement about the need to compromise on the intensity and duration of our proposed ongoing dual antiplatelet therapy.

Our management plan should be informed by discussion with hematology specialists, who have an important role in helping to diagnose some potential causes such as heparin-induced thrombocytopenia. Prophylactic platelet transfusions should be avoided since they rarely raise platelet counts and can precipitate thrombosis ²⁰ although may be necessary in cases where significant bleeding complications occur. However, it is important for the experienced interventionalist to understand that their clinical experience of post PCI thrombocytopenia will be greater than that of a clinical hematologist in most circumstances, so a high level approach that takes into account all factors remains important.

How patients who develop thrombocytopenia with no immediate bleeding complications should be managed remains unclear? The current study shows that these patients are at significantly increased risk of both bleeding and thrombotic complications and discontinuing antiplatelet therapy to a single antiplatelet in such cases would further increase the already elevated risk of thrombotic complications. Alternatively, continuing potent newer antiplatelet agents may potentiate the already elevated bleeding risk in this cohort, although the safety and clinical outcomes associated with switching to clopidogrel in such situations is unclear. In patients who have no active bleeding watchful waiting is often the dominant management strategy, and any theoretical choices related to modifying antiplatelet therapy in these circumstances are not informed by any hard data. It is clear, however, that we should

reject the choice apparently offered to us by Hobson in these patients and manage them in a personalized fashion that includes several options regarding the modification of their dual antiplatelet therapy intensity and duration.

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