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Prognostic significance of post percutaneous coronary intervention thrombocytopenia

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Abstract

Several definitions of post percutaneous coronary intervention (PCI) thrombocytopenia (TC) were formulated. Recent studies demonstrated that a relative drop in platelet count ⩾ 25% is the most appropriate criterion. By this definition a population is detected that is exposed not only to increased risk of hemorrhagic complications but also to increased risk of ischemic events, which may appear a paradox. In patients with acute coronary syndromes undergoing PCI, several conditions might be associated with TC: cardiopulmonary bypass and the presence of extra corporeal membrane oxygenators, intra aortic balloon pump (IABP), cardiogenic shock, thrombolytic drugs and anticoagulant or antiplatelet drugs. Several studies demonstrated that TC and ischemic outcomes are related although it is unclear whether this is a direct relationship or TC is just a secondary effect of another cryptic protagonist. It is suggested that further investigations determine whether there is a real link between TC, a probably well defined covariate, and ischemic outcomes or whether IABP is the joining link between these two variables and whose presence needs in any case be considered in multivariable statistics. Post-PCI TC could be only a secondary effect of IABP use. On turn, the prolonged use of heparin necessarily accompanying the use of IABP, and producing a paradoxical pro-thrombotic TC, might also be implicated.

Key words: Thrombocytopenia; Outcome; Percutaneous coronary intervention; Intra aortic balloon pump

Core tip: This minireview suggested that further investigations are needed to determine whether there is a real link between thrombocytopenia (TC), a probably well defined covariate, and ischemic outcomes or whether intra-aortic balloon (IABP) is the joining link between these two variables and whose presence needs in any case be considered in multivariable statistics. Post-percutaneous coronary intervention TC could be only a secondary effect of IABP use. On turn, the prolonged use of heparin necessarily accompanying the use of IABP, and producing a paradoxical pro-thrombotic TC, might also be implicated.

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THROMBOCYTOPENIA: DETERMINATION AND DEFINITION

Thrombocytopenia (TC) is a clinical condition related to decreased production, sequestration or increased de-

Table 1 An overview of the studies whereby post-percutaneous coronary intervention thrombocytopenia was differently defined and analysed as an outcome variable

Ref.	Number of thrombocytopenic patients *n* (%)	Definition of thrombocytopenia	Mortality rate[1]	Hemorrhagic outcomes[1]	Composite Ischemic outcomes[1]
Berkowitz *et al*[10]	81/2099 (3.9)	Nadir PLT count < 100×10^9/L	12.1% *vs* 1.1% at 1 mo	48.7% *vs* 9.5% at 1 mo	NSC
McClure *et al*[8]	633/10948 (7.0)	Nadir PLT count < 100×10^9/L or delta PLT > 50%	7.4% *vs* 3.3% at 1 mo	75.8% *vs* 27.8% at 1 mo	30% *vs* 14.1% at 1 mo
Eikelboom *et al*[3]	87/10141 (1)	Nadir PLT count < 100×10^9/L	11.50% at 6 mo	8% *vs* 1.4% at 6 mo	33.3% *vs* 30.8%[2] at 6 mo[3]
Merlini *et al*[4]	99/4809 (2.9)	Nadir PLT count < 100×10^9/L or delta PLT ⩾ 25%	2.0% *vs* 0.4% at 1 mo	5.1% *vs* 0.7%	12.2% *vs* 6.6% at 1 mo
Nikolsky *et al*[9]	50/2082 (2.5)	Nadir PLT count < 100×10^9/L	10% *vs* 3.9% at 12 mo	10% *vs* 2.7%	26.1% *vs* 17.4% at 12 mo
Shenoy *et al*[32]	41/1302 (3.1)	Nadir PLT count < 100×10^9/L or delta PLT > 50%	10% *vs* 2% at 6 mo	37% *vs* 3%	39% *vs* 15% at 6 mo
Wang *et al*[6]	4697/36182 (13)	Nadir PLT count < 150×10^9/L and/or delta PLT > 50%	6.9% *vs* 2.6% in hospital stay	26.7% *vs* 10%	NC
De Labriolle *et al*[11]	1644/10146 (16.95)	Delta PLT ⩾ 25%	11% *vs* 4.2% at 12 mo	21% *vs* 2.6%	22.9% *vs* 16.01% at 12 mo
Caixeta *et al*[7]	740/10836 (6.8)	Nadir PLT count < 150×10^9/L	6.5% *vs* 3.4% at 12 mo	14.0% *vs* 4.3%	22.8% *vs* 15.1% at 12 mo
Kiviniemi *et al*[35]	46/929 (9.7)	Nadir PLT count < 100×10^9/L or delta PLT > 50%	12% *vs* 11%[2] at 12 mo	23% *vs* 22%[2] at 12 mo	24% *vs* 19%[2] at 12 mo

[1]Thrombocytopenic *vs* non thrombocytopenic patients; [2]Not statistically different; [3]There was a significant difference at 7 d only. Inclusion and exclusion criteria were different in all studies. NC: Not considered; NSC: Not statistically considered; PCI: Percutaneous coronary intervention; PLT: Platelets.

struction of platelets. Isolated TC is more likely due to peripheral destruction[1]. In the setting of acute coronary syndromes (ACS) the use of heparin[2,3], platelet glycoprotein Ⅱb/Ⅲa receptor inhibitors[4] and intra-aortic balloon pump (IABP)[5] is associated to improved outcomes but, on the other hand, it exposes patients to higher risk of bleeding and decline in platelet count. When the magnitude of the platelet drop is large enough, one of the main definitions of "acquired" TC may be met. A summary of the main definitions is available in Table 1. Classically, acquired TC was defined as a decrease of platelet levels from normal baseline count (> 150×10^9/L) to thrombocytopenic levels (< 150×10^9/L)[6,7] or as a nadir platelet count < 100×10^9/L[8-10] during the in-hospital phase or as a ⩾ 50% drop in platelet count from pre-intervention platelet values[6,8].

More recently, De Labriolle *et al*[11] proposed a novel threshold of ⩾ 25% decrease in platelet count to define acquired TC. The latter definition is important to detect a population that is exposed not only to increased risk of hemorrhagic complications but also, as might be easily foreseen, to higher risk of ischemic events[11]. However, although the first correlation is intuitive, the second one seems a real paradox. The purpose of this review is to examine the subset of thrombocytopenic patients in the setting of ACS and to define the clinical relevance of TC for prognosis.

POST-PCI THROMBOCYTOPENIA: POSSIBLE CAUSES

Several causes of TC are known but, in many instances, they cannot be identified[12]. In patients with ACS undergoing percutaneous coronary intervention (PCI), several conditions might be associated with TC.

Cardiopulmonary by-pass and extracorporeal membrane oxygenation

These conditions may cause TC and platelet dysfunction related to the artificial membrane oxygenators used in these settings[1,13].

Intra aortic balloon pump

Platelet count decrease is correlated primarily to the device itself, independently from the use of intravenous heparin in one study[5]. It is a predictable platelet count decrease characterized by distinct features: it rapidly recovers if the device is removed or it stabilizes after 4 d if IABP remains in place[5,14].

Cardiogenic shock

Several studies demonstrated that TC is common in shocked patients[5,15]. This could be related to decreased bone marrow productive activity in severely ill patients, but these patients will also more likely receive an IABP[5,15,16]. Therefore some investigators in post-PCI TC *de facto* excluded shocked patients from the study population[4,9,11] and probably made a major selection bias.

Thrombolytic drugs

In the setting of ACS, thrombolytic therapy is widely used since it improves mortality rate, although it is associated with TC and therefore to increased risk of hemorrhage and death[17]. Since this is a well-known cause of platelet count reduction, some studies in post-PCI TC excluded all patients undergone thrombolysis[8,9,11].

Heparin

Since Silver, Rhodes and Dixon first identified central features of Heparin Induced TC (HIT) where TC and thrombosis have an immune pathogenesis, HIT has been

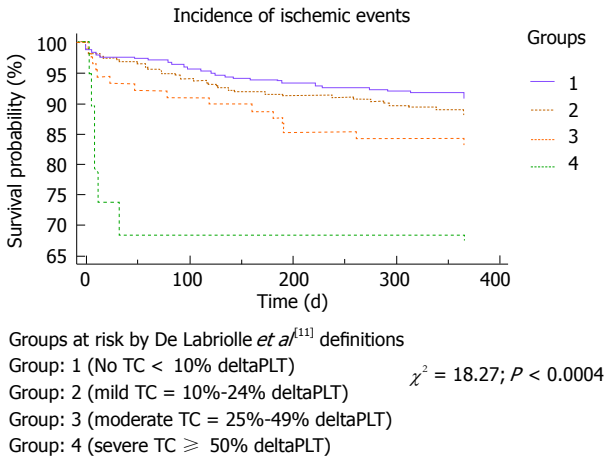

Figure 1 Kaplan-Meier curves for the incidence of composite ischemic events during 1 yr among thrombocytopenic groups. The ROC curves subdivided in accordance with De Labriolle *et al*[11], modified from Schiariti *et al*[34]. TC: Thrombocytopenia.

deeply investigated[18]. HIT is due to a peculiar heparin-dependent and platelet-activating antibody (IgG)[18,19] and seems related to heparin preparations[2] with typical features: it is usually moderate and more frequently begins later than 5-14 d (typical onset) after the drug administration, although it can occur after 7-40 d (delayed onset) or, in patients who received it in the previous 100 d, within 24 h (rapid onset)[18,20].

Glycoprotein Ⅱb/Ⅲa receptor inhibitors

Patients undergone triple antiplatelet therapy based on glycoprotein Ⅱb/Ⅲa receptor inhibitors (GPI) have a better prognosis in the setting of ACS. However, based on a recent meta-analysis[21], GPI therapy seems to have no beneficial effect in elective PCI. The latter study does not clarify whether patients undergoing elective PCI were or not pretreated with a dual antiplatelet therapy before receiving a downstream GPI treatment[21]. GPI-related TC mostly occurs rapidly, within few hours from drug administration and, differing from HIT, it can be profound (platelet count < 20×10^9/L). It is related to the presence of drug-dependent antiplatelet antibodies[1,22,23]. This type of TC, independently from the specific GPI molecule administered, seems to follow a distinct clinical course when compared to other etiologies: it is more profound but has a quicker recovery[12,24,25]. Nevertheless, it seems also associated to increased rate of ischemic events[4].

P2Y-12 inhibitors

Thienopyridines are a rare but possible cause of TC[26]. Ticlopidine-associated TC can occur 2-12 wk after its first administration, whereas clopidogrel-related TC is a rarer but earlier event[27,28].

Other causes

In the setting of ACS other medications, particularly ACE-inhibitors and statins, can be a rare cause of TC[29,30]. On the other hand, TC has also to be differentiated from pseudo TC, a laboratory artifact resulting from platelet aggregation[31].

FEATURES OF THROMBOCYTOPENIC PATIENTS

Thrombocytopenic patients have some peculiar features: they are more likely men[6-11], with a lower body mass index[6,8-11], diabetics[6,9] and with arterial hypertension[6]. Medical history of thrombocytopenic patients is typically characterized by previous myocardial infarction[6], previous PCI[6-8], previous stroke[6] and heart failure[6,11]. Looking at their home therapy they more likely are on statins and oral hypoglycemic therapy[9,11] and less likely treated with aspirin[9]. Looking at laboratory parameters, these patients have a lower baseline platelet count[6,7,9,11] and baseline renal insufficiency[7,11]. All these parameters should be therefore taken into account when defining the independent role of TC.

POST-PCI THROMBOCYTOPENIA: CLINICAL OUTCOMES

Since its identification, post-PCI TC was classically related to hemorrhagic events[1,10,17,24]. Nevertheless, platelet count decline was also related to ischemic outcomes[3,4,7-9,11,32]. Several hypotheses were formulated to explain this relationship. Early discontinuation of antiplatelet agents for the onset of acute TC was considered causative of unfavorable clinical outcome[6,7], but other studies confuted this hypothesis[10]. It was also hypothesized that platelet consumption was associated with platelet activation, leading to downstream thrombotic events[6]. It was demonstrated that mean platelet volume was significantly increased despite concomitant decrease in platelet count in patients with ACS or stroke and animal models supported this, pointing to the fact that large platelets seem to have a higher thrombotic potential[33]. Moreover, TC was suspected to have a direct pathogenetic influence on adverse ischemic events[11] or it may be considered a simple marker of poor prognosis[6,32].

A clear-cut evolution in the definition of acquired TC and its relationship with ischemic outcomes may be seen between 1998 and 2013 (Table 1). Contrary to early studies defining TC only on the basis of absolute platelet count drop[7,9,10], more recent investigations clearly showed that post-PCI TC should be defined only based on relative drop in platelet count[11,34]. The different definitions of acquired TC are variously related to mortality and to ischemic or hemorrhagic outcomes (Table 1).

It is thus possible to identify individuals with substantial falls in platelet count, not reaching thrombocytopenic levels, that are at increased risk of ischemic events. We showed evidence[34] illustrated by Kaplan-Meyer curves (Figure 1) for a strong reverse relationship between platelet count[11] and the incidence of cumulative ischemic outcome. In 2013 Kiviniemi *et al*[35], assessing hemorrhagic and ischemic complications in patients on oral anticoagulation undergoing PCI, found a similar risk of adverse

outcome in patients with acquired TC compared with the control group. On the other hand, we indicated[34] that in the setting of TC there might be a cryptic protagonist: IABP. Indeed, in ACS, previous studies did not consider the important association with IABP itself, apart that from the concomitant presence of shock, among the determinants of TC[3,6,7] or interpreted it as a simple predictor of acquired TC[8,11].

Since there is a well known relationship between ischemic events and IABP use[36], the question is whether post-PCI TC is causative of ischemic events or whether the other protagonist (IABP) may have a con-causal (mechanic) role. Under these perspectives, cardiogenic shock should be considered a further etiologic factor for TC[5,14,16,34]. On the other hand, as IABP is necessarily associated with concomitant heparin utilization, it is for further study to assess and quantify the impact of prolonged heparin on TC and long-term ischemic outcome.

IS POST-PCI THROMBOCYTOPENIA A COVARIATE?

An important question is whether TC, defined following the more recent investigations (Table 1) pointing to a $\geqslant$ 25% drop in platelet count from baseline to post-PCI, might be considered a covariate to be fed into multivariable statistics for prediction of ischemic or hemorrhagic outcomes. We tried to reply to this question by re-analyzing our data on 873 ACS patients treated by PCI[34] and of whom 867 had complete data (Figure 1): 107 (12%) of these were with TC according to the above-mentioned definition[11]. We then run a logistic regression in forced mode and the area under the ROC curve was 75% (log likelihood -267, model r^2 = 0.17) by fitting 13 covariates (age, gender, presence of shock, the occurrence of primary or rescue PCI, the number of vessels with significant coronary stenoses, the values of baseline platelet count, hemoglobin, red blood cells, creatine kinase, glomerular filtration rate by Modification of Diet in Renal Disease formula, absence of GPI inhibitors and presence of IABP). There were only 4 contributors to predict TC: age (P = 0.06008), the occurrence of primary (P = 0.00207) or rescue (P =0.00098) PCI and the presence of IABP (P = 0.00001) with a significant intercept (P = 0.02168). From these data it might be concluded that TC is indeed a potential covariate, although in order to fully disclose its predictive role in post-PCI investigations aimed at assessing long-term impact on ischemic outcome, it is essential to fit other confounders and among these latter: age, IABP and the type of PCI performed.

CONCLUSION

Post-PCI TC was classically related to increased mortality and incidence of bleeding and large evidence exists. On the other hand, TC was also related to higher risk of ischemic events. Although several hypotheses were formulated to define the latter relationship, no evidence proved that ischemic outcomes are related to TC *per se* or they might be just an ancillary phenomenon. It is suggested that further investigations determine whether there is a real link between TC, a probably well defined covariate, and ischemic outcomes or whether IABP is the joining link between these two variables. In any case presence of IABP should be considered in multivariable statistics. Post-PCI TC could be only a secondary effect of IABP use, possibly also related to the concomitant use of heparin, although precise quantification of this is lacking.

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