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Immature platelet fraction in cardiovascular diagnostics and antiplatelet therapy monitoring

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ABSTRACT

Immature platelet fraction (IPF), circulating platelets still containing RNA, can be easily calculated by automated flow cytometry, this makes them an accessible biomarker. Higher IPF concentrations were reported in patients with thrombocytopenia, patients who were smokers, and also those who were diabetics. Several studies have reported their diagnostic and prognostic importance in patients presenting with acute coronary syndromes, especially ST-segment myocardial infarction, where increased IPF level is an independent predictor of cardiovascular death. In addition, higher IPF were reported in patients with inadequate response to either clopidogrel or prasugrel, suggesting their potential role in antiplatelet therapy monitoring. Their prognostic significance was also observed in both coronary artery disease and postcardiac surgery status, where their higher levels correlated with the risk of major adverse cardiac events.

The present review aims to present the current evidence on diagnostic, prognostic and potentially therapeutic roles of IPF in cardiovascular medicine.

Key words: immature platelet fraction, antiplatelet therapy monitoring, acute coronary syndromes

Introduction

Platelet circulation is held in balance between production and usage. Around 12% of circulating platelets are replaced every 24 hours to keep hemostasis. The production of platelets is controlled by many different factors, with thrombopoetin and interleukin 6 being the two most important ones [1–13]. When the demand for platelets is high, megakaryocytes in bone marrow release their higher amount into circulation. This can liberate a pool of immature platelets which are also called reticulated platelets. They differ considerably from the mature version — are larger in size and contain messenger RNA (mRNA) in their cytoplasm. This means they are able to synthesise protein. Moreover, immature platelets contain a lot of dense granules. All of this leads to being more enzymatically and metabolically active, which results in the aggravated prothrombotic potential. Immature platelet fraction (IPF) represents the percentage of the youngest circulating platelets still containing RNA in peripheral blood. This promising biomarker has many advantages including a relatively low price (around $10 per test), the feasibility of quick testing (depends

on laboratory logistics and the organisation, normally around 8 h) and determination by flow cytometry or an automated haematology analyser [1–13]. However, flow cytometry cannot rule out the nonspecific marking of other granulate components. Fully automated methods allow for more precise count of the IPF. The values obtained depend not only on the method, but also on the source and concentration of fluorochrome and the protocol that is used. Therefore, if they were to be used in clinical practice, there is a need for further standardization of the method that would be both reliable and accessible [14]. IPF is elevated in conditions with rapid platelet destruction i.e., immune thrombocytopenia, disseminated intravascular coagulation [15]. Furthermore, higher number of IPF was observed in patients suffering from gestational hypertensive disorders compared with the control group [16]. Raised values of this parameter were documented in patients with septic shock and correlated with severity scores [17]. Recently, elevated number of IPF was observed in patients with acute myocardial infarction, especially in the acute phase of ST-segment myocardial infarction (STEMI) [18]. The objective of this review is to summarize the current state of knowledge regarding the diagnostic and prognostic significance of IPF in various cardiological conditions, with particular focus on acute coronary syndromes (ACS), chronic coronary syndromes, and their pharmacological management.

IPF in acute coronary syndromes

Grove et al. [18] were first to hypothesize that IPF may contribute to coronary thrombus formation. Their study investigated IPF levels in: 22 healthy subjects, 39 patients with stable coronary artery disease (CAD), and 359 patients with ACS. IPF levels proved elevated: in patients with CAD compared to healthy subjects, in ACS, especially in STEMI. Further, it was observed that IPF levels were higher by 18% in smoking individuals, compared with non-smokers, and IPF was elevated by 16% in diabetics, compared with non-diabetics [18].

Cesari et al. [19] investigated IPF as a predictor of cardiovascular death in ACS. 229 patients were enrolled (125 with STEMI and 104 with non-STEMI/unstable angina). The study group also was analyzed for highly immature platelet fraction (H-IPF). At 1-year follow-up 22 (9.6%) patients died from cardiovascular causes. Those patients presented elevated levels of IPF ($p = 0.05$) and H-IPF ($p = 0.006$) compared to the alive. Optimal cut-off values for the prediction of cardiovascular death were presented: IPF ≥ 3.3% and H-IPF ≥ 0.9% (Table 1) [19].

IPF in coronary artery disease

It has been proven that increased platelet consumption is present in patients suffering from CAD [20]. Furthermore, high levels of IPF are correlated positively with elevated residual platelet aggregation in patients with CAD receiving antiplatelet therapy [21–23].

A study from 2014 by Larsen investigated correlations between platelet turnover parameters (including IPF), thrombopoietin and low-grade inflammation in stable, high-risk CAD patients receiving low dose of acetylsalicylic acid (ASA; 75 mg once a day) during a mono antiplatelet therapy. 581 patients, who had angiographically documented CAD were enrolled [24]. Positive moderate-to-strong correlations were found between IPF, immature platelet count (IPC), mean platelet volume (MPV), platelet distribution width (PDW) and platelet larger cell ration (P-LCR). This study observed that thrombopoetin levels were inversely correlated with the values of IPF (Fig. 1). A negative correlation was also observed between IPF and microRNA (miR) 423-3p in patients with high-risk CAD, suggesting that these miRs may play a role in platelet turnover [25]. Studies have shown that higher MPV is positively correlated with a higher mortality rate among patients suffering from stable CAD, thus IPF can significantly contribute to this factor [26]. Larger platelets are also associated with early stent thrombosis in patients with ACS treated by percutaneous coronary intervention (PCI) [27].

Furthermore, IPF levels of above 6% were associated with increased age, this is consistent with the study performed by Cesari et al. [24], which also showed that low grade inflammation does not have a significant impact on platelet turnover parameters, including IPF.

Immature platelet fraction is considered to be a potential biomarker of platelet activity and major cardiovascular events. A study by Verdoia from 2017 investigated the correlation between IPF and the extent of CAD in patients who underwent coronary angiography. 1789 patients were enrolled and divided into quartiles based on the levels of IPF. Between quartiles there was no significant correlation in angiography, however, a low degree of thrombolysis in myocardial infarction flow ($p = 0.01$) and lesions involving bifurcations ($p = 0.05$) correlated positively with higher values of IPF. This shows that IPF is not associated with the extent of CAD. On the other hand, this study showed that IPF is higher in: smoking patients ($p = 0.02$), in patients with higher levels of hemoglobin ($p < 0.001$), in patients with higher levels of uric acid ($p < 0.001$), and in patients with a lower platelet count ($p = 0.003$) [13].

Immature platelet fraction can be used as a prognostic marker for major adverse cardiovascular events (MACE) in patients with CAD. MACE was defined as all cause mortality, myocardial infarction, unplanned revascularization, or hospitalization for angina. 89 patients were enrolled and followed up for a median of 31 months. IPF was higher in patients who suffered MACE, as compared to patients without any events at the follow up (5.3 [4.3–6.4] vs. 3.7 [3.0–5.1], $p = 0.007$) (Fig. 2) [28].

In another study from 2008 performed by Cesari et al. [29] IPF was used for the assessment of platelet reactivity in CAD patients on dual antiplatelet therapy. 372 patients were enrolled, IPF was measured using a hematology analyzer and platelet function by optical platelet aggregometry (PA) on platelet-rich-plasma induced by 1 mmol arachidonic acid (AA-PA) and 10 microM ADP (ADP-PA). Residual platelet reactivity was defined as either AA-PA > 20% or ADP-PA > 70%. Significant positive correlations were found between IPF and PA, MPV. Furthermore, the higher the IPF the greater platelet aggregation by AA and ADP. Moreover, a significant diversity for IPF between patients with and without residual platelet reactivity was proven and therefore IPF influences the risk of residual platelet reactivity. This study suggested that high platelet turnover is a mechanism connected with platelet reactivity in high-risk CAD on dual antiplatelet therapy [29].

IPF in therapy for acute coronary syndrome

Funck-Jensen et al. [30] sought to evaluate IPF levels in patients suffering from ACS and receiving dual antiplatelet therapy (clopidogrel and ASA). 48 STEMI patients were enrolled. Patients had their blood tested prior to PCI, at 4 to 12 hours after administration of bolus doses, and at follow-up after 3 months. Each patient was given loading doses of ASA (300 mg) and clopidogrel (600 mg) orally in the ambulance. In the acute phase of STEMI at the time prior to PCI platelet aggregation was higher compared to 4 and 12 hours after administration of loading doses of clopidogrel and ASA ($p < 0.01$). Furthermore, IPF values were significantly elevated in the acute phase of STEMI compared to 3 months afterwards ($p < 0.0001$). This proves that platelet aggregation is much higher in the acute phase of STEMI even though patients were given loading doses of antiplatelet drugs. This can be explained by a high platelet turnover during the acute phase of STEMI which results in an impaired response to clopidogrel and ASA [30].

Moreover, a study performed on 100 patients with STEMI or NSTEMI showed, that IPF levels tend to decline during a day after a successful PCI ($p < 0.001$) and remain stable

over the first month [31]. It also revealed, that high IPF levels correlate with increased troponin levels ($p = 0.001$), which might be a ground for future studies to exploit another feature of the IPFs, as the troponin level was shown to correlate with infarct size [32, 33].

Current trends aim at a personalized antiplatelet therapy. IPF may be a vital marker for choosing a $P2Y_{12}$ receptor inhibitor and defining the optimum time interval of drug administration. The primary difference between ticagrelor and thienopyridines i.e., prasugrel is a reversible binding of the $P2Y_{12}$ receptor. The hypothesis arises that IPF may respond poorly to therapy with ticagrelor compared to therapy with prasugrel. Bernlochner et al. [34] assessed the influence of IPF on ADP-induced platelet aggregation in ACS patients treated with either prasugrel or ticagrelor. 124 patients were enrolled, all of whom received ticagrelor or prasugrel loading doses prior to PCI and a continuation of either drug for 12 months as well as ASA in a dual antiplatelet strategy. Venous blood was obtained before drug administration and 6 to 48 hours after application of a loading dose of studied drugs [34].

The study showed ADP-induced platelet aggregation was significantly lower in patients treated with prasugrel than with ticagrelor ($p = 0.001$) [34]. Furthermore, in prasugrel treated patients, the platelet aggregation correlated positively with IPF ($p < 0.001$). On the other hand, no such correlation was observed in ticagrelor treated patients ($p = 0.51$) (Fig. 3) [34].

Additionally, this study aimed to assess the expression of P-selectin as a marker for platelet activation in immature platelets versus in mature platelets. A subgroup of the study population ($n = 28$, $n = 15$ prasugrel treated patients, $n = 13$ ticagrelor treated patients) was enrolled for this test. ADP-induced P-selectin expression was measured in the dependence of the time point of drug administration. Whole blood was analyzed at two different time points, the first — 2 hours after the last dose, the second — 1 hour before the next dose. This came to 26 measurements (14 at the first time point and 16 at the second) in the prasugrel group and 22 measurements (12 at the first time point and 12 at the second) in the ticagrelor group. The study proved that P-selectin expression is significantly higher in IPF compared to those without IPF in both prasugrel and ticagrelor treated patients ($p < 0.0001$). This suggests that immature platelets have a larger prothrombotic potential. Moreover, P-selectin expression in immature platelets was significantly higher in patients treated with prasugrel compared with those treated with ticagrelor ($p = 0.047$) [34].

Another study aimed to evaluate high on-treatment platelet reactivity (HPR). 101 male patients with the ACS were enrolled, and these patients had measured platelet function in the acute phase (T0), at 6 months (T1) and 12 months (T2) after the ACS. The study group identified three subgroups of patients: persistent (HPR at T0, T1, and T2), acute non persistent (HPR only at T0), and late (HPR only at T1 and T2). Patients with persistent HPR were more frequently with higher values of body mass index, carried CYP2C19*2 variant, and were diabetics. Significantly higher levels of IPF at T1 as well as T2 were present in patients with late HPR. Furthermore, IPF was the only variable that correlated with late HPR ($p = 0.016$). The study group concluded that late HPR presented by an elevated level of IPF is most likely correlated with inflammation [35].

The research performed so far also demonstrated that IPF has a greater prothrombotic potential than mature platelets [23]. Their importance in adverse ischemic events after cessation of dual antiplatelet therapy (DAPT) is still under investigation. Recently, a study conducted on a group of 62 patients with CAD after myocardial infarction showed that cessation of the $P2Y_{12}$ inhibitor treatment is associated with increased IPF in patients [36]. This occurred in either, patients receiving clopidogrel, ticagrelor or prasugrel and may partly explain the increased incidence of ischemic events after the exclusion of $P2Y_{12}$ inhibitor from DAPT [37–39].

IPF in therapy

A study from 2016 evaluated whether IPF can predict antiplatelet response to thienopyridines. 300 patients undergoing elective coronary stenting who received prasugrel or clopidogrel were enrolled. IPF correlated positively with ADP-induced platelet reactivity ($p < 0.01$) [40].

A study from 2011 performed by Ibrahim et al. [41] assessed the modulation of antiplatelet effects after administration of 75 mg clopidogrel for a week. 29 healthy subjects were enrolled and had their blood tested for IPF 1 week prior to daily dosing of the drug and 1 week after daily dosing of the drug. The study population was divided based on IPF concentrations into tertiles. Baseline platelet aggregation responses to 2, 5, and 20 μM ADP were indistinguishable in all three tertiles. After 1 week of treatment with clopidogrel platelet aggregation was higher in the upper tertile than in the lower tertile in response to 5 μM ADP ($p = 0.02$). This proves that IPF can be associated with an impaired response to the antiplatelet effect of clopidogrel [41].

A study from 2010 sought to determine whether a higher level of IPF was correlated with stent thrombosis in patients who underwent percutaneous cardiac intervention and were treated with a 75 mg dose of ASA once a day. 117 patients were enrolled, 39 patients had suffered from stent thrombosis and the remaining 78 patients served as a control group. The study showed that a trend was observed towards an elevated IPF in patients who suffered from stent thrombosis but it missed statistical significance ($p = 0.13$) [42].

In order to implement IPF in routine clinical care, it should be measured with whole blood count parameters on admission to hospital and during hospitalization. Afterwards, the IPF concentration should be assessed, and the optimal pharmacological treatment ought to be chosen. Among patients with chronic coronary syndromes with high IPF concentration, a more potent $P2Y_{12}$ inhibitor post PCI could be considered in preference to clopidogrel, though such an approach still needs to be confirmed in randomized clinical trials.

IPF post cardiac surgery

A study from 2017 evaluated whether IPF can be used as a biomarker for predicting MACE or other thromboembolic events after intermediate and high-risk non-cardiac surgery. The endpoint was defined as MACE, deep vein thrombosis, or pulmonary embolism during hospital stay (modMACE). A total of 732 patients were enrolled and IPF was measured preoperatively and postoperatively in the post anesthesia care unit. Preoperatively there were no differences in IPF between patients with and without modMACE. However, postoperatively patients with modMACE presented elevated levels of IPF compared with those who did not suffer from modMACE ($p = 0.011$). The study group suggested an optimal cut off value of IPF > 5.4%. This proves IPF can be used for risk stratification of surgical patients [43].

Conclusions

Immature platelet fraction is a novel and promising biomarker that may be derived using flow cytometry analysis in a relatively straightforward manner. There is evidence indicating the association between IPF concentrations and various cardiovascular diseases have potential utility as a prognostic tool among patients presenting with ACS. Furthermore, initial reports hint at the potential role of IPF in antiplatelet therapy monitoring. Further studies addressing the diagnostic, prognostic and potentially therapeutic roles of IPF are warranted.

Conflict of interest: None declared

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Figure 1. Thrombopoietin concentration and immature platelet fraction (IPF) values. Adapted from [24].

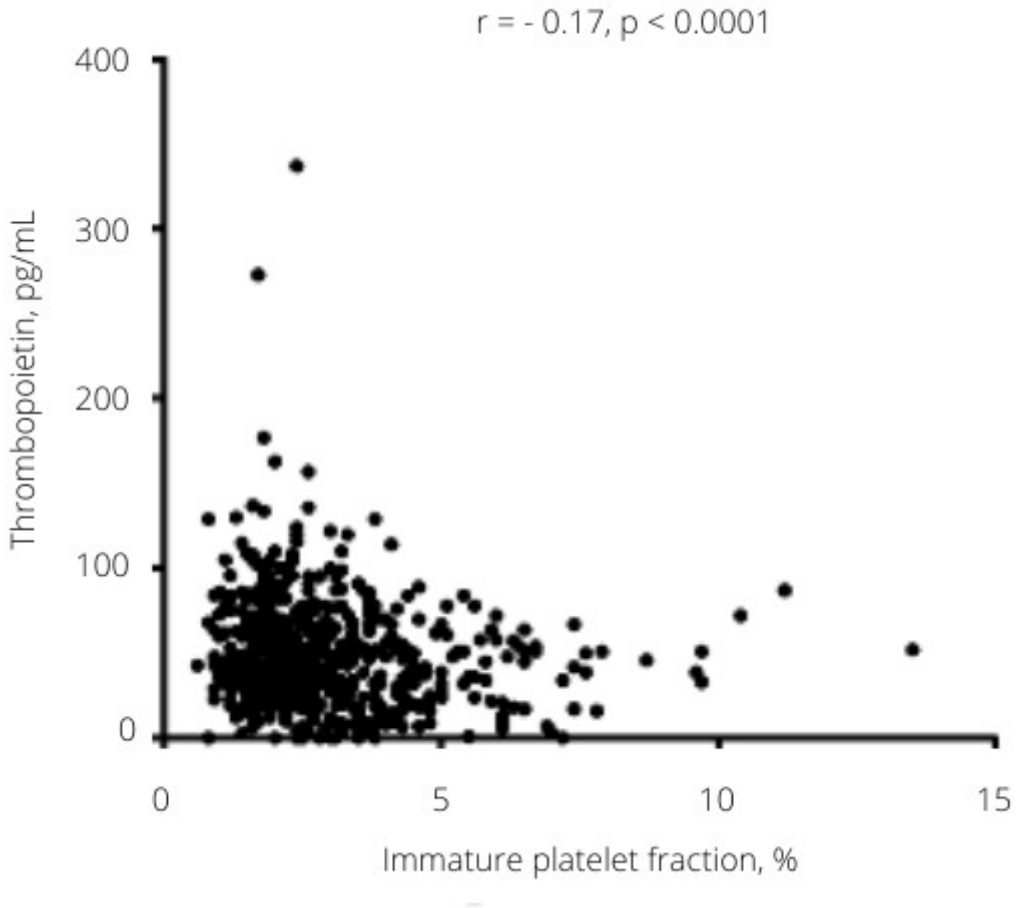

Figure 2. Outcome events stratified by immature platelet fraction tertile. Adapted from [28]; MACE — major adverse cardiovascular events; STEMI — ST elevation myocardial infarction.

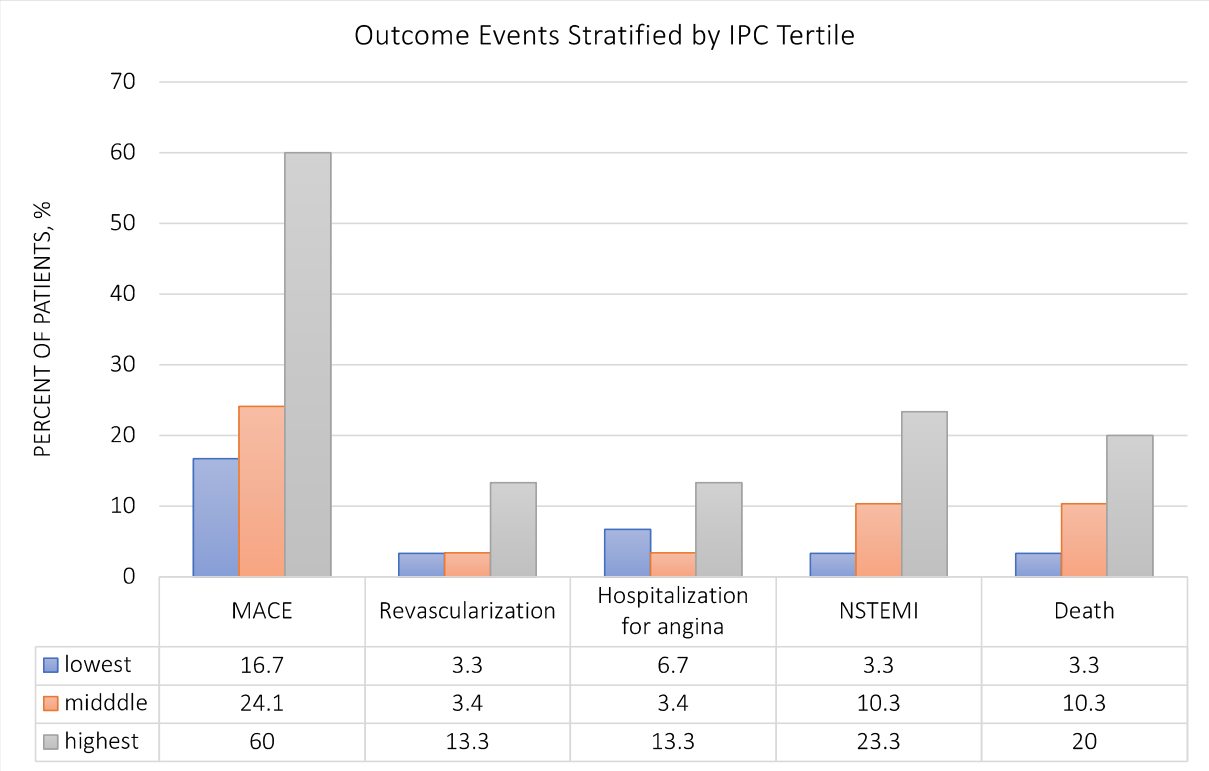

Figure 3. Immature platelet fraction (IPF) and ADP-induced platelet aggregation in ticagrelor and prasugrel treated patients. Adapted from [34].

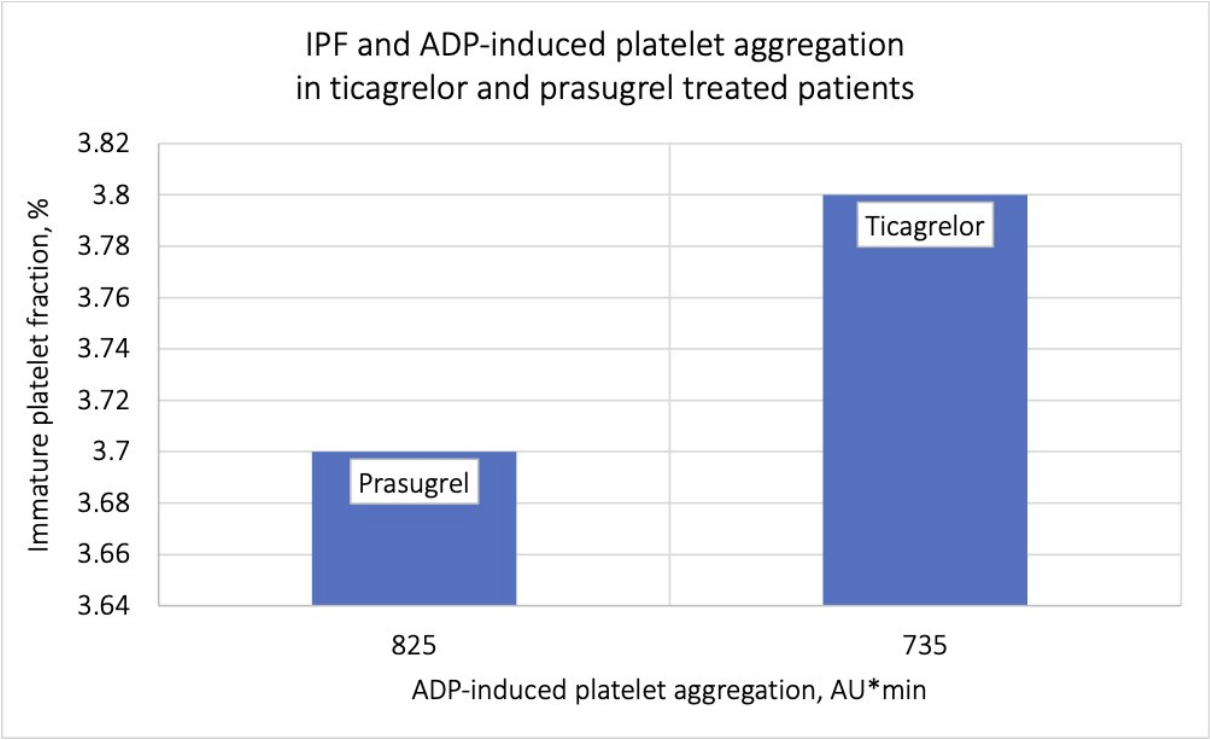
IPF and ADP-induced platelet aggregation
in ticagrelor and prasugrel treated patients
Immature platelet fraction, %
3.82
3.8
3.78
3.76
3.74
3.72
3.7
3.68
3.66
3.64
Prasugrel
Ticagrelor
825
735
ADP-induced platelet aggregation, AU*min

Figure 4. An outline of most the important information about immature platelet fraction (IPF); ACS — acute coronary syndrome; modMACE — major adverse cardiovascular events, deep vein thrombosis or pulmonary embolism during hospital stay; STEMI — ST segment elevation myocardial infarction.

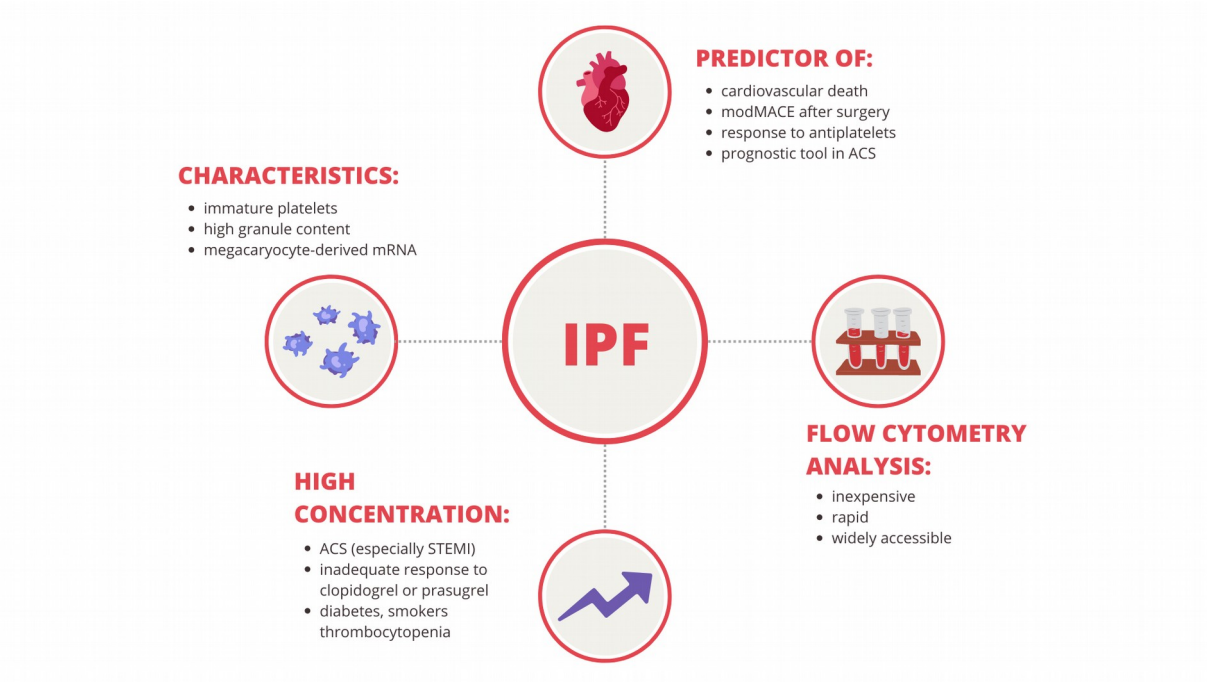

Table 1. A summary of studies regarding immature platelet fraction in cardiovascular diseases.

	Study	Population (n)	Intervention	Comparison	Outcomes
ACS					
	Cesari et al. [19]	229	PCI	IPF parameters among ACS patients and after 1-year follow-up	After one-year follow-up, IPF and H-IPF were increased in patients who died from cardiovascular causes
CAD					
	Verdoia et al. [13]	1789	Coronary angiography	Correlation between IPF and the rate of CAD or severe left main/three vessel-disease	IPF parameter should not be overlooked as a marker of coronary atherosclerosis among patients with CAD undergoing coronary angiography
	Grove et al. [22]	177	75 mg of plain ASA daily	Correlation between platelet turnover and platelet aggregation in ASA-treated patients	IPF reflects increased platelet turnover in patients with CAD. Increased platelet turnover may render aspirin less effective in patients with CAD
	Guthikonda et al. [23]	90	Elective cardiac catheterization and/or planned PCI	Correlation between size of platelets and response to antiplatelet therapy	The size proportion of circulating IPF affect response to antiplatelet therapy in patients with stable CAD
	Guthikonda et al. [23]	581	75 mg of ASA daily	Correlation between IPF, IPC, MPV, PC, PDW, P-LCR, and thrombopoietin	Increased IPF, MPF, PDW in stable CAD patients, indicate increased platelet turnover. The inverse relation between thrombopoietin and IPF, IPC, MPV, PDW and P-LCR
	Ibrahim et al. [28]	89	Observational study	Correlation between the IPC and IPF and MACE	Both the IPF and the IPC were greater in patients with MACE at follow-up
	Cesari et al. [29]	372	PCI and DAPT	Influence of IPF on platelet activity	↑ IPF and H-IPF in ACS patients Positive correlation between PA, IPF, H-IPF and MPV IPF influences the risk of RPR
Therapy ACS					

	Funck-Jensen et al. [30]	48 STEMI patients	PCI and DAPT with ASA + clopidogrel	IPF levels prior to PCI, 4–12 h after loading doses of ASA and clopidogrel, and 3 months later	↑ IPF in acute phase of STEMI
	Bernlochner et al. [34]	124 ACS patients	PCI and DAPT with ASA + either ticagrelor or prasugrel	Correlation of platelet aggregation and IPF in ticagrelor- vs. prasugrel-treated patients P-selectin expression in immature platelets vs. in the mature platelets	Prasugrel: PA correlated with IPF Ticagrelor: no correlation ↑ P-selectin in IPF P-selectin in immature platelets on prasugrel vs. ticagrelor
	Fabbri et al. [35]	101 ACS male patients divided in subgroups: persistent, non-persistent and late HPR	PCI and DAPT with ASA and clopidogrel	Evaluation of HPR	↑ IPF in late HPR patients
Therapy					
	Ibrahim et al. [41]	29 healthy subjects divided into tertials based on baseline IPF	75 mg/day of clopidogrel for a week	Platelet aggregation in response to 2, 5 and 20 mM of ADP	Baseline PA similar in all tertials ↑ PA in response to 5 mM of ADP after a week of clopidogrel in the upper vs. the lower tertial
	Wurtz et al. [42]	117	Previous PCI, treated with ASA 75 mg/day	Platelet aggregation and IPF in patients with vs. without ST	Significantly ↑ PA and not statistically significant (p = 0.13) ↑ IPF in patients with ST
Post cardiac surgery					
	Anetsberger et al. [43]	696	Intermediate or high-risk non-cardiac surgery	Pre- and postoperative IPF level in patients with vs. without modMACE	No differences preoperatively IPF in modMACE patients in the PACU

ACS — acute coronary syndrome; ASA — acetylsalicylic acid; CAD — coronary artery disease; DAPT — dual antiplatelet therapy; H-IPF — highly immature platelet fraction; IPC — immature platelet count; IPF — immature platelet fraction; MACE — major adverse cardiovascular events; modMACE — MACE, deep vein thrombosis or pulmonary embolism during hospital stay; MPV — mean platelet volume; PA — platelet aggregation; PACU — post anesthesia care unit; PCI — percutaneous coronary intervention; RPR — residual platelet reactivity; ST — stent thrombosis; STEMI — ST segment elevation myocardial infarction