Supplementary material

I. Platelet function assays: advantages and limitations

1. Light transmission aggregometry

Light transmission aggregometry (LTA) is the historical gold standard for monitoring the pharmacodynamic response to antiplatelet agents. Infrared light transmittance passing through platelet-poor plasma (PPP) is used to represent 100% aggregation, and the optical changes from 0%, set by the unstimulated platelet-rich plasma (PRP), is evaluated in response to inductors. As activated platelets aggregate after stimulation with various agonist agents, most commonly ADP and arachidonic acid, optical density decreases in the absence of antiplatelet medication. (Supplement figure 1)

The main advantage of the method is that it is the historical gold-standard tool for platelet function studies, with widespread use and with significant clinical experience regarding both pharmacodynamic and clinical studies.

Disadvantages include time-consuming, complicated sample preparation, need for trained laboratory personnel that precludes bedside testing in 24 hours/7 days of service. The lack of leukocytes and the low levels of ionized calcium during platelet aggregation are other important drawbacks of LTA. Most importantly, poor standardization due to diversity in the concentration of agonist used (5, 10, 20 μM), the preferred estimate for evaluation (peak aggregation, late aggregation), the choice of anticoagulants (citrate, hirudin or PPACK anticoagulation) and the different specifications in sample preparation techniques (centrifuging time and speed) are huge limitations. This may explain why results are poorly comparable between laboratories and why a universal cut-off for HPR is difficult (if not impossible) to determine.[24,26,31,83,84] (Supplement table 2)

2. Flow cytometric analysis of VASP phosphorylation

Measuring the phosphorylation state of vasodilator stimulated phosphoprotein (VASP) using flow cytometry is a completely $P2Y_{12}$-receptor specific method for the evaluation of ADP-receptor inhibition. VASP is a second messenger in the signaling pathway of the $P2Y_{12}$ receptor that is regulated by protein kinases and phosphatases according to the activity of the receptor. Inactive/resting platelets possess high cAMP levels that induce phosphorylation of VASP by cAMP-dependent protein kinases (VASP-P: resting state). In case of $P2Y_{12}$-receptor stimulation, the activity of the adenylate-cyclase enzyme decreases leading to dephosphorylation of VASP (VASP: active state). Therefore, the ratio of dephosphorylated and phosphorylated VASP is a

selective measure of $P2Y_{12}$-inhibition (platelet reactivity index, PRI = (MFI_{PGE1}-$MFI_{PGE1+ADP}$)/MFI_{PGE1}x100). (Supplement figure 1)

The main advantage of the method is the complete $P2Y_{12}$-receptor specificity; currently, this is the only assay that is able to evaluate the extent of $P2Y_{12}$-receptor inhibition without the influence of the $P2Y_1$-receptor. Another advantage is that the measurement is not influenced by the presence of glycoprotein IIb/IIIa receptor inhibitors while other assays are not able to give reliable results within the first 24 hours (tirofiban/eptifibatide) or even in the first week (abciximab) after GPI infusion. High levels of VASP-PRI after clopidogrel were correlated to adverse clinical outcomes.[19-21] Moreover, small studies demonstrated that VASP is able to predict both thrombotic and bleeding events in patients treated with novel $P2Y_{12}$-inhibitors.[75]

The main disadvantage is that the technique requires special laboratory environment and staff experienced in flow cytometric analysis, making the method inappropriate for routine clinical purposes; it is rather an ideal tool for platelet function research. Although the assay is completely $P2Y_{12}$-receptor specific, the proportion of patients considered as having inappropriate $P2Y_{12}$-receptor inhibition is relatively high. Although most of the observational studies that used ROC-curves for analyzing optimal cut-off points for ischaemic events suggested the use of 50% VASP-PRI value[19-21], it has been recently proposed[18,85] to use a higher cut-off (60% PRI). Since the mathematical expression of VASP-PRI (mean, geometric mean or median) significantly influences the obtained PRI values, the mean fluorescence intensity (MFI) should be calculated to reduce heterogeneity. A study reported[86] that the VASP assay is relatively insensitive for low levels of $P2Y_{12}$-receptor inhibition, underestimating $P2Y_{12}$-receptor inhibition in such patients. It should be noted that a novel, ELISA-based kit is also available that might reduce the sampling time and does not require a flow cytometer for the analysis. (Supplement table 2)

3. Multiple Electrode Aggregometry

Multiple electrode aggregometry (Multiplate, Roche Diagnostics, Switzerland) utilizes an impedance aggregometer that detects changes in electric impedance over time between two electrodes immersed into hirudin-anticoagulated whole blood diluted with saline. The measurement simulates platelet adhesion, activation and aggregation on a metal surface during continuous stirring in an ex vivo setting, mimicking the development of stent thrombosis upon platelet activation. Changes in impedance are plotted over time resulting in an aggregation curve, similarly to LTA. (Supplement figure 1) The efficacy of platelet inhibition is expressed with the area-under-the-aggregation-curve (AUC) value, obtained during 6 minutes of measurement.

The advantage of the method is that it is a semi-automated, standardized aggregometry that evaluates the efficacy of platelet inhibition in whole blood. The assessment is significantly faster and more reliable than conventional aggregometry, without the need for labor-intensive sample

preparation and with fewer possibilities to obtain laboratory artifacts. Based on the available clinical evidence, Multiplate has been shown to predict both bleeding and thrombotic events.[22,74] According to two studies[22,87], an ADP test value greater than 46 U (=468 AU) seems to be the optimal cut-off to separate patients with high risk for stent thrombosis. One study has also linked low aggregation values with Multiplate to higher risk of bleeding events, suggesting a potential therapeutic window between 19 and 46 U using Multiplate regarding $P2Y_{12}$-receptor inhibition.[78]

As a main disadvantage, the method is only partially automated, requiring sample preparation and pipetting throughout the assessment. (Supplement table 2)

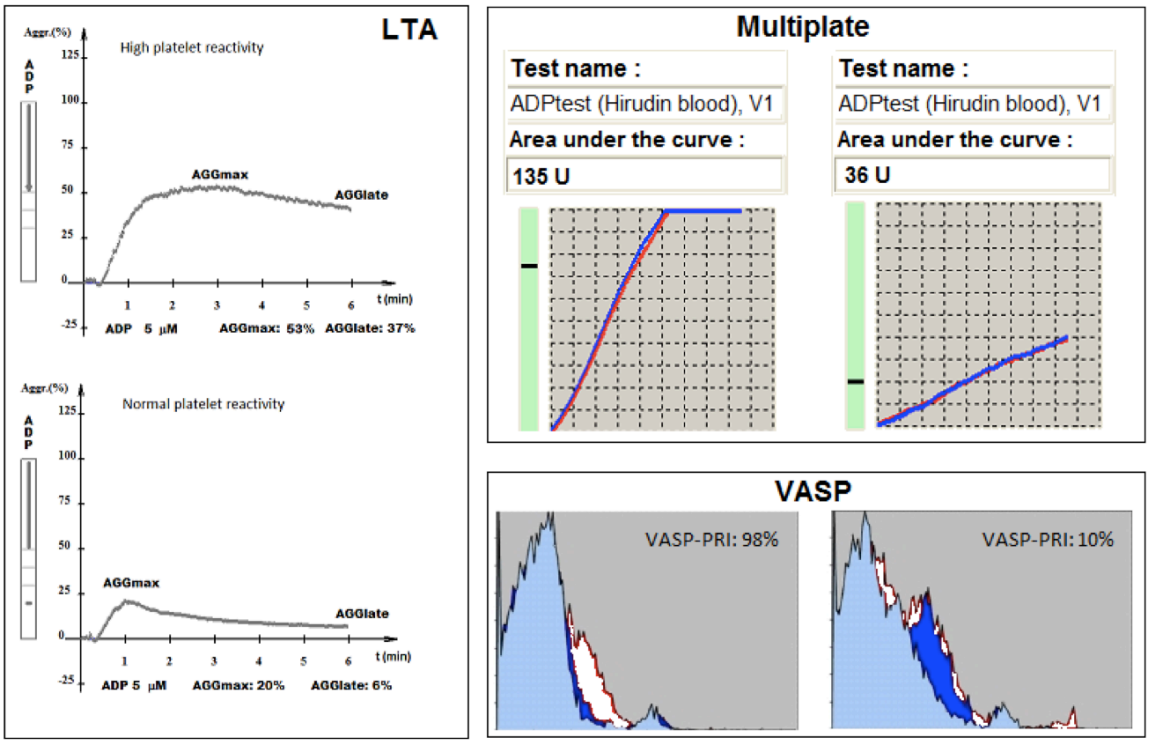
4. VerifyNow

The VerifyNow (Accumetrics, USA) device is a fully automated, standardized, point-of-care whole blood test, which is based on turbidimetric optical detection of platelet aggregation in whole blood. Cartridges contain a combination of 20 μM of ADP and 22 nM of PGE1, the latter being added to amplify the effects of $P2Y_{12}$-receptor inhibition. During assessment, activated platelets aggregate and agglutinate on the surfaces of fibrinogen-coated beads in the detection wells of the machine. As aggregation occurs, the system converts light transmittance results into $P2Y_{12}$ reaction units (PRU), with higher values indicating greater platelet reactivity.

The main ***advantage*** of the VerifyNow device is that, due to the ease of use, it has become the most widely applied ADP-specific platelet function assay in recent years. Post-clopidogrel PRU values have been correlated with ischaemic events in the largest number of patients from both clinical trials and registries.[23,35] Although initial observational studies suggested that the optimal cut-off value might be around 230 PRU[24,35,88], recent evidence from a large-scale multicenter registry and from a randomized controlled trial suggest 208 as a better threshold to define HPR.[23,25] According to a study[79], the range between 85 and 239 PRU might be the zone with the lowest risk for both bleeding and ischemic events.

Disadvantages include the relatively high rate of HPR subjects delineated by the suggested cut-offs (approx. 40-50%) that might decrease the relative risk associated with HPR compared to no HPR subjects. The measurement is highly dependent on haematocrit and platelet count, low values of these indices might result in error message during assessment. (Supplement table 2)

II. Supplement figure



Supplement figure 1.

Platelet function results using LTA, Multiplate and VASP assays

Figure shows the results of platelet function testing using light transmission aggregometry (LTA), Multiplate analyzer and vasodilator stimulated phosphoprotein (VASP) phosphorylation in a patient with low and with high on-clopidogrel platelet reactivity. In case of LTA, the maximal aggregation value, while in case of Multiplate, the area-under-the-aggregation-curve (AUC) reflects platelet reactivity to ADP. When using the VASP assay, mean fluorescence intensities (MFI) for the phosphorylated VASP (VASP-P) are calculated in resting phase (after PGE_2 stimulation, white graph) and in activated phase (after co-stimulation with ADP and PGE_2, dark blue graph). After correcting for the background intensity (light blue graph), the decrease in VASP-P levels reflects inhibition of the $P2Y_{12}$ receptor.

III. Supplement tables

Supplement table 1. Clinical guideline recommendations regarding platelet function testing			
Guideline	Statement	CoR	LoE
ESC PCI guidelines 2005[89]	*The emerging question of possible clopidogrel resistance requires more investigations.*	-	-
ACC/AHA/SCAI PCI guideline 2005[90]	*In patients in whom subacute thrombosis may be catastrophic or lethal (unprotected left main, bifurcating left main, or last patent coronary vessel), platelet aggregation studies **may be considered.***	IIb	C
ESC guidelines on myocardial revascularization 2010[69]	*Monitoring of antiplatelet response by platelet function assays is currently used for clinical research, but **not** in daily clinical practice.*	III	C
ESC NSTE-ACS guidelines 2011[1]	*Platelet function testing **may be considered** in selected cases when clopidogrel is used. Several trials currently under way may clarify the impact of adapting therapy on the basis of the results of platelet reactivity assays, but, so far, the routine clinical use of platelet function tests in clopidogrel-treated patients with ACS cannot be recommended.*	IIb	B
ACC/AHA/SCAI PCI guidelines 2011[5]	*Platelet function testing **may be considered** in patients at high risk for poor clinical outcomes. In patients treated with clopidogrel with high platelet reactivity, alternative agents, such as prasugrel or ticagrelor, might be considered. The routine clinical use of platelet function testing to screen patients treated with clopidogrel who are undergoing PCI is not recommended.*	IIb	C
ACCF/AHA UA/NSTEMI guidelines 2012[6]	*Platelet function testing to determine platelet inhibitory response in patients with UA/NSTEMI (or, after ACS and PCI) on $P2Y_{12}$-receptor inhibitor therapy **may be considered** if results of testing may alter management.*	IIb	B
ESC STEMI guidelines 2012[3]	*No specific recommendation.*	-	-
ACCF/AHA STEMI guidelines 2013[7]	*The roles of platelet function testing and genetic screening for clopidogrel metabolism in the acute phase of STEMI care are uncertain.*	-	-
CoR: Class of recommendation; LoE: Level of Evidence.			

Supplement Table 2.
Comparison between most commonly used platelet function assays

	LTA	VASP	PFA-100	VerifyNow	Multiplate
Assessment principle	turbidimetric	fluorescent intensity	shear-dependent occlusion	turbidimetric	impedance
Medium for assessment	Platelet rich plasma (PRP)	whole blood	whole blood	whole blood	whole blood
Agonist	ADP 5/10/20 μM	ADP 20 μM	ADP+collagen (C/ADP)	ADP 20 μM (P2Y12)	ADP 6,4 μM (ADP test)
Measurement time*	20-25 min	2-3 h	8 min	6 min	10 min
Automatic assessment	no	no	yes	yes	partial
Standardization	no	yes	yes	yes	yes
$P2Y_{12}$-specificity	partial	complete	partial	partial	partial
ROC-defined cut-offs for ischaemic events	***- 5 μM:*** Aradi[83]: 34%, Breet[24]: 43%, Gurbel[31]: 46% ***- 10 μM:*** Frere[84]: 70% Cuisset[26]: 67% ***- 20 μM:*** Gurbel[31]: 59% Breet[24]: 64.5%	Blindt[20]: 48% Bonello[19]: 50% Frere[84]: 53% El Ghannudi[85]: 61% Freynhofer[21]: 52%	N/A	Price[25]: 208 PRU Brar[35]: 230 PRU Price[88]: 235 PRU Breet[24]: 236 PRU Marcucci[91]: 240 PRU Stone[23]: 208 PRU	Sibbing[22]: 46U Siller-Matula[92]: 54U Siller-Matula[87]: 46U
Recommended cut-off for higher risk for stent thrombosis	Due to methodical heterogeneity, a uniform cutoff cannot be recommended	>50% PRI†	Not recommended	>208 PRU	>46 U
Potential cutoff for bleeding	-	<16% PRI[75]	-	<85 PRU[79]	<19 U[74]
Main advantages	historical gold-standard, cheap	highest $P2Y_{12}$-specificity	simulation of flow conditions	point-of-care, most widely used	fair clinical predictive value due to low[22] rate of HPR on clopidogrel
Main limitations	not standardized, cutoffs for HPR vary largely	requires flow cytometry lab	lack of clinical predictive value for stent thrombosis	low clinical predictive value due to high[25] rate of HPR on clopidogrel	not point-of-care

*: One test from sample preparation until obtaining results. †: Recent data suggest a somewhat higher cutoff (60%) that needs to be validated.

Supplement Table 3.
Studies aiming to evaluate the clinical impact of treatment adaption based platelet function testing

Author	Acronym	Date	Design	Patient No. (tailored/ control)	Clinical setting	Platelet function assay	Cut-off	Pharmaco-logical intervention	Primary endpoint	Results (tailored/ control)	P	Major bleeding (tailored/ control)
Bonello[93]	-	2008	Multicentre RCT	78 / 84	Stable angina: 52% NSTEMI: 48% STEMI: 0%	VASP	VASP-PRI >50%	Repeated 600 mg clopidogrel LD	CV death, definite ST, recurrent ACS, revascularizatio n	0% vs. 10%	0.007	1.3% vs. 1.2%
Bonello[94]	-	2009	Multicentre RCT	215 / 214	Stable angina: 48% ACS: 52% STEMI: 0%	VASP	VASP-PRI >50%	Repeated 600 mg clopidogrel LD	Early definite ST	0.5% vs. 4.7%	0.010	0.9% vs. 0.9%
Valgimigli[67]	3T/2R	2009	Multicentre RCT	79 / 91	Stable angina: 47% ACS: 53% STEMI: 0%	VerifyNow P2Y12	<40% inhibition	tirofiban 25 µg/kg bolus + 0.15 µg/kg/min infusion	Peri-procedural MI (<48h)	20.4% vs. 35.1%	0.009	0% vs. 0%
Cuisset[68]	-	2008	Single centre RCT	74 / 75	Stable angina: 100% ACS: 0% STEMI: 0%	LTA, 10 µM ADP	>70% AGGmax	abciximab 0.25 µg/kg blus + 0.125 µg/kg/min infusion	Death, def./prob. ST, recurrent ACS	19% vs. 40%	0.006	0% vs. 0%
Price[8]	GRAVITAS	2010	Multicentre RCT	1109 / 1105	Stable angina: 60% NSTEMI: 10.1% STEMI: 0.4%	VerifyNow, P2Y12	>230 PRU	600 mg LD +150 mg clopidogrel	CV death, non-fatal MI or def./prob. ST	2.3% vs. 2.3%	0.970	1.4% vs. 2.3%
Wang[95]	-	2011	Single centre RCT	150/156	Stable angina: 80% NSTEMI: 20% STEMI: 0%	VASP	VASP-PRI >50%	Stepwise increase in clopidogrel MD up to 375 mg according to VASP-PRI	CV death, definite ST, recurrent ACS and revascularizatio n	9.3% vs. 19.2%	0.008	0% vs. 0%
Aradi[96]	DOSER	2010	Single centre RCT	36 / 38	Stable angina: 100% NSTEMI: 0% STEMI: 0%	LTA, 5 µM ADP	> 34% AGGmax	600 mg LD + 150 mg MD clopidogrel	CV death, MI, TVR	3.1% vs. 24.6%	0.010	2.8% vs. 0%
Ari[97]	EFFICIENT	2011	Double centre RCT	47 / 47	Stable angina: 100% NSTEMI: 0% STEMI: 0%	VerifyNow, P2Y12	<40% inhibition	150 mg MD clopidogrel	CV death, MI, ST, TVR or recurrent ACS	4.3% vs. 17%	0.045	2.1% vs. 0%
Hazarbasanov[98]	-	2011	Single centre RCT	97 / 95	Stable angina: 43% NSTEMI: 33% STEMI: 24%	Multiplate, 6.4 µM ADP	>46 U	600 mg LD + 150 mg MD clopidogrel	CV death, MI, ST or ischaemic stroke	0% vs. 5.3%	0.022	1% vs. 1%
Trenk[9]	TRIGGER-PCI	2011	Multicentre RCT	212/211	Stable angina: 100% NSTEMI: 0% STEMI: 0%	VerifyNow, P2Y12	>208 PRU	60 mg LD + 10 mg MD prasugrel	CV death or MI	0% vs. 0.5%	N/A	1.4% vs. 0.5%
Siller-Matula[99]	MADONNA	2012	Multicentre, observationa l study	403/395	Stable angina: 63% NSTEMI: 12% STEMI: 25%	Multiplate 6.4 µM ADP	≥50U	Repeated 600 mg clopidogrel LD or prasugrel	Stent thrombosis	0.2% vs. 1.9%	0.027	1% vs. 0.3%
Collet[10]	ARCTIC	2012	Multicentre RCT	1213/1227	Stable angina: 63% NSTEMI: 27% STEMI: 0%	VerifyNow P2Y12 and aspirin	≥235	Repeated 600 mg clopidogrel LD, elevated clopidogrel MD, switch to prasugrel, high-dose aspirin or additional GPI	death, myocardial infarction, stent thrombosis, stroke, or urgent revascularizatio n	34.6% vs. 31.1%	0.100	2.3% vs. 3.3%
Aradi[66]	-	2013	Single centre registry	563	Stable angina: 0%	Multiplate, 6.4 µM ADP	>46 U	(1) High-dose clopidogrel	Vascular mortality or	3.95% vs. 10.77%	0.02	N/A

NSTEMI: 34% STEMI: 48%		(2) Switch to prasugrel	def/prob. ST in patients with HPR

Supplement table 4.

Consensus recommendations on platelet function testing

I. Clinical relevance of platelet function testing	**LoE**	**Ref**
• In routine practice, moderate-to-high risk ACS patients undergoing PCI should receive new-generation $P2Y_{12}$-inhibitors instead of clopidogrel (unless contraindications exist), and routine platelet function testing is not recommended.	A	1,3,8,10,63, 70
• Stable angina patients after successful elective PCI should receive standard dose clopidogrel and routine platelet function testing to intensify $P2Y_{12}$-receptor inhibition is not recommended.	B	8-10
• Although evidence is scarce, platelet function testing may be considered in selected ACS patients undergoing stent implantation who are pretreated with clopidogrel and in whom the presumed benefit of new-generation agents is not well established, such as (i) patients with a prior major spontaneous bleeding event or with highly elevated risk for bleeding; and (ii) patients at low risk for thrombotic events [troponin negative subjects who have no additional high-risk features]. Based on platelet function results, patients without HPR to ADP may continue clopidogrel treatment.	C	1,36
• Platelet function testing might be considered in countries where the availability of prasugrel or ticagrelor is restricted or limited to certain indications, to identify ACS patients with on-clopidogrel HPR who have high risk for thrombotic events on clopidogrel. Based on platelet function results, patients with HPR should be switched to prasugrel/ticagrelor.	C	27,66,100
• Despite the lack of clinical studies, platelet function testing may be considered to optimize $P2Y_{12}$-receptor inhibition in selected stable angina patients if results may change the $P2Y_{12}$-receptor inhibitor strategy due to: (a) an unexpected thrombotic event (especially stent thrombosis) despite being adherent to clopidogrel, (b) markedly elevated risk for stent thrombosis due to clinical and procedural features (unsatisfactory results during coronary intervention, complex interventions in high-risk patients), (c) stent thrombosis would be of catastrophic consequences (last remaining vessel PCI, left main PCI involving the bifurcation)	C	100
• Platelet function testing is not recommended in patients requiring chronic oral anticoagulation, because the clinical association between HPR and stent thrombosis has been established in patients without oral anticoagulants and triple treatment featuring oral anticoagulants and DAPT carries a remarkably elevated risk for bleeding.	C	71-73

II. The purposes of platelet function measurements:		
• To evaluate on-treatment platelet reactivity to ADP among patients receiving $P2Y_{12}$-inhibitors undergoing PCI.	B	23,32,33,35
• To refine the risk stratification of early stent thrombosis while treated with clopidogrel.	B	23
• To refine the risk stratification for bleeding in patients treated with $P2Y_{12}$-inhibitors after PCI.	B	23,74,75,80
• Not to evaluate so-called drug responsiveness (difference between baseline and post-treatment samples).	C	
• Not to measure aspirin responsiveness due to the lack of evidence for its prognostic value after PCI.	B	23,42
• **III. Timing of platelet function assessments**		
• Since the majority of thrombotic events are clustered within the first 30 days of PCI, it is relevant to schedule the first platelet function assessment before hospital discharge.	B	23,35
• Since platelet reactivity might change over time, control assessment during maintenance phase might be considered to assess long-term risk of ischaemic and bleeding events.	C	25,79
• Platelet function testing should be performed ideally at 6-24 hours after receiving a loading dose of clopidogrel in patients not receiving GPI (except for VASP assessment that is not affected by GPIs).	C	101,102
• Platelet function testing should be performed 24 hours after discontinuation of eptifibatide or tirofiban or one week after abciximab infusion to prevent false negative results (except for VASP assessment, which is not influenced by GPIs).	B	84
• **IV. Preferred assays for platelet function testing:**		
• Based on the available evidence, the following ADP-specific assays and cutoffs can be recommended for platelet function testing to define high on-clopidogrel platelet reactivity to ADP:		
(a) VerifyNow P2Y12 assay: 208 PRU	B	9,23,25
(b) Multiplate analyzer (ADP test): 46 U	B	22,87
(c) VASP phosphorylation assay: 50% PRI (mean MFI)	B	19-21
• LTA with ADP stimulation is recommended only in absence of a standardized assay. In case of LTA, a universal cutoff cannot be defined due to the significant methodical heterogeneity in the assay.	C	32
• **V. Clinical interpretation of platelet function results:**		
• ACS patients with HPR to ADP should be switched to new-generation $P2Y_{12}$-inhibitors unless contraindications exist.	C	63,66
• In ACS patients with HPR to ADP, increasing the dose of clopidogrel is discouraged.	B	8,10,27,66
• It is not recommended to increase the dose of clopidogrel or to give prasugrel/ticagrelor in patients requiring chronic oral anticoagulation after PCI.	C	71-73
• It is not recommended to increase the maintenance dose of aspirin based on platelet function testing due to lack of efficacy and the higher risk for gastrointestinal bleeding.	B	59,61,62

Supplement Table 5.
Clinical studies correlating platelet function results with higher risk for bleeding

Study	N	Device	Setting	Outcomes
Chen et al.[103]	45	LTA	Patients on clopidogrel within 6 days of CABG	In-hospital transfusion of red blood cells and platelet concentrates
Cuisset et al.[80]	597	VASP	NSTEMI patients with PCI on maintenance dual antiplatelet therapy	Non-CABG related bleedings at 30 days
Mokhtar et al.[104]	346	VASP	Elective or ACS patients with PCI on clopdiogrel and aspirin	In-hospital non-CABG related major TIMI bleedings
Michelson et al.[105]	125	VASP	ACS patients with PCI on prasugrel or clopidogrel in addition to aspirin (TRITON-TIMI 38 trial)	Haemorrhagic events ≥ 3 days post PCI
Poston et al.[106]	82	TEG	Patients on aspirin with off-pump CABG	Haemoglobin loss at 24 hours
Rahe-Meyer et al.[107]	60	MEA	Patients on aspirin undergoing elective cardiac surgery	In-hospital transfusion of platelet concentrates
Campo et al.[79]	300	VerifyNow	PCI-treated patients	TIMI bleeding events at 1 month
Serebruany et al.[108]	363	LTA	Patients with CAD or ischaemic stroke on aspirin therapy	Bleed score minor bleedings until clopidogrel discontinuation
Sibbing et al.[74]	2533	MEA	All Patients with PCI after clopidogrel loading 600 mg	In-hospital TIMI major bleedings
Stone et al.[23] (ADAPT-DES)	8,583	VerifyNow	PCI-treated patients	Major bleeding
Cuisset et al.[76]	107	VASP	PCI-treated diabetic patients	BARC 1, 2, 3, 5 bleedings

ACS: acute coronary syndrome, BARC: bleeding academic research consortium classification, CABG: coronary artery bypass graft, LTA: light transmission aggregometry, MACE: major adverse cardiovascular event, MEA: Multiple electrode aggregometry, PCI: percutaneous coronary intervention

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