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Increased risk of adverse events in patients with low-on clopidogrel platelet reactivity after percutaneous coronary intervention: A systematic review and meta-analysis

Alexandra Bálint et al., Bleeding risk associated with LPR

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Abstract

Background: Clinical evidence has been controversial regarding the influence of low platelet reactivity (LPR), ischemic and bleeding outcomes among patients receiving coronary stent implantation. Hence, the present study performed a meta-analysis to systematically evaluate the significance of LPR on adverse cardiovascular events.

Methods: MEDLINE, EMBASE and CENTRAL databases were searched up to November 2020 for relevant studies including patients with acute coronary syndrome undergoing percutaneous coronary intervention. LPR was the exposed arm while the non-LPR group represented the control. The primary outcome of interest was bleeding risk including major and minor bleeding events. Secondary outcomes included all-cause mortality, repeated revascularization, nonfatal myocardial infarction, and stent thrombosis. Study-level outcomes were evaluated in random-effect models.

Results: A total of 20 studies with 19,064 patients were included. Pooled analysis showed that LPR was associated with an increased bleeding risk (relative risk [RR] 2.80, 95%

confidence interval [CI] 1.95–4.02, p < 0.01). Patients with LPR had a lower risk of non-fatal myocardial infarction (RR 0.59, 95% CI 0.38–0.91, p < 0.05) and of serious vascular events (RR 0.50, 95% CI 0.30–0.84, p < 0.01).

Conclusions: LPR is associated with an increased bleeding risk of patients who underwent coronary stent implantation. The results suggest possible benefits of this marker in risk stratification, with potential improvement in risk prediction. There are potential advantages using combinations with other factors in prediction models, however, they require further study. PROSPERO registration number: CRD42019136393).

Key words: low platelet reactivity, acute coronary syndrome, percutaneous coronary intervention, bleeding risk, clopidogrel

Introduction

Dual antiplatelet therapy consisting of aspirin and adenosine diphosphate (ADP) receptor antagonist is essential for patients undergoing percutaneous coronary intervention (PCI) [1]. Clopidogrel used to be the gold standard therapy before the introduction of new P2Y12 inhibitors, such as prasugrel and ticagrelor, which have demonstrated their clinical advantages in large randomized controlled trials (RCTs) involving acute coronary syndrome (ACS) patients [2, 3]. Both prasugrel and ticagrelor provide more effective inhibition of platelet function than acetylsalicylic acid, however, their use was followed by an increased bleeding risk [2, 3].

Platelet function testing assesses individual response to antiplatelet drugs and platelet reactivity (PR) strongly relates to clinical outcomes after ACS [4–6]. Numerous studies have shown a relationship between high platelet reactivity (HPR) and thrombotic events [7–9]. Recent studies have also found that platelet function testing and/or genetic testing may provide important information guiding antiplatelet therapy [10, 11].

With the use of more effective agents, the prevalence of HPR has decreased and an increasing proportion of patients have very low on-treatment ADP reactivity. However, the clinical significance of LPR is less well established and it is not routinely measured. The effect of LPR was investigated in some studies raising a signal of increased bleeding risk which remains debated, partly due to contradictory results [12–14]. The objective herein,

was to perform a systematic review and meta-analysis aimed at assessing the impact of LPR on efficacy and safety outcomes after PCI.

Methods

Search strategy

A systematic review and meta-analysis were performed with reference to the PRISMA guideline [15]. The National Library of Medical Publications (MEDLINE); including its subset, PubMed, the Excerpta Medica Database (EMBASE) and Cochrane Library databases were searched for relevant articles with no restriction of time in November 2020 by using a search strategy that combined the following: Medical Subject Headings and free-text search terms: “acute coronary syndrome” OR “ACS” AND “PCI” OR “percutaneous coronary intervention” AND “platelet reactivity” OR “thrombocyte reactivity”. No language restriction was used. The PICO format was adapted to set the inclusion criteria. The PICO items selected were the following: (P) patients with acute coronary syndrome and/or undergoing PCI and receiving dual antiplatelet therapy consisting of acetylsalicylic acid and clopidogrel, prasugrel or ticagrelor, (I) LPR (C) non-LPR or HPR based on the measurement of on-treatment PR defined by an ADP-specific platelet function assay and (O) major adverse cardiac events (MACE) and bleeding. The non-LPR group consisted of HPR or HPR plus normal platelet reactivity (NPR) where data was given for NPR. The clinical outcomes of interest evaluated at the longest available follow-up of ADP-receptor inhibitor treatment were (a) major bleeding events (defined using the trials internal definitions using BARC 3–5 or Thrombolysis in Myocardial Infarction [TIMI] major criteria), and (b) minor bleeding events (BARC 1–2 or TIMI minor) [16], (c) definite/probable stent thrombosis (ST), (d) non-fatal myocardial infarction (MI) (type 1, 4a, 4b), (e) a composite endpoint of the reported serious vascular events that included cardiovascular death, non-fatal MI or non-fatal stroke, (f) repeated target vessel revascularization, and (g) all-cause mortality.

Studies that assessed responsiveness to clopidogrel, which was the difference between baseline and posttreatment PR (inhibition of platelet aggregation [IPA]), were excluded from the analysis. The reference lists in the articles were also checked to capture all relevant articles published within the topic of interest.

Data extraction

Observational studies and cohorts — regardless of their prospective/retrospective design — were identified. Two investigators (A.B. and A.K.) independently screened the retrieved titles, abstracts and studies for eligibility and relevant full texts were systematically retrieved for further assessment. Disagreements between reviewers were solved by consensus. The retrieved studies were examined to exclude duplicate or overlapping data. Unpublished data and meeting abstracts were not considered for the present analysis because results could not be considered as certain and definitive.

Risk of bias

The methodological qualities of the studies were assessed using the Prediction model Risk Of Bias Assessment Toll (PROBAST) for assessing the quality of cohorts and the Newcastle-Ottawa Scale with reference to observational studies [17, 18].

Publication bias was estimated using funnel plots. Visual evaluation and Egger's regression intercept were used to the check for asymmetry.

Statistical analysis

Statistical computations were performed using R (v 4.0.03) package 'dmetar' designed for the evaluation of meta-analyses and OpenMeta [Analyst] open source statistical softwares. A random-effect model was applied at all the analyses with DerSimonian-Laird estimation to derive risk ratios (RR) on dichotomous outcomes and weighted mean difference (WMD) on continuous data with a 95% confidence interval [CI]. Heterogeneity was tested with the χ^2 heterogeneity statistic for which a p-value < 0.1 was considered potentially heterogenous. Consistency was assessed using I^2 statistics [19]. Sensitivity analyses were carried out omitting one study at a time and calculating the effect size with the 95% CI to investigate the influence that a single study has on the final estimation regarding LPR with increased bleeding risk.

Ethical approval

Ethical or board review approval was not required for this meta-analysis.

Results

Search results and effect of LPR on the clinical outcomes

Twenty studies, involving 19,064 patients met the inclusion criteria. The process of the literature search and bias assessment is summarized in Figure 1 and for online **Supplementary Figure S4**.

Table 1 describes the main characteristics of the included studies. Based on pooled results of the random-effects model meta-analysis, LPR was associated with a significantly increased risk for major and minor bleeding events compared to non-LPR (RR 2.80, 95% CI 1.95–4.02, $p < 0.01$) (Fig. 2).

Patients with LPR had significantly lower risk of non-fatal MI and of serious vascular events (RR 0.59, 95% CI 0.38–0.91, $p < 0.05$ and RR 0.50, 95% CI 0.30–0.84, $p < 0.01$, respectively; Fig. 3). The risk for ST was 45% lower in the case of LPR, however, this difference did not reach the level of statistical significance (RR 0.55, 95% CI 0.27–1.11, $p = 0.10$; Fig. 3). Even though the mortality of LPR patients was numerically higher the difference between the two groups remained insignificant (RR 1.57, 95% CI 0.69–3.57, $p = 0.28$; Fig. 3). No significant difference was found regarding repeated revascularization (RR 0.96, 95% CI 0.57–1.60, $p = 0.84$; Fig. 3). Body mass index was significantly lower in the LPR group (SMD –0.18, 95% CI –0.32 to –0.05, $p < 0.01$; **Suppl. Fig. S1**).

Heterogeneity and subgroup analyses

The rate of LPR demonstrated a mean prevalence of 27% (95% CI for mean 20–35%, range 4.5–82%). Overall heterogeneity concerning major and minor bleeding events was considerable ($I^2 = 80\%$, $p < 0.01$). To find possible determinants of the observed heterogeneity, the prevalence of LPR and bleeding events was analyzed according to the following grouping factors: type of platelet function device, definition of bleeding events and amount of clopidogrel loading dose (LD).

The analysis confirmed that all the selected ADP-specific assays were able to predict the occurrence of bleeding events and the higher risk of patients with LPR was consistent regardless of the clinical presentation. Noticeably, considerable heterogeneity was observed in the results between studies using VASP-P and Verify Now assays; however, the Multiplate assay showed more homogenous findings (**Suppl. Fig. S2**). Subgroup analysis was also performed to assess the potential influence of different

clopidogrel LD regimes. Despite the different types of clopidogrel loading dose, heterogeneity remained high (**Suppl. Fig. S2).**

When bleeding events were divided into major and minor events separately the heterogeneity was reduced considerably for major bleeding (I^2 = 34%) while heterogeneity remained high for minor bleeding (I^2 = 82%; **Suppl. Fig. S3**).

Publication bias

Based on visual estimation of the funnel plot for bleeding events, no major asymmetry suggestive for publication bias was found. Furthermore, Egger's regression test confirms no small-study effect (**Suppl. Fig. S4**). Analysis of bias showed high quality of the source information with low probability of possible bias (**Suppl. Fig. S4**).

Discussion

The key finding of this meta-analysis is that patients with LPR after PCI are at a higher risk of bleeding. LPR detected by an ADP-specific laboratory assay is also associated with a lower risk of non-fatal MI. The composite endpoint of serious vascular events demonstrated lower risk with LPR. All-cause mortality did not differ significantly between LPR and non-LPR patient groups. Importantly, despite the differences in the methodology, patient selection and cut-off definition among studies, the increased risk of bleeding was homogenously reflected.

To date, this is the first meta-analysis of studies testing the role of LPR on bleeding and ischemic events in patients who underwent PCI.

In the first study reporting on the impact of enhanced response to clopidogrel treatment including 2,533 patients with coronary artery disease undergoing planned PCI, LPR was found to be associated with a two-fold higher risk for in-hospital major bleeding events [7]. Further reports suggested that LPR is a marker for a higher risk of bleeding events also among prasugrel-treated patients [25, 26].

Some recent studies, however, do not necessarily support that optimal PR does denote the same range in every patient population. In the TRILOGY ACS trial involving ACS patients without PCI, the relationship between LPR and risks of major bleeding was missing. Among medically managed non-ST-segment elevation ACS patients receiving prolonged dual antiplatelet therapy, platelet reactivity unit (PRU) values were not

significantly associated with the long-term risk of major bleeding events, suggesting that LPR does not independently predict serious bleeding risk [37].

Aimed at assessing the potential influence of different clopidogrel LD regimes, a subgroup analysis was performed. The results showed no association between different LDs of clopidogrel and rate of bleeding events. These findings are in line with a recent meta-analysis that compared the use of different LDs of clopidogrel and found that these are not associated with an increased risk for major bleeding within 30 days. However, it also suggested that the administration of 600 mg LD of clopidogrel is associated with a lower risk of MACE [38]. This observation is further supported by a retrospective study of patients with stable coronary artery disease which shows no difference between different LD groups in terms of major bleeding and hemoglobin drop post PCI (39).

When interpreting data from platelet function studies, the complex mechanisms of bleeding should be considered. Besides the potential impact of platelet inhibition, several clinical factors also influence the risk of these events. Residual PR, as an independent risk factor also has several associations with patient characteristics and these may also influence the expressed risk. HPR is more frequently encountered in obese and diabetics, while LPR may more likely arise in patients with advanced age and lower body weight [40, 41]. A significant association of LPR was revealed with lower body mass index in the current analysis. These characteristics may also impact the prognosis and when analyzed in multivariate models, the magnitude of risk, as in cases of ischemic risk with HPR, this risk is considerably reduced [42].

Importantly, periprocedural bleeding risk is substantially influenced by the access site selection, being significantly higher with transfemoral interventions. Bleeding avoidance strategies like routine use of the transradial approach may interfere with this risk by reducing bleeding and improving outcomes among high-risk ACS patient [43]. In the present analysis, the rate of transradial approach reached 59% (reported in 8 studies including 8,667 [45%] patients). However, since this data was not presented in a considerable proportion of studies this impedes the further analysis of potential impact of access site selection.

The findings herein, are partly in line with the results of a previous meta-analysis published in 2015 including 17 trials with a total of 20,839 patients validating standardized cut-off points for platelet function testing. In that study thienopyridine-treated patients with

HPR were associated with 2.73-fold higher risk for ST ($p < 0.00001$) and a 1.5-fold higher risk for mortality ($p < 0.05$) compared with those with optimal PR following PCI, meanwhile patients with LPR were associated with a 2-fold increased risk for major bleeding complications without any further reduction in the risk of ST [38]. In the present study, there was no significant difference between LPR and non-LPR groups in case of mortality, ST or repeated revascularization. However, the risk of serious vascular events resulted in a significant difference favoring the LPR group. Regarding risk of non-fatal MI, the event rate was significantly lower in the LPR group.

However, there are some limitations that may impact the interpretation of the current results. Observational studies were included that are usually unbalanced regarding baseline clinical characteristics of the patients. These studies could reflect the real-world practice better, meanwhile due to a lack of monitoring drug compliance, underreporting negative results and incomplete follow-up, their interpretation may be more difficult and might carry ascertainment biases. To balance possible confounding factors, data were pooled with logarithmic transformation according to the random-effect model via generic inverse weighting with the intent of methodical compensation of these factors.

It should be mentioned that the patients were not treated uniformly regarding the LDs of clopidogrel and that platelet function assessments were performed at different time points after PCI with different devices and cut-offs for LPR that may have contributed to heterogeneity. There are multiple tests in the field with a real-gold standard evidently missing. Considering the plethora of available platelet function tests, the aim to restrict the analyses to those that implement a method based on ADP dependent in vitro platelet activation was used in order to best assess the efficacy of ADP receptor dependent activation pathway. From this perspective, acceptable methodologies were not restricted based on the final readout of the method. The use of different P2Y12 inhibitors may also have influenced residual platelet reactivity. Due to a lack of patient-level data, subgroup analyses were not done to identify drug related efficacy. It is also important to note that different definitions of bleeding may have contributed to heterogeneity. The aim to collect data according to the two most widely used and standardized definitions, the TIMI bleeding and BARC criteria were used.

Conclusions

In conclusion, this meta-analysis supports that LPR is associated with important clinical outcomes of patients who underwent coronary stent implantation. The possible benefit of this marker in risk stratification or improvement of risk prediction, if combined with other factors in prediction models remains to be established by further studies.

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Conflict of interest: Dr. András Komócsi reports personal fees from Bayer Pharma AG, Pfizer, Krka, d. d., Merck & Co., and Servier, outside of the submitted work. The other authors report no conflicts of interest.

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Table 1 Detailed characteristics of studies included in the meta-analysis.

First author	Kabbani [20]	Patti [21]	Sibbing [7]	Tsukahara [22]	Huczek [23]	Patti [24]	Bonello [25]	Cuisset [26]	Mangiacapra [27]	Cuisset [13]
Publication year	2003	2008	2010	2010	2011	2011	2012	2012	2012	2013
Acronym	–	ARMYDA-PRO	ISAR	–	–	ARMYDA-BLEEDS	–	–	ARMYDA-PROVE	POBA
Design	P, O, single center	P, O, single center	P, O, single center	R, O, single center	P, O, single center	P, O, single center	P, O multicenter	P, O, single center	P, O, multicenter	P, O, single center
Clinical setting	SCAD	ACS, DES	CAD	DES, ACS	ACS	SA, NSTEMI, MI	ACS	ACS	SA	NSTEMI, STEMI
Number of patients	112	160	2533	184	374	310	301	107	732	1542
Platelet function test	Flow cytometry	VerifyNow	MEA	WBA-neo	VerifyNow	VerifyNow	VASP	VASP	VerifyNow	VASP
Selected cut-off for LPR	pGP IIb/IIIa act ≤ 24.9%	lowest quartile	188 AU × min	PATI > 28 µmol/L	PRU ≤ 150	Lowest quartile	PRI < 16%	PRI < 20%	PRU ≤ 178	PRI ≤ 10%
LPR, n (%)	56 (50)	40 (25)	975 (38.5)	46 (25)	124 (33)	77 (24.8)	84 (27.9)	23 (21.5)	248 (33.9)	69 (4.5)
Clopidogrel (LD/MD, mg)	300/75	600/75	600/75	300/75	600/75	600/75	–	600/75	600/75	600/75, 600/150, 60 LD
Prasugrel (LD/MD, mg)	–	–	–	–	–	–	60 LD	10 MD	–	10 MD
Definition of bleeding	NR	BARC	TIMI	BARC	TIMI	BARC	TIMI	BARC	TIMI	BARC
End point	MI, UREV, RREV	MACE, MI, TVR	Bleeding	ST, bleeding	Bleeding, D, MI	Major bleeding	ST, bleeding	ST, MI, TVR, bleeding	D, MI, TVR, bleeding	Bleeding, ST
Follow-up, months	12	1	1	16	1	1	12	1	1	6
Age (mean ± SD)	62.5	66 ± 9	67.5 ± 10.5	68 ± 9	66.6 ± 11.3	66.5	58.1	60.5 ± 10	66 ± 10	64 ± 12.5
Female, n (%)	47 (41.9)	31 (19)	599 (23.6)	52 (28.3)	144 (38.5)	67 (21.6)	34 (11.3)	16 (14.9)	196 (26.8)	70 (4.5)
Diabetes mellitus, n (%)	29 (25.9)	55 (34)	725 (28.6)	88 (47.8)	74 (19.8)	115 (37)	70 (23.3)	107 (100)	216 (29.5)	462 (30.0)
Smoking, n (%)	NR	NR	334 (13.2)	77 (42)	180 (48.1)	NR	154 (51.2)	40 (37.4)	145 (19.8)	NR
Hypertension, n (%)	NR	NR	2295 (90.6)	140 (76.0)	251 (67.1)	NR	122 (40.5)	63 (58.9)	570 (77.8)	886 (57.4)
DES, n (%)	NR	41 (26)	2533 (100)	184 (100)	16 (4.3)	95 (30.6)	NR	NR	201 (27.5)	894 (58.0)
PCI approach (%)	NR	NR	NR	Femoral: 18	Radial: 88, femoral: 12	Femoral: 100	NR	NR	Femoral: 96, radial: 4	Radial: 91, femoral: 9

Table 1 (cont.). Characteristics of the studies included in the meta-analysis.

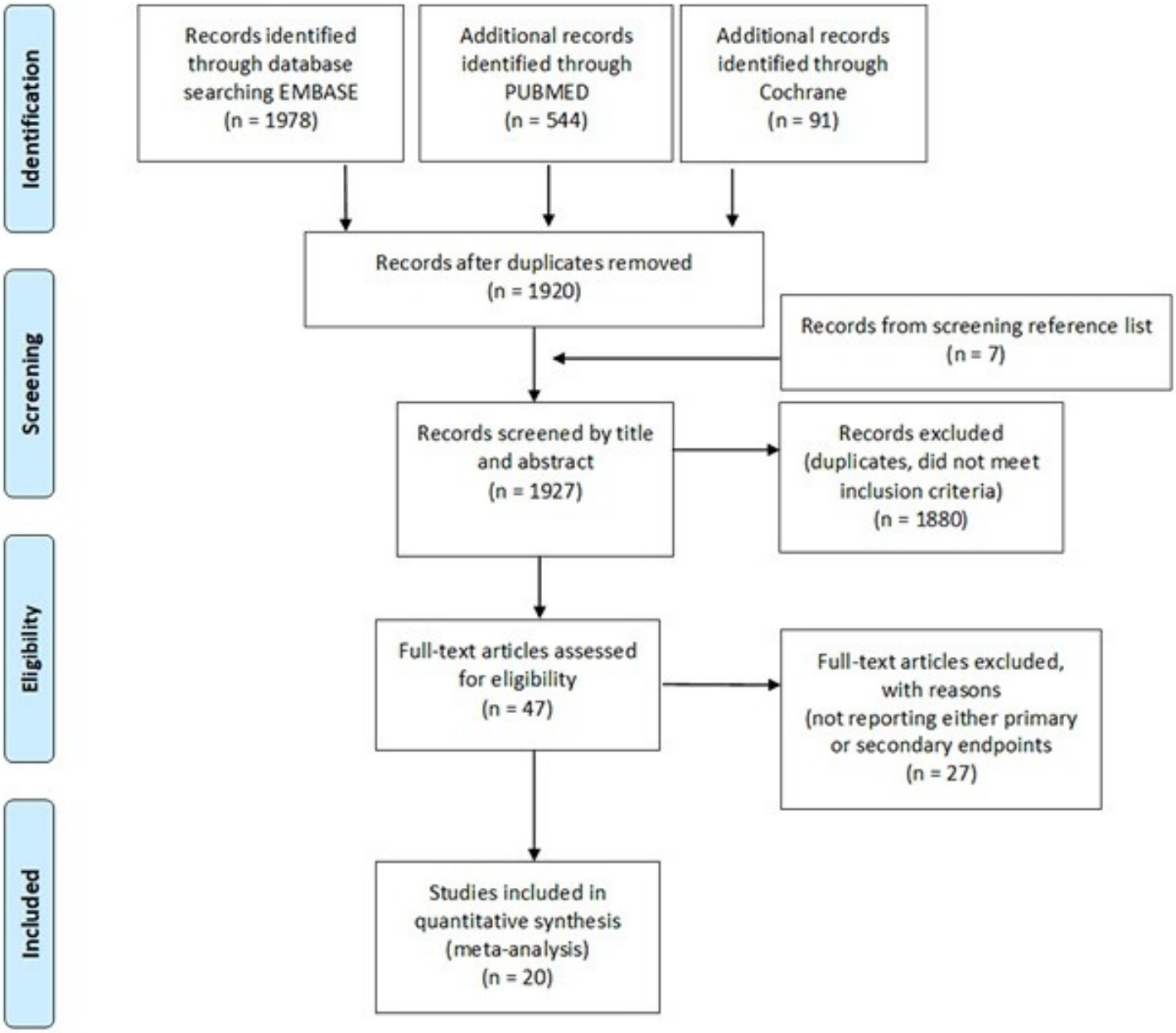
First author	Mangiacapra [28]	Alfredsson [29]	Li [30]	Jin [31]	Deharo [32]	Mangiacapra [14]	Lee [33]	Aradi [34]	Mshelbwala [35]	Nakamura [36]
Publication year	2014	2015	2016	2017	2017	2018	2019	2019	2020	2020
Acronym	–	APACHE	–	–	TOPIC	–	–	TROPICAL-ACS	–	PENDULUM
Design	P, O, multicenter	O, single center	R, O, single center	O, single center	RCT, single center	P, O, single center	R, O, single center	RCT, multicenter	R, O, single center	P, O, multicenter
Clinical setting	SCAD, NSTEMI	NSTEMI, STEMI	ACS	ACS	ACS	SCAD	SA, ACS	ACS	ACS	ACS, non-ACS
Number of patients	800	113	512	278	646	500	814	2527	252	6267
Platelet function test	VerifyNow	MEA	VerifyNow	LTA	VASP	VerifyNow	VerifyNow	MEA	VerifyNow	VerifyNow
Selected cut-off for LPR	PRU ≤ 178	AUC × min ≤ 468	PRU ≤ 85	Lowest quartile	PRI < 20%	PRU < 178	PRU < 85	ADP ≤ 18 U	PRU ≤ 208	PRU ≤ 85
LPR, n (%)	272 (34.0)	93 (82.3)	46 (8.9)	61 (21.94)	305 (47.2)	160 (32.0)	71 (8.7)	484 (19.2)	144 (57.1)	677 (10.8)
Clopidogrel (LD/MD, mg)	600/75	600/75	300/75 600/75	300/75	75 MD	600/75	600/75	600/75	600/75	300/75
Prasugrel (LD/MD, mg)	–	–	–	–	60/10	–	–	60/10	NR	20/3.75
Ticagrelor (LD/MD, mg)	–	–	–	–	180/90	-	–	–	NR	–
Definition of bleeding	TIMI	TIMI	BARC	TIMI	BARC	TIMI	BARC	BARC	BARC	BARC
Endpoint	Bleeding, ST, TVR, D	D, MI, stroke, bleeding	Bleeding	Bleeding, entry-site complication	Bleeding, stroke, D, UREV	MI, ST, RREV, bleeding	All-cause death	D, MI, TVR, bleeding	MACE	MACCE, bleeding
Follow-up, months	1	6	12	6	11.9	60	48	12	12	12
Age (mean ± SD)	67 ± 10	66 ± 12.5	65.6 ± 7.75	61.35 ± 9.79	60.1 ± 10.2	67 ± 9.8	62.3 ± 11.94	58.7 ± 10.47	61.1 ± 10.5	70±10.7
Female, n (%)	210 (26.3)	33 (29.2)	93 (18.2)	57 (20.5)	114 (17.6)	109 (21.8)	257 (31.6)	535 (21.2)	101 (40.1)	1358 (21.7)
Diabetes mellitus, n (%)	236 (29.5)	14 (12.4)	113 (22.1)	70 (25.2)	177 (27.4)	156 (31.2)	256 (31.4)	513 (20.3)	121 (48.0)	2767 (44.2)
Smoking, n (%)	NR	30 (26.5)	NR	121 (43.5)	286 (44.3)	100 (20.0)	468 (57.5)	NR	177 (70.2)	1346 (21.5)
Hypertension, n (%)	NR	41 (36.3)	NR	158 (56.8)	313 (48.5)	407 (81.4)	509 (62.5)	NR	217 (86.1)	4892 (78.0)
DES, n (%)	231 (28.9)	45 (39.8)	NR	NR	585 (90.6)	338 (67.6)	788 (96.8)	NR	234 (93.0)	6267 (100)
PCI approach (%)	femoral: (100)	NR	NR	Femoral: 12.23	Femoral: 4, radial: 96	Femoral: 96, radial: 4	NR	Brachial: 1, femoral: 40, radial: 59	NR	Femoral: 26.0, brachial: 4.3, radial: 72.1

ACS — acute coronary syndrome; ADP — adenosine diphosphate; AUC — area under the curve; BARC — Bleeding Academic Research Consortium Criteria; D — death; DES — drug-eluting stent; GP — glycoprotein; LD — loading dose; LPR —low platelet reactivity; LTA — light transmission aggregometry; MD — maintenance dose; MEA — multiplate electrode aggregometry; MACE — major adverse cardiac events; MACCE — major adverse cardiac and cerebrovascular events; MI — myocardial infarction; NR — not reported; NSTEMI — non ST segment elevation myocardial infarction; O — observational study; P — prospective; PCI — percutaneous coronary intervention; PRI — VASP-P-derived platelet reactivity index; PRU — platelet reaction units; R — retrospective; RCT — randomized controlled trial; RREV — repeated revascularization; SA — stable angina; SCAD — stable coronary artery disease; SD — standard deviation; ST — stent thrombosis; STEMI — ST segment elevation myocardial infarction; TIMI — Thrombolysis In Myocardial Infarction; TVR — target vessel revascularization; UREV — urgent revascularization; VASP — vasodilator-stimulated phosphoprotein

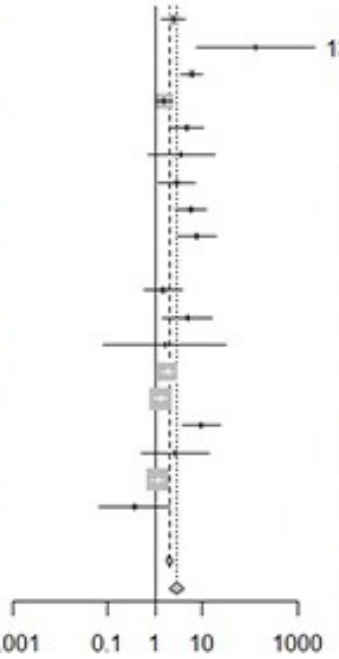
Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Figure 2. Principal pooled analysis. Forest plots of major and minor bleeding risk in studies following percutaneous coronary intervention with low platelet reactivity (LPR) versus without LPR. The grey rectangles are proportional with the study weight. The diamond represents the cumulative risk ratio (RR) and confidence interval (CI).

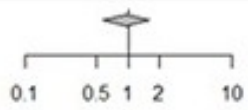
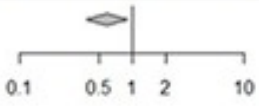
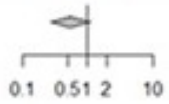
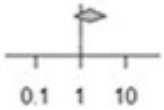
Figure 3. Summary of the outcomes of the secondary endpoints. The diamond represents the cumulative risk ratio (RR) and confidence interval (CI) of all patient groups. *Mean difference (95% CI); LPR — low platelet reactivity; MI — myocardial infarction.


Identification
Screening
Eligibility
Included
Records identified through database searching EMBASE (n = 1978)
Additional records identified through PUBMED (n = 544)
Additional records identified through Cochrane (n = 91)
Records after duplicates removed (n = 1920)
Records from screening reference list (n = 7)
Records screened by title and abstract (n = 1927)
Records excluded (duplicates, did not meet inclusion criteria) (n = 1880)
Full-text articles assessed for eligibility (n = 47)
Full-text articles excluded, with reasons (not reporting either primary or secondary endpoints (n = 27)
Studies included in quantitative synthesis (meta-analysis) (n = 20)

Study	Experimental Events	Experimental Total	Control Events	Control Total	OR	95%-CI	Weight (fixed)	Weight (random)
Mangiacapra 2018	25	160	24	340	2.44	[1.34; 4.42]	4.6%	7.2%
Cuisset 2012	10	23	0	84	131.44	[7.27; 2376.06]	0.0%	1.3%
Cuisset 2013	23	69	116	1473	5.85	[3.42; 9.99]	2.4%	7.5%
Deharo 2017	60	305	46	341	1.57	[1.03; 2.39]	12.3%	8.0%
Huczek 2011	18	124	9	250	4.55	[1.98; 10.45]	1.8%	6.1%
Lee 2019	2	71	6	743	3.56	[0.71; 17.98]	0.4%	3.2%
Li 2016	7	46	28	466	2.81	[1.15; 6.84]	1.5%	5.8%
Mangiacapra 2012	26	248	10	484	5.55	[2.63; 11.71]	2.1%	6.5%
Mangiacapra 2014	22	272	6	528	7.66	[3.07; 19.12]	1.3%	5.7%
Patti 2008	0	40	0	120			0.0%	0.0%
Patti 2011	7	77	15	233	1.45	[0.57; 3.71]	2.4%	5.6%
Tsukahara 2010	7	46	5	138	4.77	[1.44; 15.88]	0.7%	4.5%
Alfredsson 2015	3	93	0	20	1.59	[0.08; 31.90]	0.3%	1.3%
Aradi 2019	61	484	149	2043	1.83	[1.34; 2.51]	17.5%	8.4%
Sibbing 2010	76	975	95	1558	1.30	[0.95; 1.78]	23.7%	8.4%
Jin 2017	16	61	8	217	9.29	[3.75; 23.02]	0.9%	5.7%
Bonello 2012	3	84	3	217	2.64	[0.52; 13.36]	0.6%	3.2%
Nakamura 2020	50	677	346	5229	1.13	[0.83; 1.53]	25.8%	8.4%
Mshelbwala 2020	2	144	4	108	0.37	[0.07; 2.04]	1.6%	3.0%
Fixed effect model		**3999**		**14592**	**1.96**	**[1.72; 2.24]**	**100.0%**	--
Random effects model					**2.80**	**[1.95; 4.02]**	--	**100.0%**



Heterogeneity: $I^2 = 80\%$, $\tau^2 = 0.3799$, $p < 0.01$
Test for overall effect (fixed effect): $z = 9.98$ ($p < 0.01$)
Test for overall effect (random effects): $z = 5.57$ ($p < 0.01$)

Favours LPR Favours non-LPR		Risk ratio [CI 95%]	Test for overall effect	Heterogenity
	Risk of repeat revascularization	0.96 [0.57, 1.60]	Z= -0.17 (p=0.84)	χ^2=0.0293 (p=0.14), I^2= 9%
	Risk of non fatal MI	0.59 [0.38, 0.91]	Z= -2.36 (p=0.02)	χ^2=0 (p=0.55), I^2= 0%
	Risk of stent thrombosis	0.55 [0.27, 1.11]	Z= -1.66 (p=0.10)	χ^2=0 (p=0.99), I^2= 0%
	Risk of serious vascular events	0.50 [0.30, 0.84]	Z= -2.63 (p<0.01)	χ^2=0.2871 (p<0.01), I^2= 68%
	All-cause mortality	1.57 [0.69, 3.57]	Z= 1.08 (p=0.28)	χ^2=0.7265 (p=0.11), I^2= 71%