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Benefits of laboratory personalized antiplatelet therapy in patients undergoing percutaneous coronary intervention: A meta-analysis of randomized controlled trials

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Abstract

Background: *The preventive effects of laboratory personalized antiplatelet therapy (PAPT) strategy including genetic detection and platelet function testing (PFT) on major adverse cardiac events (MACEs) and bleeding events in coronary artery disease (CAD) patients undergoing stenting has been extensively studied. Despite that, no clear conclusion can be drawn. In this study, a meta-analysis was performed to explore a more precise estimation of the benefits of laboratory PAPT.*

Methods: *Randomized controlled trials were identified by the use of search databases such as PubMed, Embase, and Cochrane Controlled Trials Register up to May 2017, and the estimates were pooled.*

Results: *Fourteen studies including 9497 patients met the inclusion criteria. The laboratory PAPT reduced MACEs risk (risk ratio [RR] 0.58, 95% confidence interval [CI] 0.42–0.80, p = 0.001), stent thrombosis (RR 0.60, 95% CI 0.41–0.87, p = 0.008) and myocardial infarctions (RR 0.43, 95% CI 0.21–0.88, p = 0.02) compared to the non-PAPT group. No statistically significant difference was observed between the two groups regarding cardiovascular death (RR 0.77, 95% CI 0.51–1.16, p = 0.21), bleeding events (RR 0.96, 95% CI 0.81–1.13, p = 0.59) and ischemic stroke (RR 0.81; 95% CI 0.39–1.66, p = 0.57). The preventive effect on MACEs was more significant in patients with high on-treatment platelet reactivity (RR 0.46; 95% CI 0.27–0.80, p = 0.006).*

Conclusions: *Coronary artery disease patients after stenting could obtain benefits from laboratory PAPT.*
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Key words: personalized antiplatelet therapy, percutaneous coronary intervention, platelet function testing, genetic detection, meta-analysis

Introduction

Dual antiplatelet therapy consists of P2Y12 receptor antagonist such as clopidogrel, prasugrel, or ticagrelor, in combination with aspirin. This therapy represents the main medical treatment in patients with acute coronary syndrome (ACS) after percutaneous coronary intervention (PCI), and in secondary prevention of atherothrombotic events [1, 2].

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Among them, clopidogrel used to be the most broadly prescribed P2Y12 receptor inhibitor with undisputable benefits especially in combination with aspirin. However, since 2003, studies suggested that the pharmacodynamic effect of clopidogrel considerably varies among individuals, implying that it may lead to the occurrence of ischemic or bleeding events [3, 4]. These events were once known as clopidogrel resistance, or clopidogrel non-responsiveness, and they are now identified as high on-treatment platelet reactivity (HTPR). Up to 25–50% of patients treated with clopidogrel show inadequate pharmacological response and a consequent inadequate protection from major adverse cardiac events (MACEs) [5, 6]. The meta-analysis performed by Sofi et al. [7] revealed a significant association between residual platelet reactivity under clopidogrel treatment and recurrent cardiovascular events. Thus, in order to improve the antiplatelet effect of clopidogrel, personalized antiplatelet therapy (PAPT) is increasingly more important.

In clinical practice, some laboratory tests include platelet function test (PFT) and genetic detection andare available to fulfill PAPT in a relatively objective manner. Nevertheless, the routine measurement of platelet reactivity has not been widely implemented, and lack of consensus concerning optimal method and the best cut-off value associated with clinical risk has hindered the consideration of platelet function testing in clinical guidelines. According to a systematic review performed by Winter et al. [8], although PAPT monitored by PFT seems to be feasible, the contradictory results of smaller registry studies and larger randomized trials with regards to outcome remains uncertain. Another approach is the genotype test. As a pro-drug, clopidogrel requires enteric and hepatic transformation by the cytochrome P450 (CYP) system to exert its antiplatelet effect. CYP2C19 enzyme seems to have the most prominent role in the production of clopidogrel active metabolite, while CYP2B6, CYP1A2, CYP3A/A5, and CYP2C9 show lesser involvement [9]. According to the systematic review performed by Osnabrugge et al. [10], at least 11 meta-analyses on the association between CYP2C19 loss-of-function alleles and clinical efficacy of clopidogrel were identified until 2014. However, the conclusions of these meta-analyses were not consistent.

Recently, many studies evaluating the risk of MACEs and bleeding events were performed among patients receiving clopidogrel carrying different CYP2C19 genotypes or presenting different HTPR status as measured by PFT, including several randomized controlled trials (RCTs), such as GRAVITAS [11]. However, the conclusions of these studies are not consistent. In this study, a meta-analysis was performed to further evaluate the benefits of PAPT in coronary artery disease (CAD) patients. Compared with previous studies, our meta-analysis included all PAPT available, not only PFTs but also genetic detection as intervention.

Methods

Trial selection and search strategy

All published RCTs enrolling CAD patients treated with PAPT according to genetic detection or PFT for at least 1 month were selected. Controlled intervention was the standard antiplatelet therapy not guided by genetic detection or PFT.

The search involved various computerized databases: PubMed (up to 31 May 2017), Embase (up to 31 May 2017), and Cochrane Controlled Trials Register (up to May 2017), searching the following items: genotype OR (genetic testing) OR (genetic polymorphism) OR (platelet function testing) OR (platelet reactivity) OR (VerifyNow) OR plateletworks OR (light transmission aggregometry) OR (multiple electrode aggregometry) OR (Platelet Function Analyzer) OR (vasodilator stimulated phosphoprotein) OR (thrombelastography) OR (Cone and Platelet Analyzer)) AND (clopidogrel) OR (cangrelor) OR (elinogrel) OR (prasugrel) OR (ticagrelor), with the following filters: "Clinical Trial, Humans, English" in PubMed and "Controlled Clinical Trial, Humans, English" in Embase. In addition, the references of the collected studies were checked for additional analysis.

Trials belonging to the following categories were excluded: (i) non-RCTs; (ii) subjects not treated with P2Y12 receptor antagonist; (iii) treatment duration < 1 month; and (iv) trials with no mention of MACEs or bleeding events prevention. Two investigators (Y. Zhang and P. Zhang) independently selected the studies according to the following steps: (i) titles and abstracts examination to remove irrelevant reports; (ii) full text collection of potentially relevant reports; (iii) full-text reports examination for compliance of studies with eligibility criteria; and (iv) final decisions on study inclusion and data collection. Any discrepancies were resolved by consensus. If a consensus could not be reached, the senior author (Y.L. Hou) made the final decision for trial eligibility and data extraction.

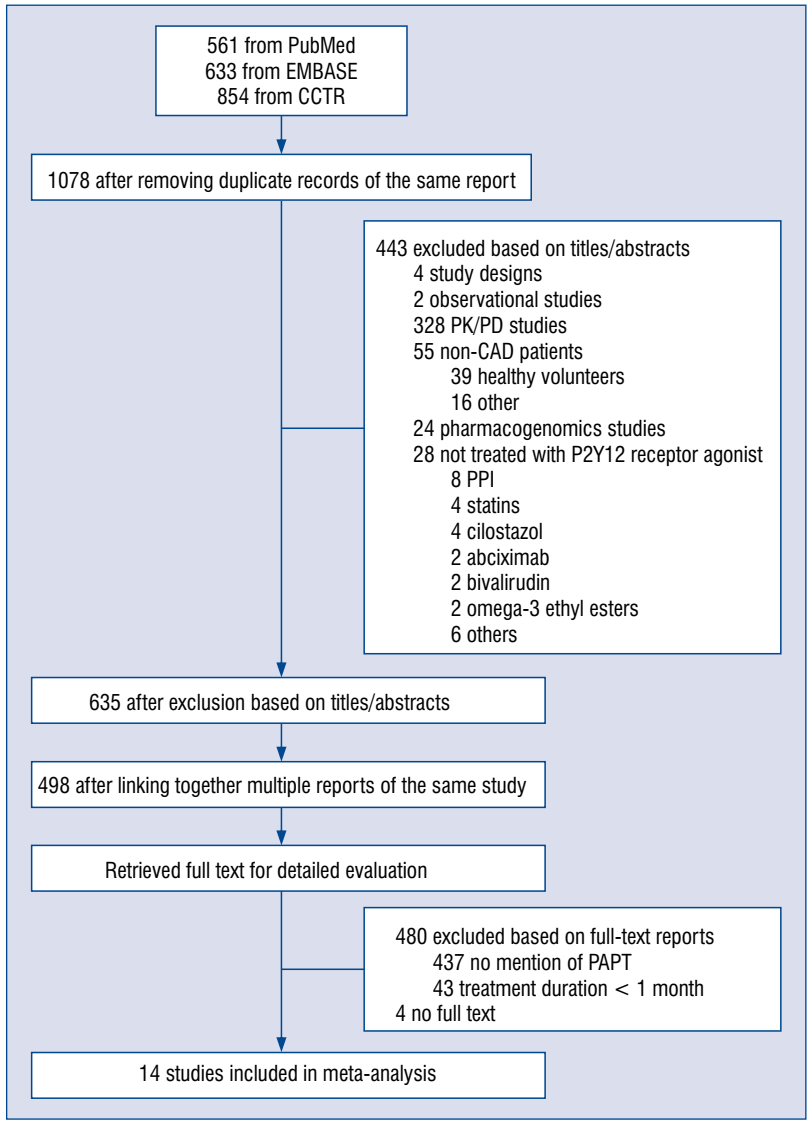

Figure 1. Flow diagram of the trial selection process; CAD — coronary artery disease; CCTR — Cochrane Controlled Trials Register; PK — pharmacokinetics; PD — pharmacodynamics; PPI — proton-pump inhibitor; PAPT — personalized antiplatelet therapy.

Statistical analysis

Results of the outcome were expressed as risk ratio (RR) with 95% confidence interval (CI) for each study. A pooled effect was calculated using a random-effects model. Heterogeneity was assessed using Q and I^2 statistic. Subgroup analysis and meta-regression were performed to localize the source of heterogeneity. Sensitivity analysis was performed through the trim and fill method. Publication bias was evaluated using funnel plot and Egger's regression method. All statistical analyses were performed using Review Manager 5.3 and STATA 12.0. Statistical significance was defined as $p < 0.05$ (2-sided).

Results

A total number of 1055 relevant articles were retrieved from PubMed (561), Embase (633), and Cochrane Controlled Trials Register (854). Among them, 14 studies [11–24] reporting the differences in terms of MACEs and bleeding events between 9497 patients with and without the PAPT were considered eligible for our meta-analysis (4878 randomized to PAPT and 4619 to control) (Fig. 1). The baseline characteristics of the patients and trials key features are shown in Table 1. All the enrolled patients suffered from CAD and underwent stenting. The antiplatelet strategy in PAPT

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

Author (study)	Year	Health condition	Test			Intervention	Number of patients		Follow-up	MACE definition	Bleeding defination
			Method	HTPR cut-off	Time		Control	Inter-vention			
Bonello L	2008	Silent ischemia (20.4%), stable angina (33.3%), NSTEMI (46.3%), and PRI > 50%	VASP	> 50% PRI	12 h after each additional boluses of CLO (up to 3 times) until PRI < 50%	Additional boluses of CLO	84	78	1 month	CVD, angiographically confirmed ST, recurrent ACS	TIMI
Bonello L	2009	Silent ischemia (19.8%), stable angina (28.7%), ACS (51.5%), and PRI > 50%	VASP	> 50% PRI	12 h after each additional boluses of CLO (up to 3 times) until PRI < 50%	Additional boluses of CLO	215	214	1 month	CVD, recurrent ACS, and urgent revascularization by coronary angioplasty or bypass surgery	TIMI
Wang XD	2011	One month after PCI; refractory angina (50.0%), silent ischemia (30.1%), NSTEACS (19.9%), and PRI > 50%	VASP	> 50% PRI	Month 1, 3, 6, 9 and 12	CLO dose adjustment	156	150	1 year	CVD, angiographically confirmed ST, recurrent ACS	TIMI
Price MJ (GRAVITAS)	2011	Stable CAD (60.2%), NSTEACS (39.8%), with HTPR	VerifyNow P2Y12 assay	≥ 230 PRU	Day 30 and month 6	CLO dose adjustment	1105	1109	6 months	CVD, nonfatal MI, or ST	GUSTO
Collet JP (ARCTIC)	2012	CAD (27% ACS)	VerifyNow P2Y12 assay	≥ 550 PRU for ASP; ≥ 235 PRU for CLO	Day 1 (before PCI), week 2–4	Administration of intravenous ASP, glycoprotein IIb/IIIa inhibitors, CLO dose adjustment or switch to PRA	1227	1213	12 months	Death from any cause, MI, ST, stroke or TIA, or urgent revascularization	According to the defination of STEEPLE study
Tang FK*	2012	CAD with ASP and CLO resistance	TEG	Inhibition rates of ASP > 50%, inhibition rate of CLO > 50%	Week 1, month 1, 3, 6, 9 and 12	ASP and CLO dose adjustment	30	30	12 months	CVD, angiographically confirmed ST, recurrent UA and MI	Intracranial and gastrointestinal hemorrhage, secondary anemia, and stroke
Jason D Roberts	2012	NSTEACS (37.4%) or stable CAD	CYP2C19*2 gene test	–	At the time of randomization	CLO switched to PRA	96	91	30 days	CVD, non-fatal MI, readmission to hospital, and ST	TIMI
Hazarbasanov D	2012	Stable CAD (43.2%), NSTEACS (32.8%), STEMI (24.0%)	MEA	> 46 U	24 h after CLO loading in all patients, 24 h after re-loading and at day 30 in HTPR patients	Re-loading and doubled maintenance dose of CLO	95	97	6 months	Cardiac death, MI, definite or probable ST or ischemic stroke	TIMI

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

Author (study)	Year	Health condition	Test			Intervention	Number of patients		Follow-up	MACE definition	Bleeding defination
			Method	HTPR cut-off	Time		Control	Inter-vention			
Xie X	2013	ACS	CYP2C19 genotype	–	At the time of randomization	CLO dose adjustment or addition of CIL	299	301	180 days	Death from any cause, MI, stroke and ischemiadriven TVR	BARC
Samardzic J	2014	ACS with HTPR	MEA	> 46 U	Day 1 (after PCI), 2, 3, 7, 30 and month 2, 3, 6, 9 and 12	CLO dose adjustment	44	43	12 months	Death, non-fatal MI, TVR and ischemic stroke	BARC
Siller-Matula M (MADONNA)	2015	Elective PCI (63.2%), acute PCI due to MI (36.8%)	MEA	≥ 50U	The day after PCI, and the the day after each re-loading with CLO or switch to PRA to ensure that HTPR was overcome	Re-loading with CLO or switch to PRA	395	403	12 months	Definite or probable ST, MI and death	TIMI
Zhu HC	2015	ACS	LTA	< 10% IPA	At admission and 24 h after CLO loading, and 3 days after administration of CIL	Additional 6-month CIL treatment	151	154	1 year	Cardiac death, MI, ischemic driven TVR or stroke	TIMI
Li Y	2015	ACS with HTPR	LTA	No mention	24 to 48 h after CLO loading, and day 30	CLO dose adjustment or additional 6-month CIL treatment	280	560	1 year	All-cause death, non-fatal MI, symptom driven TVR, and stroke	TIMI
Cayla G (ANTARCTIC)	2016	ACS	VerifyNow P2Y12 assay	≥ 208 PRU	Day 14, 28	PRA dose adjustment or replaced with CLO	442	435	12 months	CVD, MI, stroke, definite ST	BARC

*According to thromboelastography results, 90 patients were divided into control group (n = 30, both inhibition rate of aspirin and clopidogrel > 50%) and resistance group (n = 60, both inhibition rate for aspirin and clopidogrel < 50%). Patients in the resistance group were randomly assigned and given a routine dose (100 mg aspirin plus 75 mg clopidogrel per day) and a loading dose (200 mg aspirin and 150 mg clopidogrel per day) of antiplatelet therapy.
ACS — acute coronary syndrome; ASP — aspirin; BARC — Bleeding Academic Research Consortium criteria; CAD — coronary artery disease; CIL — cilostazol; CLO — clopidogrel; CVD — cardiovascular death; GUSTO — Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries criteria; HTPR — high on-treatment platelet reactivity; IPA — inhibition of platelet aggregation; LTA — light transmission aggregometry; MACE — major adverse cardiac events; MEA — multiple electrode aggregometry; MI — myocardial infarction; NSTEACS — non-ST segment elevation acute coronary syndrome; NSTEMI — non-ST elevation myocardial infarction; PCI — percutaneous coronary interwention; PRA — prasugrel; PRI — platelet reactivity index; PRU — platelet reaction units; ST — stent thrombosis; STEEPLE — Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients, an International Randomized Evaluation (N Engl J Med. 2006; 355: 1006–1017); TEG — thromboelastography; TIA — transient ischemic attack; TIMI — Thrombolysis In Myocardial Infarction criteria; UA — unstable angina; TVR — target vessel revascularization; VASP — vasodilator stimulated phosphoprotein

groups was adjusted according to genotype or PFT. In addition, there were 4 abstracts from European Society of Cardiology Congress 2016 involving the benefits of PAPT in CAD patients, but they were not included because of the lack of full text (P1835, P4214, P5598, and P5601).

The studies showed a significantly increased risk of MACEs (RR 0.58, 95% CI 0.42–0.80, p = = 0.001), stent thrombosis (ST; RR 0.60, 95% CI 0.41–0.87, p = 0.008) and myocardial infarction (MI; RR 0.43, 95% CI 0.21–0.88, p = 0.02) in patients receiving PAPT compared to the standard therapy group. Furthermore, no statistically significant difference was observed between the above two groups in cardiovascular (CV) death (RR 0.77, 95% CI 0.51–1.16, p = 0.21), bleeding events (RR 0.96, 95% CI 0.81–1.13, p = 0.59) and ischemic stroke (RR 0.81; 95% CI 0.39–1.66, p = = 0.57). However, the heterogeneity was substantial in MACEs ($Chi^2 = 58.71$, $p < 0.00001$, $I^2 = 81\%$) and MI ($Chi^2 = 35.57$, $p < 0.0001$, $I^2 = 7\,8\%$) groups (Fig. 2).

In order to identify the heterogeneity source in MACEs group, meta-regression and subgroup analyses were performed. The results revealed that the benefits of receiving PAPT had no clear linear relation with the follow-up period (Coef. = 0.120, Std. Err. = 0.059, p = 0.068) (Fig. 3). However according to subgroup analysis, there was obvious difference among the benefits after 1, 6 and 12 months (among subgroups: $Chi^2 = 8.90$, $p = 0.01$, $I^2 = 77.5\%$), but the heterogeneity was not well located (1 month: $Chi^2 = 0.01$, $p = 0.92$, $I^2 = 0\%$; 6 months: $Chi^2 = 8.33$, $p = 0.02$, $I^2 = 76\%$; 12 months: $Chi^2 = 33.57$, $p < 0.00001$, $I^2 = 82\%$). Another subgroup analysis revealed that the benefits of PAPT was more significant in the HTPR subgroup (RR 0.46; 95% CI 0.27–0.80, p = 0.006), but not in the no mention subgroup (RR 0.70; 95% CI 0.48–1.00, p = 0.05). However, the heterogeneity was substantial in each subgroup (HTPR: $Chi^2 = 13.29$, $p = 0.02$, $I^2 = 62\%$; No mention: $Chi^2 = 29.29$, $p < 0.0001$, $I^2 = 83\%$; between subgroups: $Chi^2 = 1.48$, $p = 0.22$, $I^2 = 32.3\%$). Finally, based on PAPT strategy difference, the source of heterogeneity was located. Although the numbers of trials in each subgroup were small, the heterogeneities in each subgroup were not obvious (light transmission aggregometry [LTA]: $Chi^2 = 0.63$, $p = 0.43$, $I^2 = 0\%$; multiple electrode aggregometry [MEA]: $Chi^2 = 1.36$, $p = 0.51$, $I^2 = 0\%$; VerifyNow: $Chi^2 = 0.96$, $p = 0.62$, $I^2 = 0\%$; vasodilator stimulated phosphoprotein [VASP]: $Chi^2 = 7.04$, $p = 0.03$, $I^2 = 72\%$), and it was found that all methods could obtain obvious benefits except VerifyNow and VASP (LTA: RR 0.55, 95% CI 0.37–0.83, p = 0.004; MEA: RR 0.47, 95% CI 0.32–0.67, p < 0.0001; CYP2C19 gene test: RR 0.29, 95% CI 0.14–0.64, p = 0.002; VerifyNow: RR 1.08, 95% CI 0.98–1.19, p = 0.12; VASP: RR 0.15, 95% CI 0.02–1.00, p = 0.05) (Fig. 4).

Sensitivity analysis was performed through the Trim and Fill method, and no obvious difference was found after Trim and Fill processes, suggesting that the pooled estimates in each group were relatively robust (Table 2). Another post-hoc sensitivity analysis was performed by omitting studies on the basis of subgroup analysis. It seems that VerifyNow assay is outlier, so all outcomes were redone without studies using VerifyNow, wherein similar results were obtained (Table 3). According to the funnel plot (Fig. 5) and Egger's regression (Table 2), obvious publication biases were found in MACEs (Intercept: –2.726, 95% CI –3.657 to –1.796, p = 0.000), CV death (Intercept: –1.741, 95% CI –2.472 to –1.010, p = 0.000), MI (Intercept: –1.649, 95% CI –3.090 to –0.207, p = 0.030), and ST (Intercept: –1.582, 95% CI –2.801 to –0.362, p = 0.016) groups.

Discussion

In recent years, the precision of medicine has been increasingly attracting attentions, PFTs and pharmacogenomics have been rapidly developing and are becoming an important approach for PAPT in reducing the risk of MACEs occurrence after stenting, especially in patients with HTPR, exactly as the present meta-analysis has discovered. According to a recent RCT, both genotyping (CYP2C19) and PFT (VerifyNew p2Y12 assay) all resulted in an improved platelet inhibition [25].

Platelet function testing

At present, many PFT methods are available, while the cut-off values of clopidogrel low response are different due to different test methods. A study [26] published in JAMA in 2010 compared the relationship between different PFT methods and clinical outcomes in 1069 patients undergoing elective PCI and taking clopidogrel from 2005 to 2007. LTA, VerifyNow P2Y12, Plateletworks assays, IMPACT-R and platelet function analyzer (PFA-100) were used to test the platelet activity during treatment, with the application of receiver operating characteristic curve to analyze whether the cut-off has diagnostic value, as well as an outcome event such as death, non-fatal MI, ST, and

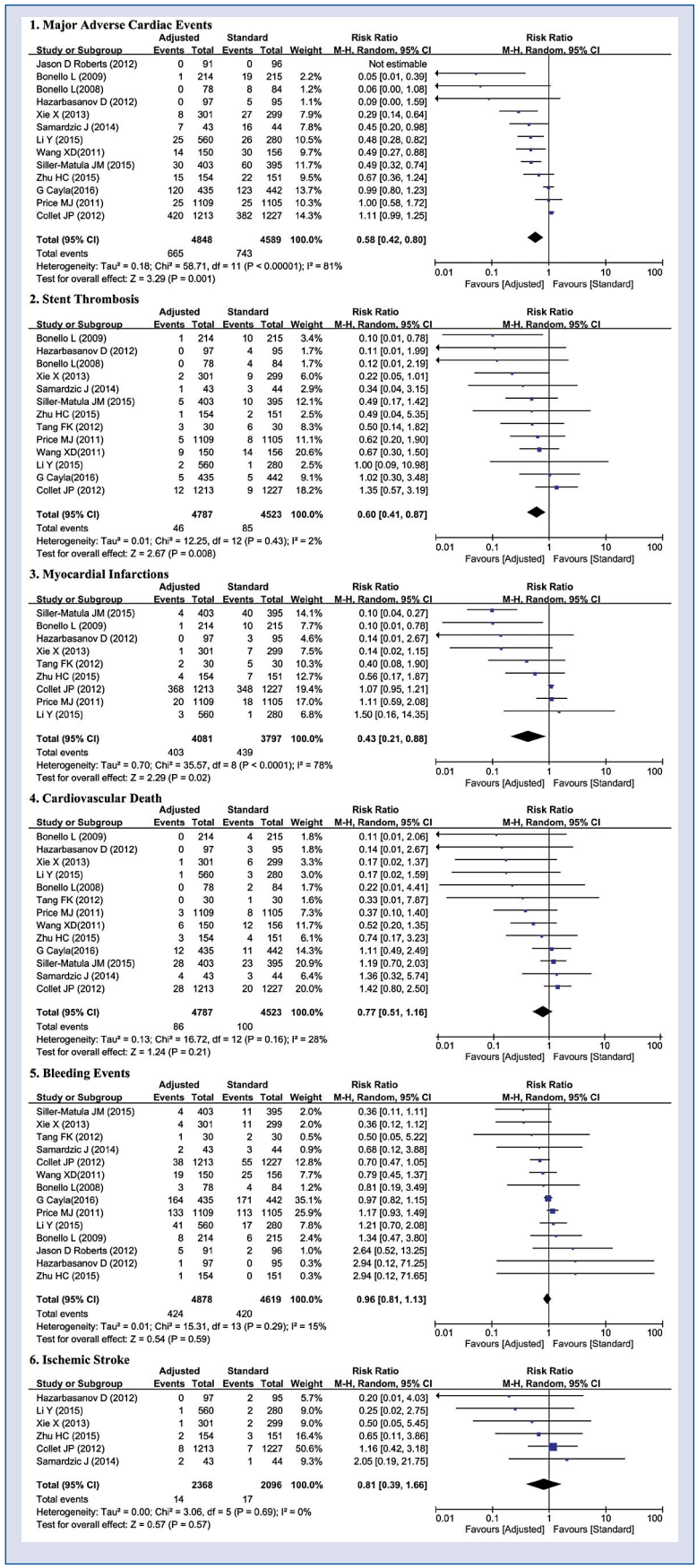

Figure 2. Forest plot comparing the effects of laboratory versus experiential personalized antiplatelet therapy; CI — confidence interval.

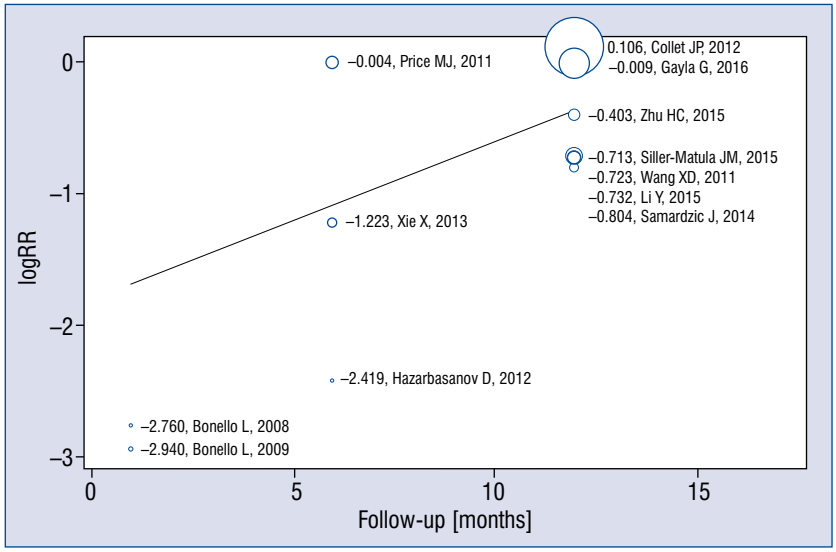

Figure 3. Meta-regression to estimate the relationship between the benefits of personalized antiplatelet therapy and follow-up period; Coef. = 0.120, Std. Err. = 0.059, p = 0.068.

ischemic stroke. After 1 year, the results showed that only LTA, VerifyNow, and Plateletworks were significantly associated with the primary end point. However, the predictive accuracy of these tests were only modest. None of the tests provided accurate prognostic information to identify low-risk patients at higher risk of bleeding following stent implantation.

The results of our meta-analysis revealed that the preventive effects of PAPT on MACEs were more evident during a short follow-up period, and the difference was statistically significant according to the subgroup analysis, specially between 1 month and 12 month subgroups (1 month: RR 0.06, 95% CI 0.01–0.29, p = 0.0006; 6 months: RR 0.44, 95% CI 0.14–1.42, p = 0.17; 12 months: RR 0.68, 95% CI 0.50–0.93, p = 0.01; heterogeneity among subgroups: Chi^2 = 8.90, p = 0.01). During antiplatelet therapy in patients after coronary stenting, the platelet function is constantly changing, suggesting that the PFT time window is potentially influencing PAPT benefits. During a short follow-up research, the proportion of this time window in follow-up period is higher, thus the benefits might be greater. However, this speculation needs more short follow-up periods or a wider PFT time window to verify.

The subgroup analysis based on PAPT strategy found that all methods could provide benefits except VerifyNow, although no statistical difference was found among all strategic results. Due to its mature detection method, VerifyNow results have high specificity and sensibility, thus the stated hypothesis was that the above non-significant results were related with the VerifyNow cut-off value. It is generally accepted that ≥ 230 U can be considered as HTPR in the VerifyNow method, but the cut-off value remains controversial. Perhaps a lower cut-off of 208 U is more suitable, as suggested in one meta-analysis [27] and ANTARCTIC study [24].

Genetic detection

Currently, several pharmacogenetic studies have found that gene loci plurality was related to cardiovascular events, which might predict the reactivity of antiplatelet medicine [28, 29]. Polymorphisms are present in many genes including P2Y12, GP IIb/IIIa, GP Ia/IIa, GP Ib/IX/V, CYP2C19, CYP2C9, CYP3A4, CYP3A5, COX-1, COX-2 and ABCB1 [29, 30]. However, at present CYP2C19 gene polymorphism is the only one related to clopidogrel antiplatelet effect [31, 32]. The loss-of-function gene (CYP2C19*2, *3) carriers show low reaction to clopidogrel [33], while carriers of gain-of-function gene (CYP2C19*17) tend to show higher hemorrhage risk [34].

Clopidogrel and prasugrel are all thienopyridine prodrugs, and all need CYP450 enzyme metabolism to translate into the activated product. Clopidogrel is predominantly converted to an inactive derivative, with only a minor fraction (15%) undergoing the 2-sequential oxidation steps to generate the active metabolite [35]. CYP2C19, CYP3A4/5 and CYP1A2 are all important enzymes in this process. The metabolic efficiency of prasugrel is relatively higher, with more than 50% of

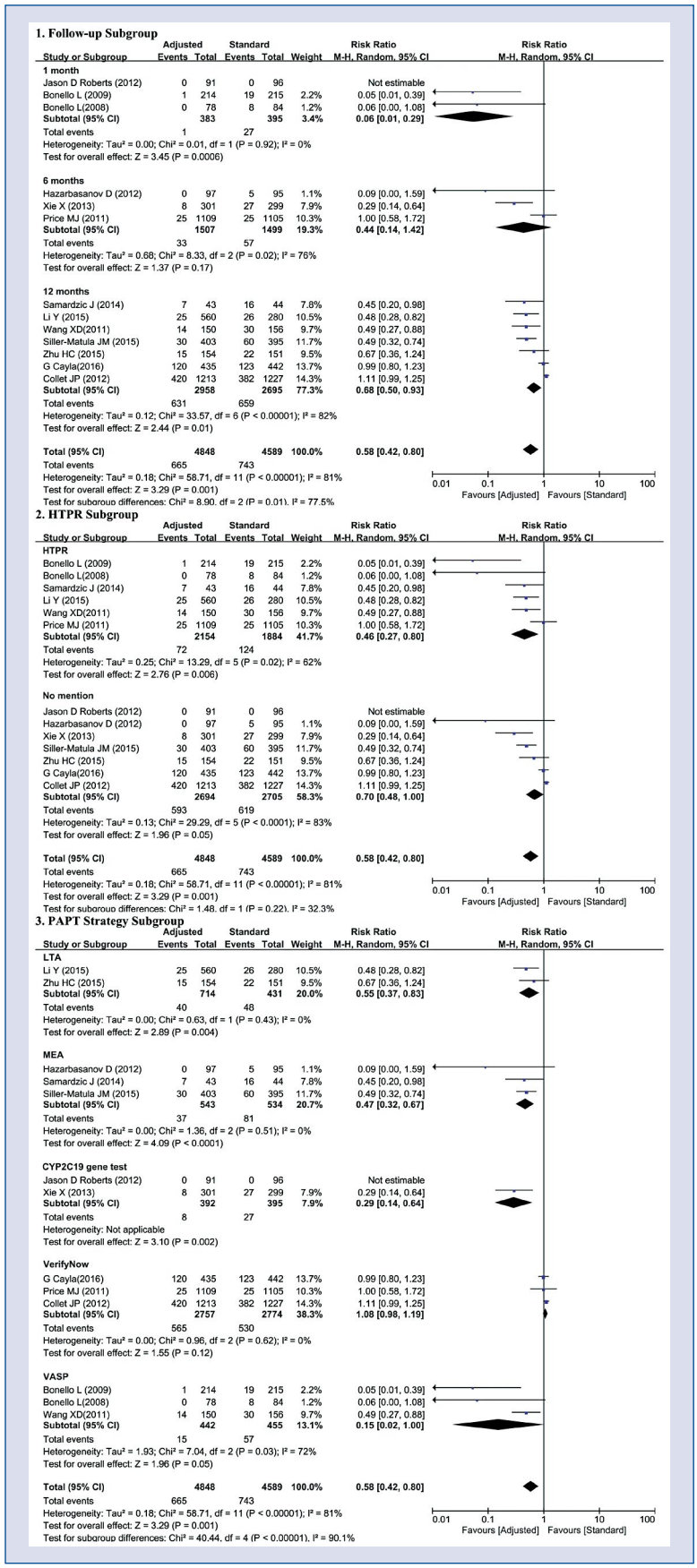

Figure 4. Subgroup analysis based on personalized antiplatelet therapy (PAPT) strategy difference; HTPR — high on-treatment platelet reactivity; LTA — light transmission aggregometry; MEA — multiple electrode aggregometry; VASP — vasodilator stimulated phosphoprotein; CI — confidence interval.

Table 2. Publication bias and sensitivity analysis.

Group	Egger's regression		Trim and Fill method			
	Intercept (95% CI)	P	Iteration	No. of Trim	RR (95% CI)	
					Before Trim and Fill	After Trim and Fill
MACE	–2.726 (–3.657 to –1.796)	0.000	2	0	0.58 (0.42–0.80)	0.58 (0.42–0.80)
Cardiovascular death	–1.741 (–2.472 to –1.010)	0.000	2	0	0.77 (0.51–1.16)	0.77 (0.51–1.16)
Myocardial infarction	–1.649 (–3.090 to –0.207)	0.030	2	0	0.43 (0.21–0.88)	0.43 (0.21–0.88)
Stroke	–1.188 (–3.153 to 0.777)	0.169	2	0	0.81 (0.39–1.66)	0.81 (0.39–1.66)
Stent thrombosis	–1.582 (–2.801 to –0.362)	0.016	2	0	0.60 (0.41–0.87)	0.60 (0.41–0.87)
Bleeding	–0.246 (–1.155 to 0.663)	0.566	2	1	0.96 (0.81–1.13)	0.96 (0.82–1.12)

CI — confidence interval; MACE — major adverse cardiac events; RR — risk ratio

Table 3. Sensitivity analysis after omitting studies using VerifyNow.

	Before omitting			After omitting		
	Number of studies	RR (95% CI)	p	Number of studies	RR (95% CI)	p
MACE	13	0.58 (0.42–0.80)	0.001	10	0.44 (0.32–0.59)	< 0.00001
Cardiovascular death	13	0.77 (0.51–1.16)	0.21	10	0.60 (0.34–1.06)	0.08
Myocardial infarction	9	0.43 (0.21–0.88)	0.02	7	0.25 (0.11–0.54)	0.0005
Stroke	6	0.81 (0.39–1.66)	0.57	5	0.56 (0.20–1.57)	0.27
Stent thrombosis	13	0.60 (0.41–0.87)	0.008	10	0.44 (0.27–0.70)	0.0006
Bleeding	14	0.96 (0.81–1.13)	0.59	11	0.89 (0.65–1.21)	0.46

CI — confidence interval; MACE — major adverse cardiac events; RR — risk ratio

the drug becoming bioactivated, and primarily mediated by CYP3A4 and CYP2B6 enzymes [36].

Currently, the effect of CYP2C19 polymorphisms on clopidogrel therapy has been extensively studied. The earliest report on the correlation between CYP2C19*2 loss-of-function gene and clopidogrel low reaction dates back to 2006 [37]. More studies performed at later dates confirmed this correlation [38–40]. CYP2C19*17 gain-of--function gene is related to a reactivity increase of clopidogrel, but recent studies found that this correlation may be due to CYP2C19*2 linkage disequilibrium [41]. However, prasugrel is not significantly influenced by gene polymorphism, although some studies suggest an association [42, 43]. Subgroup analysis of TRITON-TIMI 38 did not find significant associations between common CYP variants and active metabolite levels, platelet inhibition, or clinical CV event rates [44].

Clopidogrel and prasugrel are both substrates of p-glucoprotein efflux pump, which is encoded by the ABCB1 gene. Nevertheless, the correlation between ABCB1 polymorphism and clopidogrel pharmacodynamics is still unclear. One research paper found that patients with ABCB1 C3435T genotype had decreased clopidogrel absorption and circulating metabolite plasma levels [45], and in TRITON-TIMI 38 study, this gene polymorphism was significantly associated with an increased risk of CV death, MI, or stroke in patients under clopidogrel treatment [44]. However, the GIFT study revealed that ABCB1 polymorphism was not a significant factor in pharmacologic or clinical outcomes in patients treated with clopidogrel [46].

Multiple studies have investigated the influence of other gene polymorphisms, such as CYP2C9, CYP3A4, CYP3A5, P2Y12 on clopidogrel response variability, with results being mostly non-significant [36]. The GIFT study observed the correlation between 17 gene loci and platelet reactivity in more than 1,000 patients receiving standard or high-dose clopidogrel after PCI, and found that only CYP2C19*2 was associated with HTPR [46].

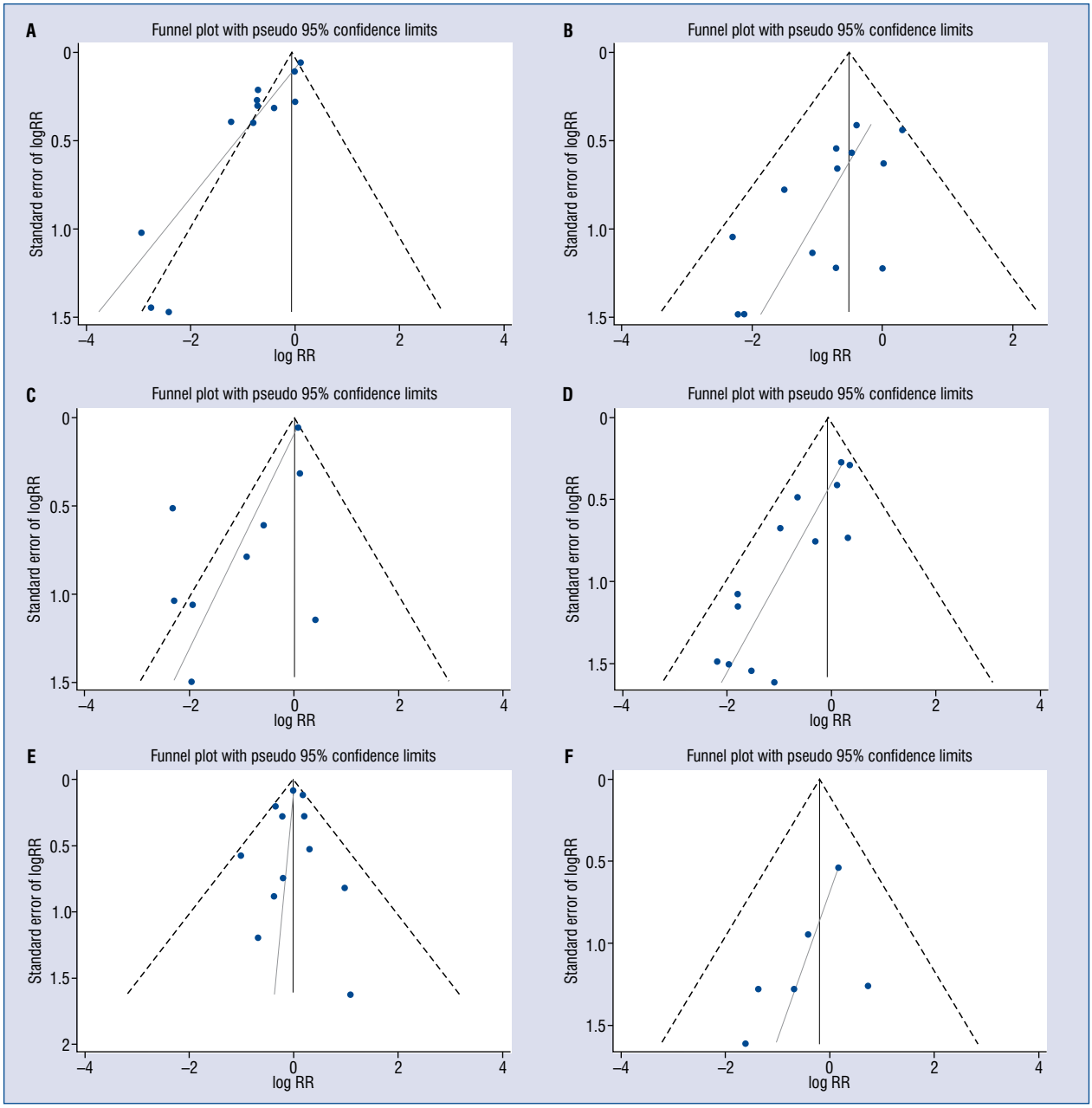

Figure 5. Funnel plot; **A.** Major adverse cardiac events subgroup; **B.** Stent thrombosis subgroup; **C.** Myocardial infarctions subgroup; **D.** Cardiovascular death subgroup; **E.** Bleeding events subgroup; **F.** Stroke subgroup.

Ticagrelor is a new non-thienopyridine antiplatelet medicine, which in 2011 was approved for use in patients with ACS or a history of MI. Studies on ticagrelor pharmacogenetics are limited, and no significant association between its effects and certain genotypes have been found. The subgroup analysis of DISPERSE and DISPERSE-2 studies investigated the correlation between P2Y12, P2Y1, ITGB3 gene polymorphism and the effects of ticagrelor, and found no association [47]. Besides, RESPOND and ONSET/OFFSET studies found that the effect of ticagrelor is unrelated to CYP2C19 and ABCB1 gene polymorphism [48]. The data of the PLATO trial were further investigated to search for potential genetic determinants, with at least 2 genome wide association study (GWAS) failing to find any significant effect of therapy associated polymorphisms on clinical outcomes [49, 50].

Publication bias

The funnel plots are obviously asymmetric, which indicate a potential publication bias in this meta-analysis. And Egger's regression was performed because the interpretation of funnel plots is largely subjective. Although the absence of a significant correlation or regression cannot be taken as evidence of symmetry, it confirmed publication bias from another perspective (Table 2). After that, a more interesting question would be what is its impact on these conclusions? It was identified from the results of trim and fill processes, which was performed in the sensitivity analysis. After the trim and fill adjustment, 3 imputed studies are shown as filled circles, and imputed point estimate in log units is shown as a filled diamond at 0.156 (0.085, 0.227), corresponding to a OR of 1.169 (1.089, 1.254). The adjusted point estimate suggests a lower benefit than the original analysis. Thus, the adjusted estimate is fairly close to the original, and it was thought that they have similar substantive implications.

Conclusions

In conclusion, patients undergoing coronary stenting, PAPT could reduce the risk of MACEs, ST and MI. The preventive effect on MACEs was more significant in patients with HTPR. However, there was no significant increase in CV death, bleeding events and ischemic stroke.

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