Thrombosis Research 179 (2019) 87–94

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Genotype-guided personalization of antiplatelet treatment: A meta-analysis of patients with ACS or undergoing PCI

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ARTICLE INFO

Keywords:
Genotype
CYP2C19
P2Y12 inhibitors
Acute coronary syndrome
Percutaneous coronary intervention

ABSTRACT

Introduction: Personalized antiplatelet treatment in patients with acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI) remains challenging in clinical practice. The present study aimed to explore the benefit of genotype-guided antiplatelet treatment with P2Y12 inhibitors in patients with ACS or undergoing PCI.

Methods: A literature search was conducted (from inception to September 2018) in the PUBMED, EMBASE and Cochrane databases. Studies were included in which the genotype-guided P2Y12 inhibitor antiplatelet strategy was compared with the standard strategy in patients with ACS or undergoing PCI. The endpoints were high on-treatment platelet reactivity (HTPR), major adverse cardiovascular events including all-cause mortality, myocardial infarction (MI), stent thrombosis (ST), stroke and target-vessel revascularization (TVR), and major bleedings.

Results: A total of 3377 patients in 9 studies (5 RCTs and 4 non-RCTs) were included, in which 91% of the patients were diagnosed with ACS and 88.5% underwent PCI. A total of 1639 patients (48.5%) were assigned to the genotype-guided group, and 1738 (51.4%) assigned to the conventional or standard (STD) group, with an average follow-up time of 7.6 months. After the pooled analysis, significantly lower risks of HTPR (HR: 0.32, 95% CI: 0.18–0.55, $P < 10^{-4}$), all-cause mortality (HR: 0.55, 95% CI: 0.37–0.83, $p = 0.005$), MI (HR: 0.43, 95% CI: 0.27–0.67, $p = 0.0002$) and ST (HR: 0.39, 95% CI: 0.16–0.97, $p = 0.004$) were observed in the genotype-guided group compared to the STD group. No significant between-group difference was found for the risk of stroke, TVR, and major bleedings after the pooled analysis.

Conclusion: Genotype-guided antiplatelet treatment could decrease the risks of HTPR, all-cause mortality, MI and ST in patients with ACS or undergoing PCI.

1. Introduction

Dual antiplatelet therapy with P2Y12 inhibitor and aspirin is the standard treatment in patients with acute coronary syndromes (ACS) or patients undergoing percutaneous coronary intervention (PCI) [1,2]. Treatment with the classical P2Y12 inhibitor of clopidogrel, combined with aspirin, effectively reduced the risk of adverse cardiovascular events in patients with ACS or undergoing PCI [3,4]. However, the inhibition of platelet reactivity is not adequate in approximately one-third of patients administered clopidogrel, leading to adverse thrombotic events among a considerable number of patients [5–9]. Clopidogrel is a prodrug that need to be converted to active metabolite by two sequential steps dependent on cytochrome P450 (CYP), with CYP2C19 affects both metabolic steps and is the most important determinant of the pharmacokinetic and pharmacodynamics response to clopidogrel [10,11]. Previous studies suggested that the loss of function (LOF) allele in CYP2C19 is the strongest predictor of the high on-treatment platelet reactivity (HTPR) and is associated with an increased risk of adverse cardiovascular events [12–15]. Compared to clopidogrel, the novel P2Y12 inhibitors, prasugrel and ticagrelor, provide stronger and more consistent antiplatelet effects [16,17]. However, the strong antiplatelet effects reduce the risk of adverse cardiovascular events, albeit at the expense of the increased risk of bleeding [18–20]. Therefore, personalization of the P2Y12 inhibitors in patients with ACS or undergoing PCI is of critical importance. Previously, multiple observational studies confirmed that genetic factors contribute to the variability of

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https://doi.org/10.1016/j.thromres.2019.05.004
Received 24 November 2018; Received in revised form 29 April 2019; Accepted 4 May 2019
Available online 06 May 2019
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clopidogrel antiplatelet efficacy [14]. However, it remains uncertain whether genotype-guided treatment with P2Y12 inhibitors could improve the antiplatelet responsiveness and clinical outcomes in patients with ACS or undergoing PCI. Compared with numerous studies on the association between genotypes and clopidogrel antiplatelet efficacy [12–15,21–23], few studies have focused on the effectiveness of genotype-guided selection of P2Y12 inhibitors. To date, the routine use of genetic testing for clopidogrel antiplatelet is not recommended [2]. Recently, some published prospective studies and randomized clinical trials (RCTs) showed that the individualized selection of P2Y12 inhibitors, according to the genotypes of CYP2C19 LOF alleles, might improve the antiplatelet effects in patients with ACS or undergoing PCI [24–31]. However, due to the limitation of sample size and varied outcome definitions, the evidence was considered to be inconsistent and inconclusive. By integrating multiple related studies, a systematic review or meta-analysis is a powerful strategy to overcome the limits of individual investigation and to demonstrate the utility of the clinical implementation of pharmacogenetics [32]. To date, no meta-analysis has been conducted to evaluate the effectiveness of genotype-guided antiplatelet treatment with P2Y12 inhibitors in patients with ACS or those treated with PCI. In the present study, we performed a meta-analysis of the published RCTs and non-RCTs, in which the strategies of genotype-guided and conventional treatment with P2Y12 inhibitors were compared. We aimed to determine whether the personalized P2Y12 inhibitors treatment based on genotypes would lead to better pharmacodynamics efficacy and clinical feasibility in patients with ACS or those undergoing PCI.

2. Material and methods

2.1. Literature search

A systematic literature search was conducted from the database inception to September 2018. We searched three electronic databases, including PUBMED, EMBASE and Cochrane Library computerized database. The search terms were genotype-guided and P2Y12 inhibitors. The study language was restricted to English. The search was performed to identify all published studies (RCTs and non-RCTs) in which genotype-guided antiplatelet therapy was compared with conventional or standard strategy among patients with ACS or those undergoing PCI. The detailed keywords and subject headings of the search strategy are presented in Appendix A.

2.2. Study inclusion criteria

The following inclusion criteria were applied. (i) All studies were RCTs or non-RCTs (cohort studies) and contained independent data. (ii) The P2Y12 inhibitors were administered with aspirin for patients with ACS or invasively managed by PCI. (iii) The platelet function or clinical outcomes were reported as the primary endpoints. The platelet function outcome of high on-treatment platelet reactivity (HTPR) was defined as the measurement of a P2Y12 reaction unit (PRU) value > 208, according to a verifyNow assay [33]. The clinical ischemic outcomes were defined as major adverse cardiovascular events (MACEs), including a composition of all-cause mortality, myocardial infarction, stroke, target-vessel revascularization, or stent thrombosis. The clinical safety outcomes of major bleeding were defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria, Thrombolysis In Myocardial Infarction (TIMI) criteria or Bleeding Academic Research Consortium (BARC) criteria of BARC 3 to 5 [34–36]. (iv) Genotype-guided P2Y12 inhibitors antiplatelet therapy, according to the CYP2C19 LOF allele carrier status (Genotype-guided group strategy), was compared to the conventional P2Y12 inhibitors antiplatelet therapy (STD group strategy).

2.3. Study exclusion criteria

We excluded studies based on the following criteria: (i) animal studies, case reports, conference papers, review articles and abstracts, (ii) studies with insufficient data, (iii) no access to the original articles and duplicate publications, (iv) the protocol or study was solely based on the establishment of genotype-guided strategies, (v) a lack of platelet function measurements or clinical outcomes, (vi) a lack of the genotyping for CYP2C19 LOF alleles, and (vii) the studies focused solely on the association between genotypes and antiplatelet efficacy.

2.4. Data extraction and validity assessment

Two investigators reviewed all studies independently and extracted the data using a standardized form. We resolved disagreements about the study data extraction through consensus or discussion with a third reviewer, who was independent from the research group. The characteristics of each study, including the study design, population, ethnic origin, number of patients, mean age, treatment strategies, follow-up intervals, primary and secondary endpoints, were extracted independently. The methodological quality of each RCT study was assessed using the validated scale of Cochrane Collaboration, and the risk of bias was evaluated by the 5-point Jadad scale [37]. The rating system of Newcastle-Ottawa Scale (NOS) was used to evaluate the included cohort studies (non-RCTs) [38].

2.5. Statistical analysis

We pooled studies using random- or fixed-effects models. The primary analysis focused on the comparison of HTPR, MACEs or major bleeding events between the genotype-guided and conventional groups. The endpoint results were presented as the hazard ratio (HR), with 95% confidence interval (CI). The heterogeneity of risk was tested using the Cochran's Q test and was regarded as significant if the P value was < 0.1. Meanwhile, the I^2 value was used to quantify the heterogeneity and to represent the extent of inconsistency among the trials, with I^2 of 50% or less representing low heterogeneity, and > 50% representing a high degree of inconsistency, respectively [39]. When the P value was ≥ 0.1 or $I^2 \leq 50\%$, the fixed effects model was selected, otherwise, the random effects model was selected. If heterogeneity was found, sensitivity analysis was applied by deselecting the studies one by one in chronological order to detect the potential influence of each study on the pooled results. Publication bias was examined with a funnel plot and analyzed with Egger's test [40]. To evaluate the presence and extent of publication bias more closely, we used the nonparametric trim and fill method, adding missing studies virtually to obtain symmetry and assessing the pooled results with the missing studies included [41]. If the pooled results with the included missing studies did not change (according to the P values), it suggested that the meta-analysis result was robust. All analyses were performed with the Review-Manager software (RevMan, version 5.3 for Windows; The Cochrane Collaboration, Oxford, UK; 2008). All P values were two-sided, with the level of statistical significance defined as < 0.05.

2.5.1. Results

Overall, 3377 participants from 9 eligible studies (Fig. 1) were included in the meta-analysis (Table 1). Among the included studies, 5 were designed as RCTs and 4 as prospective cohort studies (non-RCTs).

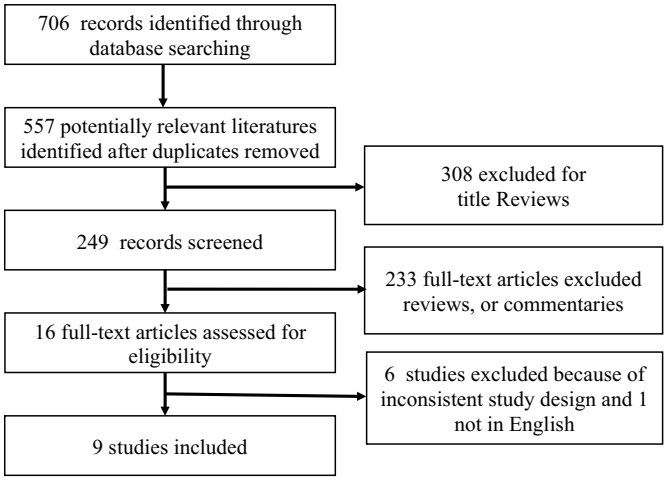

Fig. 1. A flow diagram showing the number of citations identified, retrieved, extracted, and included in the final analysis.

The average patient age was 62.8 ± 10.6 years, and 2472 patients (73%) were male. A total of 3076 (91%) were diagnosed with ACS, and 2990 (88.5%) underwent PCI. The average follow-up time was 7.6 months. There were 1639 patients (48.5%) allocated to the genotype-guided group and 1738 (51.4%) allocated to the conventional or standard (STD) group. The antiplatelet strategy of P2Y12 receptor inhibitors was implemented before PCI in 7 studies, after PCI in 1 study, and after the diagnosis of ACS in 1 study. No significant difference for the pooled baseline characteristics was found between the treatment groups in the RCTs or non-RCTs (data not shown).

In the Genotype-guided group, strong antiplatelet strategy was personalized to the CYP2C19 LOF allele carriers, with ticagrelor applied in 4 studies [24,25,28,30], prasugrel in 6 studies [27–31,42], a higher dose of clopidogrel in 2 studies [24,26], and clopidogrel plus cilostazol in 1 study [26]. In the STD group, the selection of the P2Y12 receptor inhibitors was based on the routine clinical practice or the clinicians' preferences, with the prescription of clopidogrel in 9 studies [24–31,42], ticagrelor in 2 studies [28,30], and prasugrel in 3 studies [28,30,42] (Table 1).

As the endpoint, HTPR was found in 3 studies, all measured through VerifyNow assays [25,27,29]. MACEs were designated as the endpoint in 8 studies, and major bleeding was the safety endpoint in 8 studies [24–28,30,31,42]. The average Jadad score for the RCTs was 4.5 (ranging from 4 to 5), which was considered to be high quality, meeting the general requirement for meta-analysis. The average NOS score for the included non-RCTs was 9 (ranging from 5 to 9), indicating high quality in the studies [43] (Table 1).

2.5.2. Genotype-guided antiplatelet treatment and HTPR outcomes

Three studies (2 RCTs and 1 non-RCT) investigated the risk of HTPR among 409 patients after the genotype-guided antiplatelet treatment [25,27,29] (Fig. 2A). Overall, 104 of the 409 patients experienced the HTPR endpoint. In the RCT studies, a significantly lower risk of HTPR was observed in the Genotype-guided group compared to the STD group (HR: 0.27, 95% CI: 0.10–0.71, $P = 0.008$). After including the non-RCTs, a significantly lower risk for HTPR was still observed in the Genotype-guided group (HR: 0.32, 95% CI: 0.18–0.55, $P < 10^{-4}$) (Fig. 2A).

2.5.3. Genotype-guided antiplatelet treatment and MACEs

Eight studies (5 RCTs and 3 non-RCT) investigated the risk of MACEs after genotype-guided antiplatelet treatment [24–28,30,31,42]. Overall, 210 of the 1867 patients (11.2%) in the RCTs and 111 of the 1412 patients (7.8%) in the non-RCTs experienced MACEs. In terms of individual endpoints, all-cause mortality was reported in 105 (3.3%) patients, myocardial infarction in 93 patients (2.7%), stroke in 26 patients (0.8%), stent thrombosis in 23 patients (0.6%), and target vessel revascularization in 30 patients (0.9%). We meta-analyzed the studies according to each endpoint of the MACEs. As a result, a total of 6 studies (3 RCTs and 3 non-RCTs) had the endpoint of all-cause mortality. After the pooled analysis, significantly lower risk of all-cause mortality could be found in genotype-guided group [HR: 0.55, 95% CI: (0.37–0.83), $p = 0.005$]. For the endpoint of the myocardial infarction, 6 studies (4 RCTs and 2 non-RCTs) were included for the analysis, with significantly lower risk of myocardial infarction found in genotype-guided group [HR: 0.43, 95% CI: (0.27–0.67), $p = 0.0002$]. Four studies (2 RCTs and 2 non-RCTs) were analyzed for the endpoint of stent thrombosis, with significantly lower risk of stent thrombosis found in genotype-guided group [HR: 0.39, 95% CI: (0.16–0.97), $p = 0.004$]. There was a trend for the lower risk of both target vessel revascularization [1 RCT and 2 non-RCTs; HR: 0.46, 95% CI: (0.21–1.01), $p = 0.05$] and stroke in genotype-guided group [3 RCT and 2 non-RCTs; HR: 0.48, 95% CI: (0.21–1.08), $p = 0.11$] (Fig. 2B).

2.5.4. Genotype-guided antiplatelet treatment and major bleeding events

The influence of genotype-guided antiplatelet treatment on the risk of major bleeding events was investigated in 4 RCTs and 2 non-RCTs. Overall, 68 of the 2043 patients (3.3%) experienced major bleeding events. No significant between-group difference was found in the risk of major bleedings after the meta-analysis of the RCTs (HR: 0.76, 95% CI: 0.43–1.34, $P = 0.35$) or after the pooled analysis of the RCTs and non-RCTs (HR: 0.72, 95% CI: 0.44–1.18, $P = 0.23$). (Fig. 2C).

2.5.5. Heterogeneity and sensitivity analysis

Evidence of heterogeneity was found when comparing the endpoint of HTPR in RCTs ($I^2 = 54\%$, $P = 0.14$) between the genotype-guided groups and STD groups. Hence, the random effects model was used in the analyses. No statistically significant heterogeneity was found for the subgroup analysis of MACEs and major bleeding events. We conducted the sensitive analyses by deselecting studies one by one in chronological order. None of the results were affected by the omission of any individual study.

2.5.6. Publication bias

No publication bias was detected on funnel plots or with Egger's test in all analyses. When the publication bias was evaluated through trim and fill analysis, no missing study was shown for the influence of genotype-guided treatment on the risk of HTPR, as well as the risk of MACEs (data not shown).

2.5.7. Discussion

By performing a collaborative meta-analysis, we found that genotype-guided (primarily based on CYP2C19 LOF alleles) personalized antiplatelet treatment with P2Y12 receptor inhibitors had a significantly lower risk of HTPR and MACEs in patients with ACS or undergoing PCI compared with conventional treatment. Thus, the genotype-guided antiplatelet treatment had the potential to benefit CYP2C19 LOF alleles carriers, who were more likely to experience recurrent ischemic events, despite being treated with standard doses of clopidogrel. To the best of our knowledge, the present study is the first meta-analysis to confirm the benefits of genotype-guided antiplatelet strategy on antiplatelet laboratorial and clinical outcomes, which could encourage the translation of pharmacogenetics into clinical practice.

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

Ref.	Study design	Patient	Ethnics	No. of genotype guided/STD patients	female,% genotype guided/STD	Age, mean (SD) genotype guided/STD	Time for strategy	genotype guided group strategy	STD group strategy	Follow-up interval	Primary outcomes	Secondary outcomes	Trial quality (Score)
Roberts, 2012 [27]	RCT	PCI for ACS	White: 95% Others: 5%	91/96	21.0/23.0	59.5(9.3)/ 60.8(8.7)	After PCI	MD: Carriers of *2: P 10 mg/d Noncarrier of *2: C 75 mg/d	LD:not mentioned MD: C 75 mg/d	7–30 d	HTPR: PRU > 234	MACE: death, MI, ST Safety outcomes: TIMI major bleeding	High (5)
Tam, 2017 [25]	RCT	ACS	Not mentioned	65/67	21.5/17.9	61.6(11.8)/ 60.3(12.2)	Before PCI	LD: (PCI for NSTEMI or UA, or STEMI without PCI) MD: Carriers of *2/*3: T 90 mg/bd. Noncarrier of *2/*3: C 75 mg/d	LD: C 600 mg (PCI for STEMI), 300 mg (PCI for NSTEMI or UA, or STEMI without PCI) MD: C 75 mg/d	1 month	HTPR: PRU > 208	Not mentioned	High (5)
Xie, 2013 [26]	RCT	PCI for CAD	Chinese	301/299	19.9/24,1	57.9(10.7)/ 57.8(10.3)	Before PCI	LD: *1/*1: C 300 mg. *1/*2 or*1/*3: C 600 mg *2/*2,*2/*3 or*3/*3: C 600 mg/d + Cil 200 mg MD: *1/*1: C 75 mg/d. *1/*2 or*1/*3: C 150 mg/d *2/*2,*2/*3 or*3/*3: C 150 mg/d + Cil 100 mg/bd	LD: C 300 mg MD:C 75 mg/d	6 months	MACE: Death, MI, Stroke, TVR	MACE Safety outcomes: BARC defined all bleeding	High (4)
Notarangelo, 2018 [30]	RCT	ACS	European ancestry	448/440	34.2/29.6	71.1(12.3)/ 70.7 (12.1)	After the diagnosis of ACS	Based on the combination of genotypes ABCB1 3435, CYP2C19*2 and *17	Based on clinical characteristics and the clinicians' preference	12 months	MACE: Death, MI, Stroke, ST	Safety outcomes: BARC 3 to 5 defined major bleeding	High (5)
Tomaniak , 2017 [31]	RCT	PCI for CAD	European ancestry	34/26	22.2/23.3	61.8(10.6)/ 62.3 (7.6)	Before PCI	MD: *1/*1: C 75 mg/d *1/*2: P (60 mg) 2 h before PCI then 10 mg/d	MD:C 75 mg/d	12 months	MACE: Death, MI, Stroke, ST	Safety outcomes: BARC 3 to 5 defined major bleeding	High (4)
Shen, 2016 [24]	Non-RCT	PCI for CAD	Chinese	309/319	35.0/32.9	68.4(10.4)/ 69.6(11.3)	Before PCI	LD: C 600 mg MD: *1/*1: C 75 mg/d *1/*2 or *1/*3: C 150 mg/d *2/*2,*2/*3 or*3/*3: T 90 mg/d	LD: C 600 mg MD:C 75 mg/d	1 month 6 months 12 months	MACE: death/MI/TVR	Safety outcomes: GUSTO defined all bleedings	High (9)
Sanchez-Ramos, 2016 [28]	Non-RCT	PCI for CAD	Not mentioned	317/402	24.9/22.1	64.1(12.1)/ 64.6 (11.5)	Before PCI	*2/*2,*2/*3 or *3/*3 or ABCB1TT: P or T	Based on the routine clinical practice	12 month	Cardiovascular death, ACS, or stroke	Safety outcomes: TIMI major or minor bleeding	High (9)

(*continued on next page*)

Table 1 (*continued*)

Ref.	Study design	Patient	Ethnics	No. of genotype guided/STD patients	female,% genotype guided/STD	Age, mean (SD) genotype guided/STD	Time for strategy	genotype guided group strategy	STD group strategy	Follow-up interval	Primary outcomes	Secondary outcomes	Trial quality (Score)
Lee, 2016 [29]	Non-RCT	PCI for AMI	Korean	50/48	6.0/20.8	56.0(9.1)/ 60.2(10.2)	Before PCI	Noncarrier of *2/*3 or ABCB1TT: C LD: P 60 mg MD: *2/*2,*2/*3 or*3/*3: P 10 mg/d for 5 w Others: P 10 mg/d for 3 w, C 75 mg/d for 2 w	LD: C 300–600 mg MD:C 75 mg/d	5 weeks	HTPR: PRU > 208 or 275	Not mentioned	High (9)
Ozawa, 2018 [41]	Non-RCT	PCI for ACS	Japan	24/41	20.8/34.1	64.5(9.3)/ 68.1(12.6)	Before PCI	LD: P 20 mg MD: *1/*1 or PCI naïve *1/ *2 or PCI naïve *1/*3: C 75 mg/d *1/*2 or *1/*3:P 3.75 mg/d	LD: C 300 mg MD:C 75 mg/d	12 month	Death, cardiac death, MI, TVR. ST, or stroke.	Safety outcomes: BARC 3 to 5 defined major bleeding	High (9)

RCT: randomized controlled trial. AMI: acute myocardial infarction. PCI: percutaneous coronary intervention. ACS: acute coronary syndromes. STD: conventional group. P: prasugrel. C: clopidogrel. T: ticagrelor. Cil: cilostazol. MD: maintenance dose. MACE: major adverse cardiovascular events, the definition was different in the analyzed studies. HTPR: high on-treatment platelet reactivity. CAD: coronary artery disease. MI: myocardial infarction. ST: stent thrombosis TVR: target-vessel revascularization. LD: loading dose. Trial Quality (Score): Jadad 5-point scale for RCT, Newcastle-Ottawa Scale (NOS) for non-RCT. *2:CYP2C19*2. *3:CYP2C19*3. TIMI: Thrombolysis In Myocardial Infarction. BARC: Bleeding Academic Research Consortium. GUSTO: Global Use of Strategies to Open Occluded Arteries. PRU: P2Y12 reaction unit.

Previous studies have provided strong evidence that CYP2C19 LOF alleles were associated with a reduced exposure to the active drug metabolite, less platelet inhibition, and less protection from recurrent ischemic events in patients treated with clopidogrel. These studies consistently confirmed the contribution of CYP2C19 LOF alleles to HTPR in patients with ACS treated with clopidogrel [44]. Accordingly, the present study confirmed that genotype-guided antiplatelet treatment could reduce the risk of HTPR in patients with ACS or in those undergoing PCI. Although HTPR was strongly related to the high risk of MACEs [45], there is controversy over the relationship between CYP2C19 LOF alleles and MACEs, which may be explained by the different type and/or risk of the included patients [46,47]. Increasing evidence has suggested that patients with ACS undergoing PCI might benefit from the genotype-guided antiplatelet treatment [48]. Accordingly, patients included in the present meta-analysis were diagnosed as ACS or treated with PCI, thus, it was reasonable that genotype-guided antiplatelet treatment could reduce the risk of MACEs in such patients. After the stratification according to the individual MACE, we found the risk of all-cause mortality, MI and ST significantly decreased in the Genotype-guided group. The particular benefit could be explained by the personalized application of the strong P2Y12 inhibitors, including ticagrelor and prasugrel, in the Genotype-guided groups, as both novel agents were confirmed to be more effective than clopidogrel in the reducing the number of deaths and nonfatal MI cases [16,17]. Observational studies showed that CYP2C19 LOF genotypes were related to a 2 to 4 time higher rate of stent thrombosis among patients undergoing PCI [44,47,49–51]. As expected, we found that lower risk of stent thrombosis was observed in the patients receiving genotype-guided treatment. Compared with clopidogrel, strong antiplatelet agents might lead to an increased risk of bleeding events [16,17,52]. However, in the present meta-analysis, a trend for lower risk of major bleeding was found in the genotype-guided patients. It indicated that personalized antiplatelet according to genotype could potentially reduce the risk of bleedings.

Several limitations of the present meta-analyses should be mentioned. First, One of the major limitations of the present meta-analysis might attribute to the small number of studies with different endpoints, different treatment strategies and different lengths of follow up. Even though the small number of the included studies, all the included studies (RCTs and non-RCTs) were confirmed to be high quality after the quality evaluation; therefore, the pooled results of the meta-analysis should be reliable. Despite the application of a highly sensitive search strategy for the retrieval of potentially eligible studies, there remains a possibility that some studies may have been overlooked. For the varying clinical outcomes, due to the shortage of the included studies, it was difficult to make powerful meta-analysis for each endpoint, although we did such subgroup analysis according to each endpoint of MACEs (Table 2). We defined the MACEs which were commonly applied in previous large scale RCTs concerning with DAPT in patients with ACS or after PCI [14,17,53]. Therefore, only patients with the above-mentioned MACEs were included for the pooled analysis. For the bleeding endpoints, only patients with major bleeding events were included for the meta-analysis. Therefore, the strict definitions for the endpoints could facilitate the clinical value of the analysis. As for the different treatment strategies were found in patients included in the genotype-guided group. However, the different genotype-guided treatment strategies for the included studies actually shared the same principle, with strengthened antiplatelet for carriers of CYP2C19 loss-of-function alleles, and routine clopidogrel treatment for non-carriers. Therefore, from the whole point-of-view, it is of clinical value to compare the difference strategies between genotype-guided group and STD group. In addition, the different lengths of follow up time could limit the impact of the current study. Therefore, we included the studies with the follow-up intervals of at least 1 month for the present meta-

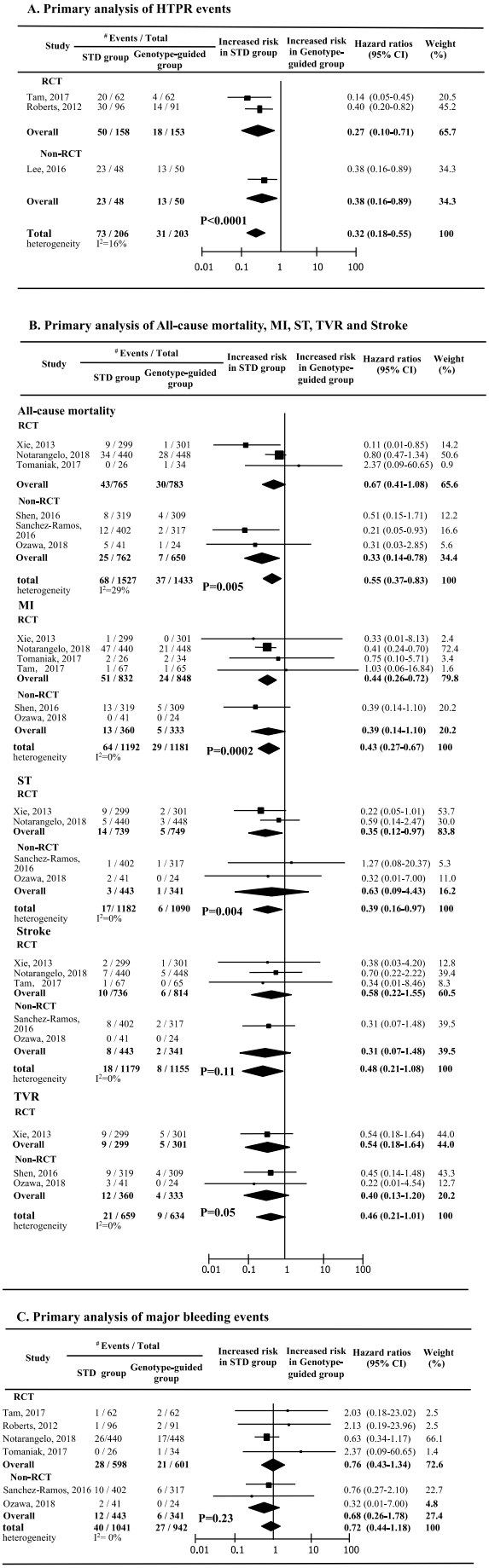

Fig. 2. Forest plots of the primary meta-analysis for the clinical outcomes in genotyped-guided therapy compared to conventional therapy. **A** indicates the primary analysis of HTPR defined as the measurement of a P2Y12 reaction unit (PRU) value > 208, according to a verifyNow assay; **B** B indicates the primary analysis according to the each composition of MACEs, including the all-cause mortality, myocardial infarction (MI), stroke, target-vessel revascularization (TVR), or stent thrombosis (ST); **C** indicates the primary analysis of major bleeding events, defined according to the GUSTO, TIMI or BARC criteria. #Events/Total represents patients involved with events versus the total number of patients. 95% CI: corresponding 95% confidence intervals. STD: conventional group.

analysis, which could capture most of the ischemic and bleeding events after discharge in the patients with ACS or treated by PCI.

In addition, one of the included non-RCT used historical controls, which might confound the results, as improvements in PCI techniques over time may contribute to better outcomes in the genotype group [28]. However, sensitivity analysis showed that a more significant reduction in MACE could still be found when this study was excluded from the meta-analysis. Third, heterogeneous results were observed for the major bleeding risk, which might attribute to the lower power of the included studies for the evaluation of the relatively rare events. Therefore, more studies should be included before drawing a definitive conclusion concerning the influence of genotype-guided antiplatelet therapy on the risk of major bleeding. Finally, a lack of studies hampered the comparison of the effects between the different personalized strategies, according to the number of CYP2C19 LOF alleles. Subgroup meta-analysis of the present study showed that personalized strategies based on the 2 CYP2C19 LOF alleles might result in more benefits than the strategies based on at least 1 CYP2C19 LOF alleles (data not shown). Thus, further study is warranted to confirm the difference.

For the perspectives, well-designed RCTs with powerful sample sizes are necessary to resolve the uncertainties and produce satisfactory answers concerning the role of genotype-guided antiplatelet therapy. The ongoing trials of TAILOR-PCI [54] and POPular Genetics [55] will help to determine whether genotype-identified patients with clopidogrel resistance could have improved clinical outcomes when clopidogrel was switched to novel P2Y12 inhibitors. These trials will also potentially support the evidence of whether personalized use of stronger P2Y12 inhibitors in carriers of the CYP2C19 LOF alleles can minimize the bleeding risks. The use of electronic health records with the pre-emptively integration of genotypes is promising for the clinical implementation of pharmacogenetics [56]. Whether such pragmatic approaches will preclude the need for genotype-based RCTs remains to be seen.

In conclusion, Genotype-guided antiplatelet treatment could decrease the risks of HTPR, all-cause mortality, MI and ST in patients with ACS or undergoing PCI.

Acknowledgements

This work was supported by grants from the General Program of Natural Science Foundation of Beijing (No. 7152129), the Clinical Supporting Foundation of Chinese PLA General Hospital (2015FC-ZHCG-2002), the Opening Project of the National Clinical Research Center for Geriatric Diseases PLA General Hospital (NCRCG-PLAGH-2017002), and the Key Research Project of Chinese Military Logistics (BWS17J026).

Table 2
Subgroup meta-analysis, according to MACEs.

	Events, n (%)		Pooled HR (95% CI)	P value	I^2 (%)	P value for heterogeneity
	Genotype guided group	STD group				
All-cause mortality	37 (2.5)	68 (4.4)	0.55 (0.37–0.83)	0.005	29	0.22
MI	29 (2.4)	64 (5.3)	0.43 (0.27–0.67)	0.0002	0	0.94
ST	6 (0.4)	17 (1.4)	0.39 (0.16–0.97)	0.04	0	0.66
TVR	9 (0.5)	21 (3.2)	0.46 (0.21–1.01)	0.05	0	0.86
stroke	8 (0.6)	18 (1.4)	0.49 (0.22–1.11)	0.11	0	0.87

STD: conventional group; MI: myocardial infarction; ST: stent thrombosis; TVR: target-vessel revascularization; HR: hazard ratio; CI: confidence intervals; I^2: the value is used to test for the heterogeneity, with a I^2 value of < 50% and > 50% representing a low and high degree of inconsistency, respectively.

Conflicts of interest

None.

Appendix A. Search strategies

The following search terms were used: (genotype or polymorphism or pharmacogenetic or pharmacogenomic or genetic or genomic or genotyping or variant or variation or cyp2c19 or cytochrome *p*450 2c19) AND (guide or personalized or guided or guiding or tailored or individualized or individualizing or individualization or directed or directing) AND (antiplatelet or antithrombosis or clopidogrel or Iscover or Plavix or ticagrelor or prasugrel or thienopyridine or P2Y12 inhibitors) AND (Acute Coronary Syndromes or ACS or Percutaneous Coronary Interventions or PCI or Percutaneous Coronary Revascularizations or Coronary Intervention).

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