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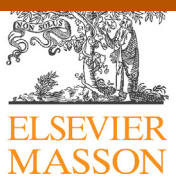

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CLINICAL RESEARCH

Cytochrome CYP2C19 polymorphism and risk of adverse clinical events in clopidogrel-treated patients: A meta-analysis based on 23,035 subjects

Polymorphisme du cytochrome CYP2C19 et risque d'évènements indésirables chez des patients traités par clopidogrel : méta-analyse de 23 035 sujets

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KEYWORDS
CYP2C19;
Clopidogrel;
Meta-analysis;
Coronary artery disease

Summary
Background. — Previous studies have investigated the relationship between CYP2C19 polymorphism and clinical prognosis in coronary artery disease patients treated with clopidogrel, but the results were inconsistent.
Aims. — To assess the impact of CYP2C19 polymorphism on the risk of adverse clinical events by performing a meta-analysis of relevant studies in the last few years.
Methods. — Prospective cohort studies or post-hoc analyses of randomized controlled trials were identified from the databases of PubMed/Medline, EMBASE and the Cochrane Library. Endpoints were fatal or non-fatal myocardial infarction, cardiovascular or all-cause death, definite or probable stent thrombosis, target vessel revascularization, target lesion revascularization, urgent revascularization, ischaemic stroke and bleeding. Pooled effects were measured by odds ratios (ORs) with 95% confidence intervals (CIs).

Abbreviations: ACS, Acute coronary syndrome; CAD, Coronary artery disease; CI, Confidence interval; CYP, Cytochrome P450; MI, Myocardial infarction; OR, Odds ratio; PCI, Percutaneous coronary intervention; PCR, Polymerase chain reaction; ST, Stent thrombosis; TLR, Target lesion revascularization; TVR, Target vessel revascularization.

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Results. — A total of 21 studies involving 23,035 patients were included. Compared with non-carriers of the CYP2C19 variant allele, the carriers were found to have an increased risk of adverse clinical events (OR 1.50, 95% CI 1.21—1.87; $P = 0.0003$), myocardial infarction (OR 1.62, 95% CI 1.35—1.95; $P < 0.00001$), stent thrombosis (OR 2.08, 95% CI 1.67—2.60; $P < 0.00001$), ischaemic stroke (OR 2.14, 95% CI 1.36—3.38; $P = 0.001$) and repeat revascularization (OR 1.35, 95% CI 1.10—1.66; $P = 0.004$), but not of mortality ($P = 0.500$) and bleeding events ($P = 0.930$).
Conclusion. — CYP2C19 polymorphism is significantly associated with risk of adverse clinical events in clopidogrel-treated patients.

MOTS CLÉS
Clopidogrel ;
Méta-analyse ;
Maladie coronaire

Résumé
Justification. — Des études ont été réalisées établissant le lien entre polymorphisme du cytochrome CYP2C19 et le pronostic des patients coronariens traités par clopidogrel, mais les résultats sont divergents.
Objectifs. — Évaluer l'impact du polymorphisme CYP2C19 sur le risque d'évènements indésirables en réalisant un méta-analyse des études publiées récemment.
Méthode. — Les études de cohortes prospectives ou les analyses post-hoc des essais randomisés ont été identifiées à l'aide d'une analyse des bases de données PubMed, Medline, Embase et la collaboration Cochrane. Le critère de jugement était la survenue d'un infarctus du myocarde fatal ou non, le décès cardiovasculaire ou toute cause, la thrombose de *stent* probable ou certaine, la revascularisation des vaisseaux cible, la revascularisation de la lésion cible, l'indication à une revascularisation urgente, la survenue d'un accident ischémique cérébral et le saignement. Les effets ont été évalués par la détermination des *odds ratio* et des intervalles de confiance à 95 %.
Résultats. — Un total de 21 études incluant 23 035 patients ont été inclues dans l'analyse. En comparaison des patients non porteurs de l'allèle variant CYP2C19, les porteurs avaient un risque accru d'évènements cliniques (*odd ratio* 1,50, IC 95 % 1,21—1,87, $p = 0{,}0003$), le risque d'infarctus du myocarde (*odd ratio* 1,62, IC 95 % 1,35—1,95, $p < 0{,}00001$), de thrombose de *stent* (*odd ratio* 2,08, IC 95 % 1,67—2,60, $p < 0{,}00001$), d'accident ischémique cérébral (*odd ratio* 2,14, IC 95 % 1,36—3,38, $p = 0{,}001$) et l'indication de revascularisation répétée (*odd ratio* 1,35, IC 95 % 1,10—1,66, $p = 0{,}004$). Il n'y avait pas d'augmentation significative du risque de décès ($p = 0{,}500$) et de saignement ($p = 0{,}930$).
Conclusion. — Le polymorphisme du cytochrome CYP2C19 est significative associé avec un risque d'évènements clinique, décès et infarctus du myocarde, chez les patients traités par clopidogrel.

Introduction

As an irreversible inhibitor of the adenosine diphosphate P2Y12 receptor, clopidogrel plays an important role in the prevention of stent thrombosis (ST) in coronary artery disease (CAD) patients undergoing percutaneous coronary intervention (PCI) [1,2]. However, about 4—30% of the patients treated with clopidogrel display no or a low anti-platelet response [3—5]. This phenomenon is called clopidogrel resistance or clopidogrel non-responsiveness [6]. According to previous studies [7,8], these patients may have an increased risk of ischaemic cardiovascular events.

The mechanisms of this phenomenon are not fully elucidated. We know that clopidogrel is an inactive prodrug that requires oxidation by the hepatic cytochrome P450 (CYP) system to generate an active metabolite. As a result, mutations in the genes for these CYP enzymes may affect clopidogrel responsiveness [6,9]. Among these genes, *CYP2C19* is of great concern. The CYP2C19*17 allele, which will not be discussed in this article, may enhance platelet response to clopidogrel in acute coronary syndrome (ACS) patients [10]. On the other hand, loss-of-function alleles, such as CYP2C19*2 and CYP2C19*3, which we will discuss in this article, are responsible for reduced activation of clopidogrel and increase the risk of recurrent cardiovascular events in CAD patients [11—13]. Recently, to evaluate the association between *CYP2C19* polymorphism and adverse cardiovascular events in CAD patients treated with clopidogrel, more and more studies have been performed [10,14—22]. However, the results have not been consistent. Thus, we performed a meta-analysis of cohort studies or post-hoc analyses of randomized controlled trials to investigate the effects of *CYP2C19* polymorphism, especially CYP2C19*2, on adverse clinical events in clopidogrel-treated patients.

Methods

Search methods and selection criteria

Two reviewers (CJ and HD) independently performed electronic searches for *CYP2C19* polymorphism and clopidogrel in PubMed/Medline, EMBASE and the Cochrane Library,

with the following search strategy ''(clopidogrel) and (P450 2C19 OR CYP2C19) and (coronary heart disease or coronary artery disease)'', from their inception through to February 2013. The language was restricted to English or Chinese. The selection criteria for eligible studies were as follows: study type (prospective cohort studies or post-hoc analyses of randomized controlled trials); participants (coronary artery disease patients treated with clopidogrel); definite clinical endpoints (fatal or non-fatal myocardial infarction [MI], cardiovascular death, all-cause death, definite or probable stent thrombosis [ST], target lesion revascularization [TLR], target vessel revascularization [TVR], urgent revascularization, ischaemic stroke and bleeding); genotyping (loss-of-function genotypes [CYP2C19*2—*8], especially CYP2C19*2, should be detected in the studies); comparison (comparison of the outcomes between mutant gene carriers and non-carriers). Meeting abstracts, case reports, editorials and reviews were excluded.

Data extraction and quality assessment

Data extraction was completed by two investigators (LM and LC), independently. Study type, country, population characteristics, number of patients, mean age, clopidogrel dose, combination of aspirin, genotyping method, genotype distribution, length of follow-up, study endpoints, number of each event, adjustment for confounding factors and conclusions were collected. Any occurrence of events, such as fatal or non-fatal MI, cardiovascular or all-cause death, definite or probable ST, TVR, TLR, urgent revascularization, ischaemic stroke or bleeding, was considered to be an adverse clinical outcome in our meta-analysis. Disagreements were resolved by discussion between the two investigators.

The Newcastle-Ottawa quality assessment scale was used to assess the quality of the included studies [23,24]. This scale consists of three categories: selection (representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and demonstration that the outcome of interest was not present at the start of the study); comparability (comparability of cohorts on the basis of the design or analysis); and outcome (assessment of outcome, follow-up long enough for outcomes to occur, adequacy of follow-up of the cohorts). The highest score that a study can be awarded is nine.

Statistical analysis

In this article, the *P* value was set at 0.10 for heterogeneity tests and at 0.05 for others. All the *P* values were two-tailed. Cochran's Q test and I^2 were used to investigate heterogeneity; the funnel plot analysis was used to evaluate publication bias. I^2 values > 25%, > 50% and > 75% were considered as evidence of low, moderate and severe statistical heterogeneity, respectively. If I^2 was > 50% or *P* was < 0.10, a random-effect model was chosen. Accordingly, we ran a fixed-effect model if I^2 was < 50% or *P* was > 0.10. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of the association between cytochrome *CYP2C19* polymorphism and clinical prognosis. All statistical tests were performed with Review Manager 5.1 for Windows, available from the Cochrane Collaboration.

Results

Study selection

A total of 421 relevant publications were evaluated initially. Finally, 21 studies met the inclusion criteria [13,17—22,25—38]. The study selection flow diagram is shown in Fig. 1. In total, 23,035 patients were included in this meta-analysis. Among these patients, 7670 were carriers of the CYP2C19 variant allele (mostly CYP2C19*2); the other 15,365 patients were non-carriers. Eight studies [13,18—20,22,25—27] were from Asia and thirteen [15,21,28—38] were from Europe or the USA. The loading dose of clopidogrel was 300 mg or 600 mg in 18 studies [13,15,18—20,22,25—27,29,31—38] and all the participants were given a maintenance dose of 75 mg/day. The TaqMan (Applied Biosystems, Foster City, CA, USA) polymerase chain reaction (PCR) was chosen as the genotyping method in 61.9% of the studies. The length of follow-up ranged from 1 month to 4 years. Study characteristics are reported in Table 1.

Association between *CYP2C19* polymorphism and adverse clinical events

Heterogeneity test results indicated statistical heterogeneity among the included studies [13,15,18—22,26—38] (I^2 = 67%, *P* < 0.00001) and a random-effect model was selected accordingly (Fig. 2). The results of twenty comparisons showed that carriers (*n* = 6868) of the CYP2C19 variant allele had a higher risk of adverse

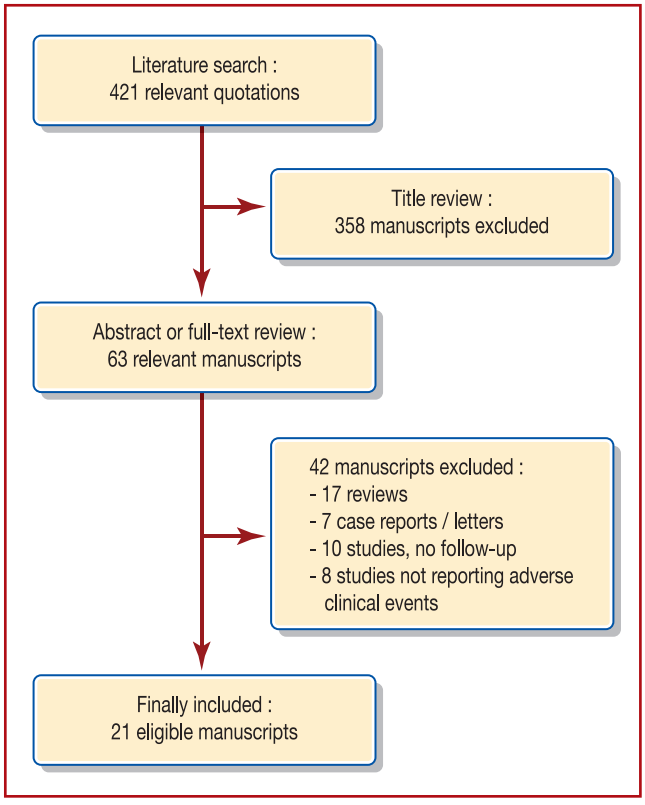

Figure 1. Flow diagram of the systematic review process.

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

Study	Year	Country	Study population	Age (years)	Carriers/non-carriers (*n*/*n*)	Clopidogrel dose (LD→MD)	Follow-up (months)	Endpoints	Genotyping method	Genetic variant	NOS
Nishio et al. [18]	2012	Japan	PCI	69.8	100/60	300 mg → 75 mg/day	21.5	Death, ST, MI, TLR	TaqMan PCR	*2, *3	9
Peng et al. [20]	2013	China	CAD	64.9	271/235	300 mg → 75 mg/day	12	Non-fatal MI, death, stroke, revascularization	TaqMan PCR	*2	9
Trenk et al. [37]	2008	Germany	Elective PCI	66.3	245/552	600 mg → 75 mg/day	12	RPA, death, non-fatal MI	TaqMan PCR	*2	9
Harmsze et al. [30]	2010	Netherlands	PCI	62.7	193/403	NA	12	ST	PCR	*2, *3	8
Tang et al. [22]	2012	China	PCI	58.9	384/286	300 mg → 75 mg/day	12	Cardiovascular death, MI, TVR, ST	LDR	*2, *3, *17	9
Bouman et al. [15]	2011	Germany	CAD + PCI	61.2	37/75	600 mg → 75 mg/day	18	ST	TaqMan PCR	*2	9
Sawada et al. [26]	2011	Japan	PCI	69.6	42/58	300 mg → 75 mg/day	18.2	ST, death, MI, TVR	TaqMan PCR	*2	7
Pare et al. [33]	2010	Canada	NSTE-ACS	63.8	650/1880	300 mg → 75 mg/day	12	Death, non-fatal MI, stroke	TaqMan PCR	*2, *3	9
Yamamoto et al. [13]	2010	Japan	Stable CHD	68.6	62/36	300 mg → 75 mg/day	12	Death, non-fatal MI, ischaemic stroke	PCR	*2, *3	8
Giusti et al. [29]	2009	Italy	ACS + PCI	NA	247/525	600 mg → 75 mg/day	6	ST	PCR	*2	9
Collet et al. [28]	2009	France	MI	40.1	73/186	NA → 75 mg/day	> 48	Death, non-fatal MI, urgent revascularization	TaqMan PCR	*2	9
Shuldiner et al. [34]	2009	America	Elective PCI	65.1	67/158	600 or 300 mg → 75 mg/day	12	MI, stroke, ST, death	SNPlex[a]	*2	9
Wallentin et al. [38]	2010	America, Europe	ACS	62.5	1388/3516	600 or 300 mg → 75 mg/day	12	Cardiovascular death, MI, stroke	TaqMan PCR	*2∼*8, *17	8
Tiroch et al. [36]	2010	Germany	Acute MI	64.8	248/680	600 mg → 75 mg/day	12	TLR, death, MI	TaqMan PCR	*2, *17	9
Mega et al. [32]	2009	America, Europe	ACS + PCI	60.1	395/1064	300 mg → 75 mg/day	15	Cardiovascular death, MI, stroke	PCR	*2	9
Sibbing et al. [35]	2009	Germany	CAD + PCI	66.5	680/1805	600 mg → 75 mg/day	1	ST	TaqMan PCR	*2	8
Simon et al. [21]	2009	France	Acute MI	66.2	617/1561	300—900 mg → 75 mg/day	12	Death, non-fatal MI, stroke	SNPlex[a]	*2∼*5, *17	8

Table 1 (*Continued*)

Study	Year	Country	Study population	Age (years)	Carriers/non-carriers (*n*/*n*)	Clopidogrel dose (LD→MD)	Follow-up (months)	Endpoints	Genotyping method	Genetic variant	NOS
Malek et al. [31]	2008	Poland	ACS + PCI	60.0	21/84	300 or 600 mg → 75 mg/day	12	Death, MI	TaqMan PCR	*2	8
Tang et al. [27]	2011	China	CHD + PCI	58.0	137/130	300 mg → 75 mg/day	12	Death, angina recurrence, MI, urgent revascularization, ST	MALDI-TOF MS	*2	9
Luo et al. [25]	2011	China	CHD + PCI	70.8	802/936	300 mg → 75 mg/day	6	ST, death, MI, ischaemic stroke, bleeding	TaqMan PCR	*2	9
Oh et al. [19]	2011	Korea	PCI	60.8	1011/1135	300 or 600 mg → 75 mg/day	12	Death, non-fatal MI, ST, TVR, TLR	TaqMan PCR	*2	9

ACS: acute coronary syndrome; CAD/CHD: coronary artery disease; LD: loading dose; LDR: ligase detection reaction; NSTE: non-ST-segment elevation; MALDI-TOF MS: matrix-assisted laser desorption/ionization-time of flight mass spectrometry; MD: maintenance dose; MI: myocardial infarction; NA: not available; NOS: Newcastle-Ottawa scale; PCI: percutaneous coronary intervention; PCR: polymerase chain reaction; RPA: residual platelet aggregation; ST: stent thrombosis; TLR: target lesion revascularization TVR: target vessel revascularization.
[a] Applied Biosystems, Foster City, CA, USA.

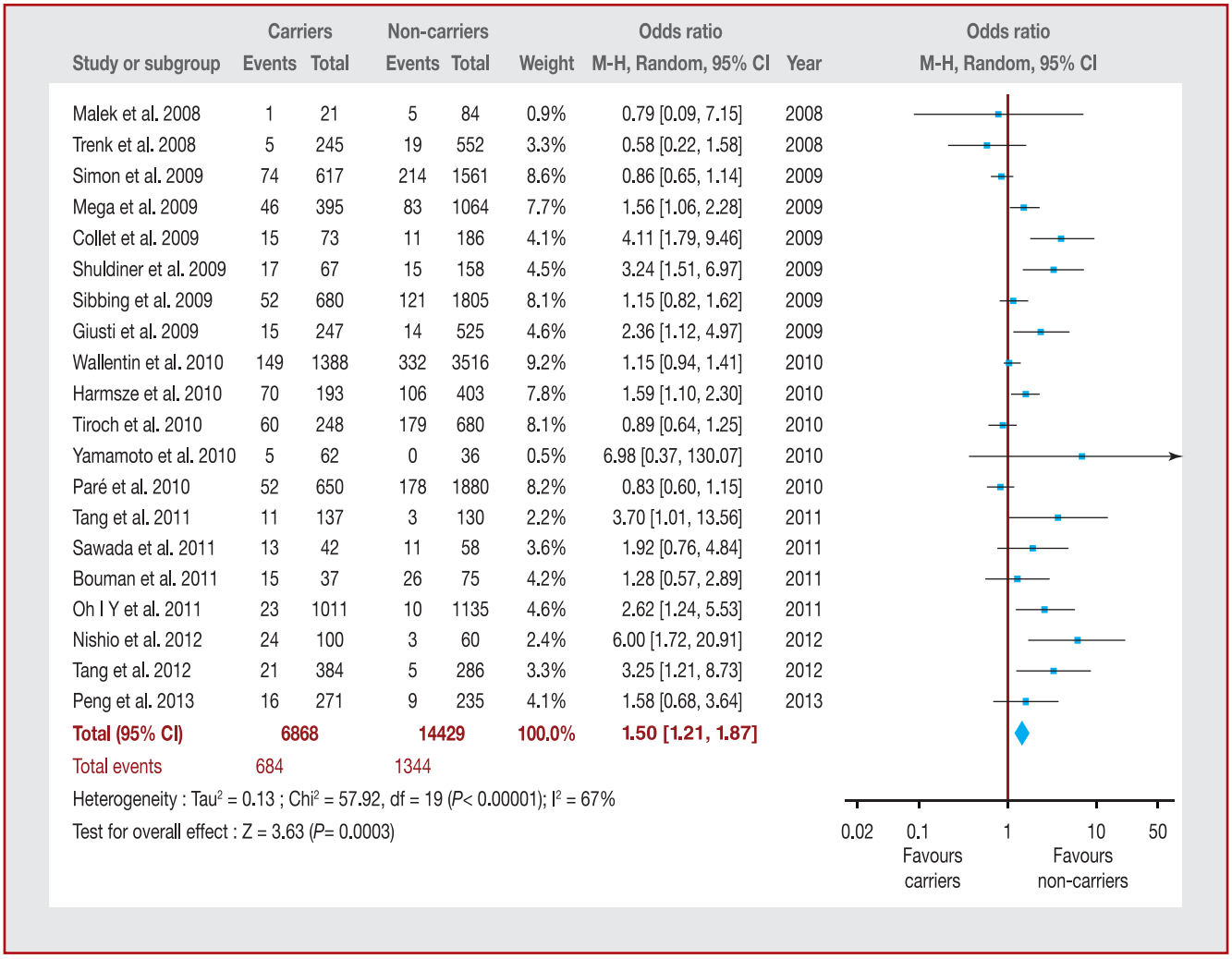

Figure 2. Forest plot of odds ratios for the occurrence of adverse clinical events (the composite of fatal or non-fatal myocardial infarction, cardiovascular or all-cause death, definite or probable stent thrombosis, target lesion revascularization, target vessel revascularization, urgent revascularization, ischaemic stroke and bleeding), according to *CYP2C19* gene variant.

clinical events than the 14,429 non-carriers (OR 1.50, 95% CI 1.21—1.87, $Z = 3.63$; $P = 0.0003$). In the subgroup analysis, we divided the studies into two subgroups according to ethnicity. The Asian and Caucasian subgroups consisted of seven studies [13,18—20,22,26,27] and 13 studies [15,21,28—38], respectively. In contrast to the Caucasian group ($I^2 = 68\%$; $P = 0.0002$), no statistical heterogeneity was found in the Asian group ($I^2 = 0\%$; $P = 0.61$); the results were also different (OR 1.27, 95% CI 1.02—1.58 vs OR 2.75, 95% CI 1.88—4.01, respectively). These data are shown in detail in Supplementary data, Figs. A and B.

Association between *CYP2C19* polymorphism and the risk of myocardial infarction

As shown in Fig. 3, 11 studies [13,18,19,25—28,31,32,35,36] involving 9745 participants were included here to assess the association between *CYP2C19* polymorphism and the risk of MI. As no statistical heterogeneity was found in this analysis ($P = 0.13$, $I^2 = 33\%$), we selected a fixed-effect model. The results showed that patients who carried a loss-of-function allele, mainly CYP2C19*2, had a higher risk of MI during follow-up (OR 1.62, 95% CI 1.35—1.95, $Z = 5.15$; $P < 0.00001$).

Association between *CYP2C19* polymorphism and the risk of stent thrombosis

Fig. 4 shows the result of the meta-analysis of the association between CYP2C19 polymorphism and the risk of ST. Thirteen studies [15,18,19,25,27—32,35,36,38] involving 14,261 patients were included in this analysis. There was no evidence of significant heterogeneity ($I^2 = 28\%$; $P = 0.16$) and data were assessed by the fixed-effect model. There was a two-fold increase in the rate of ST in carriers who underwent stent implantation compared to the non-carriers (OR 2.08, 95% CI 1.67—2.60, $Z = 6.51$; $P < 0.00001$).

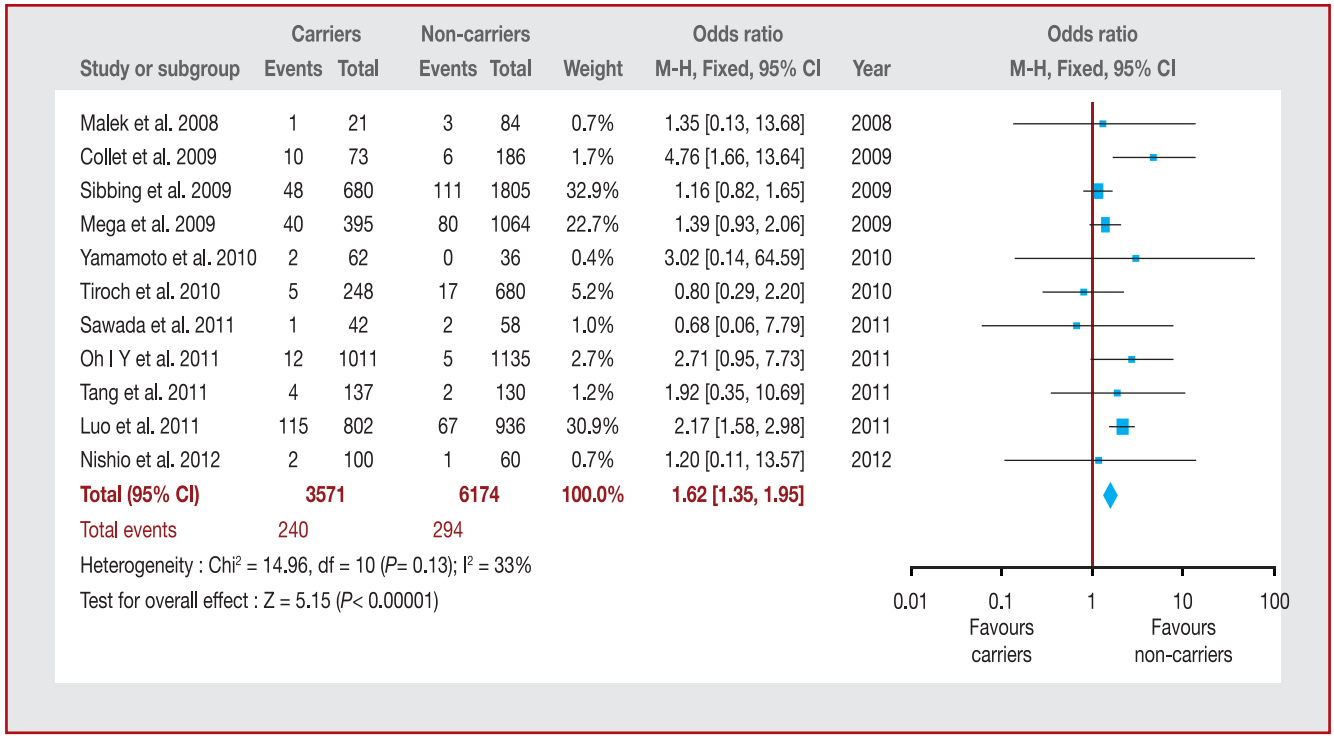

Figure 3. Forest plot of odds ratios for the occurrence of myocardial infarction, according to *CYP2C19* gene variant.

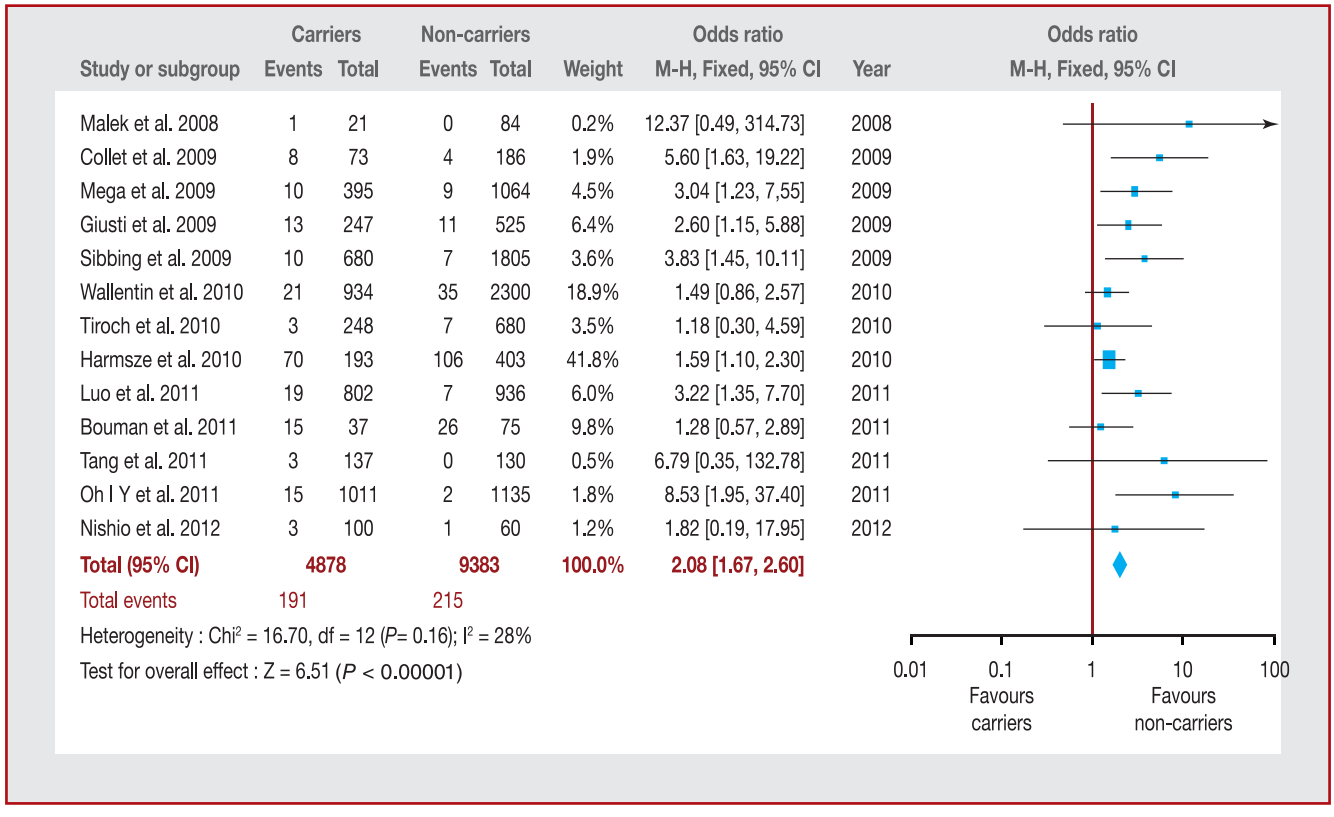

Figure 4. Forest plot of odds ratios for the occurrence of stent thrombosis, according to *CYP2C19* gene variant.

Table 2 Results of meta-analysis of the occurrence of other adverse clinical events, according to *CYP2C19* gene variant.

Comparisons	Carriers/non-carriers (*n*/*n*)	I^2 (%)	Analysis model	OR	95% CI	*P*
Mortality	4089/6934	36	Fixed	1.12	0.81—1.55	0.500
Ischaemic stroke	2187/4521	33	Fixed	2.14	1.36—3.38	0.001
Bleeding events	3609/7669	0	Fixed	1.01	0.85—1.19	0.930
Repeat revascularization	1882/2484	49	Fixed	1.35	1.10—1.66	0.004

CI: confidence interval; OR: odds ratio.

Association between *CYP2C19* polymorphism and the risk of mortality, ischaemic stroke, repeat revascularization and bleeding events

Overall, mortalities (cardiovascular death or all-cause death) were reported in 13 articles [13,18—20,25—29,31,32,35,36]. The numbers of studies that recorded occurrences of strokes, repeat revascularizations and bleeding events were five, seven and six, respectively. Data are shown in detail in (Supplementary data, Figs. C—F). Table 2 shows the results of the meta-analysis of these adverse clinical events. Carriers had a higher risk of ischaemic stroke (OR 2.14, 95% CI 1.36—3.38, $Z = 3.27$; $P = 0.001$) and repeat revascularization (OR 1.35, 95% CI 1.10—1.66, $Z = 2.87$; $P = 0.004$) than non-carriers. However, no statistically significant difference was found between the two groups in terms of risk of mortality or bleeding events.

Discussion

The combination of aspirin and clopidogrel is the mainstay anti-platelet strategy for preventing ischaemic events after PCI [39]. Clopidogrel is an inactive prodrug that requires oxidation by the CYP system. About 50% of the clopidogrel taken by patients is absorbed in the gastrointestinal tract. Only 15% of this clopidogrel is metabolized and activated in the liver. The thiophene ring of clopidogrel is oxidized to form an intermediate metabolite (2-oxo-clopidogrel). In the further oxidizing process, 2-oxo-clopidogrel opens the thiophene ring and breaks up into a carboxyl and thiol group. The reactive thiol group forms a disulphide bridge between one or more cysteine residues of the P2Y12 receptor and irreversibly blockades the platelet [6]. Despite the widespread use of clopidogrel and aspirin, the incidence rate of thrombotic stent occlusion after coronary stenting has been shown to be as high as 4.7% [4]. Recently, gene polymorphism of cytochrome *CYP2C19* was reported to be responsible for the high risk of adverse clinical outcomes in patients undergoing stent implantation [29,40]. The *CYP2C19* gene polymorphism is not uncommon. About 30% of Caucasians and 55% of Asians have one or more loss-of-function allele of CYP2C19.

Using the Newcastle-Ottawa quality assessment scale, we selected the potential articles strictly. All the included studies had a score of seven or more, which indicates the high quality of the evidence in this meta-analysis. According to the funnel plot shown in Supplementary data, Fig. G, the publication bias was acceptable. Some studies reported major adverse cardiovascular events [28,31,32,35,37,38,41], but others did not [15,25,30]. Finally, because of the different endpoints in the included studies, we defined these outcomes as ''adverse clinical events'' in this meta-analysis.

Using data from all 21 studies (7670 carriers and 15,365 non-carriers), we found that *CYP2C19* polymorphism was significantly associated with an increased risk of adverse clinical events among clopidogrel-treated patients. However, there was a statistical heterogeneity among the 20 included studies [13,15,18—22,26—38] ($I^2 = 67\%$; $P < 0.00001$). As a result, we chose a random-effect model. In the subgroup analysis, we found that carriers in Asia were more prone to adverse clinical events than patients in Western countries. In comparison with the Caucasian group, no statistical heterogeneity was found in the Asian group. In our opinion, ethnic diversity could be responsible for the heterogeneity in this meta-analysis. In addition, the difference in endpoints, follow-up periods and disease severities in the studies also contributed to the heterogeneity. Furthermore, no statistical heterogeneity was found in the analysis of MI and ST. Our results suggested a two-fold increase in the rate of ST and a 1.64-fold increase in the rate of MI in carriers compared with non-carriers during the follow-up period. Similar findings were observed in the meta-analyses performed by Jang et al. [41] and Zabalza et al. [42].

The relationships between *CYP2C19* polymorphism and mortality, ischaemic stroke, repeat revascularization and bleeding events were also assessed in our study. Although similar findings were reported by Jin et al. [43], previous systematic reviews [41—44] did not analyse the association between *CYP2C19* polymorphism and the risk of repeat revascularization. Here, we also found that *CYP2C19* variant gene carriers were more likely to experience repeat revascularization and ischaemic stroke.

Recently, the United States Food and Drug Administration added a warning to clopidogrel stating that patients with decreased *CYP2C19* function because genetic polymorphisms may metabolize clopidogrel poorly and have higher rates of cardiovascular events after ACS and PCI than patients with normal *CYP2C19* function [45]. Our findings present support the evidence for this warning. Given these findings, we think that pharmacogenomic testing for CAD patients who need long-term clopidogrel therapy, especially in Asian populations, will be necessary and helpful. By this means, we will then be able to predict their response to clopidogrel and make individualized treatment decisions. We

believe that this kind of genetic guided therapy is promising and may play a key role in our clinical practice in the foreseeable future. It just goes to show that P4 (predictive, preventive, personalized, participatory) medicine is coming [46].

If patients are *CYP2C19* variant gene carriers and display low or no anti-platelet response, other drugs should be taken into consideration [47]. The Food and Drug Administration has approved two additional P2Y12 receptor inhibitors for use in patients with ACS. Prasugrel and ticagrelor were more effective than clopidogrel at reducing clinical events, but at the expense of an increased risk of bleeding [48]. Prasugrel is a prodrug that requires conversion to its active metabolite. At least two observational studies have demonstrated no significant decrease in plasma concentrations of prasugrel active metabolite or platelet inhibition activity in carriers of at least one loss-of-function allele of the *CYP2C19* isoenzyme [49,50]. On the other hand, ticagrelor, the latest FDA-approved P2Y12 receptor inhibitor, is a reversible direct acting oral antagonist of the P2Y12 receptor that does not require transformation to an active metabolite [51]. Clinical use of genotyping and platelet function testing for prasugrel and ticagrelor is not rigorously established but it is less likely to be necessary given the lesser degree of variation in response than clopidogrel. According to the evidence [51], prasugrel should not be prescribed to patients with a history of transient ischaemic attack or stroke, or with active pathological bleeding for bleeding prevention. To reduce the risk of gastrointestinal hemorrhage, co-administration of proton pump inhibitors has also been recommended for patients who are at a higher risk of bleeding events [52].

Study limitations

Some limitations should be considered. First, only publications in English and Chinese were considered in our search process; some studies in other languages were inevitably lost. Second, the predetermined endpoints in the included studies were different. We could only extract information in part from these studies. Furthermore, the genotyping methods were not the same in the included studies. As a result, there is a detection bias to a certain degree. Besides, some included studies did not have adequate power to detect possible risk for *CYP2C19* polymorphism because of their small sample sizes. Lastly, the length of follow-up varied from 1 month to 4 years across the included studies. There is also an attrition bias to a certain degree. However, Peng et al. [20] recently reported that the adverse impact of the CYP2C19*2 gene mutation was significantly reduced after 1 year of discharge. Is *CYP2C19* polymorphism responsible for long-term prognosis in clopidogrel-treated patients? More studies are still needed.

Conclusions

In conclusion, the synthesis of available evidence indicates that *CYP2C19* polymorphism is significantly associated with clinical prognosis in coronary artery disease patients treated with clopidogrel.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Equal contributions were made to this article by Dr Chen Jian, Dr Liu Changzhi and Dr Liu Mao.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.acvd.2013.06.055.

References

[1] King 3rd SB, Smith Jr SC, Hirshfeld Jr JW, et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. J Am Coll Cardiol 2008;51:172—209.

[2] Savi P, Herbert JM. Clopidogrel ticlopidine: P2Y12 adenosine diphosphate-receptor antagonists for the prevention of atherothrombosis. Semin Thromb Hemost 2005;31:174—83.

[3] Lev EI, Patel RT, Maresh KJ, et al. Aspirin and clopidogrel drug response in patients undergoing percutaneous coronary intervention: the role of dual drug resistance. J Am Coll Cardiol 2006;47:27—33.

[4] Muller I, Besta F, Schulz C, et al. Prevalence of clopidogrel non-responders among patients with stable angina pectoris scheduled for elective coronary stent placement. Thromb Haemost 2003;89:783—7.

[5] Nguyen TA, Diodati JG, Pharand C. Resistance to clopidogrel: a review of the evidence. J Am Coll Cardiol 2005;45:1157—64.

[6] Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. J Am Coll Cardiol 2007;49:1505—16.

[7] Matetzky S, Shenkman B, Guetta V, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. Circulation 2004;109:3171—5.

[8] Sofi F, Marcucci R, Gori AM, et al. Clopidogrel non-responsiveness and risk of cardiovascular morbidity. An updated meta-analysis. Thromb Haemost 2010;103:841—8.

[9] Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Contribution of gene sequence variations of the hepatic cytochrome P450 3A4 enzyme to variability in individual responsiveness to clopidogrel. Arterioscler Thromb Vasc Biol 2006;26:1895—900.

[10] Frere C, Cuisset T, Gaborit B, et al. The CYP2C19*17 allele is associated with better platelet response to clopidogrel in patients admitted for non-ST acute coronary syndrome. J Thromb Haemost 2009;7:1409—11.

[11] Brandt JT, Close SL, Iturria SJ, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. J Thromb Haemost 2007;5:2429—36.

[12] Kim KA, Park PW, Hong SJ, et al. The effect of CYP2C19 polymorphism on the pharmacokinetics and pharmacodynamics of

clopidogrel: a possible mechanism for clopidogrel resistance. Clin Pharmacol Ther 2008;84:236—42.
[13] Yamamoto K, Hokimoto S, Chitose T, et al. Impact of CYP2C19 polymorphism on residual platelet reactivity in patients with coronary heart disease during anti-platelet therapy. J Cardiol 2011;57:194—201.
[14] Akhlaghi A, Shirani S, Ziaie N, et al. Cytochrome P450 2C19 polymorphism in Iranian patients with coronary artery disease. ARYA Atheroscler 2011;7:106—10.
[15] Bouman HJ, Schomig E, van Werkum JW, et al. Paraoxonase-1 is a major determinant of clopidogrel efficacy. Nat Med 2011;17:110—6.
[16] Hwang SJ, Jeong YH, Kim IS, et al. The cytochrome 2C19*2 and *3 alleles attenuate response to clopidogrel similarly in East Asian patients undergoing elective percutaneous coronary intervention. Thromb Res 2011;127:23—8.
[17] Malek LA, Przyluski J, Spiewak M, et al. Cytochrome P450 2C19 polymorphism, suboptimal reperfusion and all-cause mortality in patients with acute myocardial infarction. Cardiology 2010;117:81—7.
[18] Nishio R, Shinke T, Otake H, et al. Effect of cytochrome P450 2C19 polymorphism on target lesion outcome after drug-eluting stent implantation in japanese patients receiving clopidogrel. Circ J 2012;76:2348—55.
[19] Oh IY, Park KW, Kang SH, et al. Association of cytochrome P450 2C19*2 polymorphism with clopidogrel response variability and cardiovascular events in Koreans treated with drug-eluting stents. Heart 2012;98:139—44.
[20] Peng Y, Chen M, Liu XJ, et al. The CYP2C19 genotype does not impact the long-term prognosis of patients with coronary artery disease. Atherosclerosis 2013;227:106—11.
[21] Simon T, Verstuyft C, Mary-Krause M, et al. Genetic determinants of response to clopidogrel and cardiovascular events. N Engl J Med 2009;360:363—75.
[22] Tang XF, Wang J, Zhang JH, et al. Effect of the CYP2C19 2 and 3 genotypes ABCB1 C3435 T and PON1 Q192R alleles on the pharmacodynamics and adverse clinical events of clopidogrel in Chinese people after percutaneous coronary intervention. Eur J Clin Pharmacol 2013;69:1103—12.
[23] Wells G, Beaton D, Shea B, et al. Minimal clinically important differences: review of methods. J Rheumatol 2001;28:406—12.
[24] Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.; 2013 [Available at: http://www.ohri.ca/PROGRAMS/CLINICAL_EPIDEMIOLOGY/OXFORD.ASP (accessed 12 Feb. 2013)].
[25] Luo Y, Zhao YT, Verdo A, et al. Relationship between cytochrome P450 2C19*2 polymorphism and stent thrombosis following percutaneous coronary intervention in Chinese patients receiving clopidogrel. J Int Med Res 2011;39:2012—9.
[26] Sawada T, Shinke T, Shite J, et al. Impact of cytochrome P450 2C19*2 polymorphism on intra-stent thrombus after drug-eluting stent implantation in Japanese patients receiving clopidogrel. Circ J 2011;75:99—105.
[27] Tang XF, He C, Yuan JQ, et al. Impact of cytochrome P450 2C19 polymorphisms on outcome of cardiovascular events in clopidogrel-treated Chinese patients after percutaneous coronary intervention. Zhonghua Xin Xue Guan Bing Za Zhi 2011;39:617—20.
[28] Collet JP, Hulot JS, Pena A, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. Lancet 2009;373:309—17.
[29] Giusti B, Gori AM, Marcucci R, et al. Relation of cytochrome P450 2C19 loss-of-function polymorphism to occurrence of drug-eluting coronary stent thrombosis. Am J Cardiol 2009;103:806—11.
[30] Harmsze AM, van Werkum JW, Ten Berg JM, et al. CYP2C19*2 and CYP2C9*3 alleles are associated with stent thrombosis: a case-control study. Eur Heart J 2010;31:3046—53.
[31] Malek LA, Kisiel B, Spiewak M, et al. Coexisting polymorphisms of P2Y12 and CYP2C19 genes as a risk factor for persistent platelet activation with clopidogrel. Circ J 2008;72:1165—9.
[32] Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med 2009;360:354—62.
[33] Pare G, Mehta SR, Yusuf S, et al. Effects of CYP2C19 genotype on outcomes of clopidogrel treatment. N Engl J Med 2010;363:1704—14.
[34] Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the anti-platelet effect and clinical efficacy of clopidogrel therapy. JAMA 2009;302:849—57.
[35] Sibbing D, Stegherr J, Latz W, et al. Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. Eur Heart J 2009;30:916—22.
[36] Tiroch KA, Sibbing D, Koch W, et al. Protective effect of the CYP2C19 *17 polymorphism with increased activation of clopidogrel on cardiovascular events. Am Heart J 2010;160:506—12.
[37] Trenk D, Hochholzer W, Fromm MF, et al. Cytochrome P450 2C19 681G>A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. J Am Coll Cardiol 2008;51:1925—34.
[38] Wallentin L, James S, Storey RF, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. Lancet 2010;376:1320—8.
[39] Gasparyan AY, Watson T, Lip GY. The role of aspirin in cardiovascular prevention: implications of aspirin resistance. J Am Coll Cardiol 2008;51:1829—43.
[40] Desta Z, Zhao X, Shin JG, et al. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. Clin Pharmacokinet 2002;41:913—58.
[41] Jang JS, Cho KI, Jin HY, et al. Meta-analysis of cytochrome P450 2C19 polymorphism and risk of adverse clinical outcomes among coronary artery disease patients of different ethnic groups treated with clopidogrel. Am J Cardiol 2012;110:502—8.
[42] Zabalza M, Subirana I, Sala J, et al. Meta-analyses of the association between cytochrome CYP2C19 loss- and gain-of-function polymorphisms and cardiovascular outcomes in patients with coronary artery disease treated with clopidogrel. Heart 2012;98:100—8.
[43] Jin B, Ni HC, Shen W, et al. Cytochrome P450 2C19 polymorphism is associated with poor clinical outcomes in coronary artery disease patients treated with clopidogrel. Mol Biol Rep 2011;38:1697—702.
[44] Hulot JS, Collet JP, Silvain J, et al. Cardiovascular risk in clopidogrel-treated patients according to cytochrome P450 2C19*2 loss-of-function allele or proton pump inhibitor coadministration: a systematic meta-analysis. J Am Coll Cardiol 2010;56:134—43.
[45] Holmes Jr DR, Dehmer GJ, Kaul S, et al. ACCF/AHA Clopidogrel clinical alert: approaches to the FDA ''boxed warning'': a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association. Circulation 2010;122:537—57.
[46] Auffray C, Charron D, Hood L. Predictive, preventive, personalized and participatory medicine: back to the future. Genome Med 2010;2:57.
[47] Cuisset T, Cayla G, Silvain J. Clopidogrel resistance: what's new? Arch Cardiovasc Dis 2010;103:349—53.

[48] Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2012;60:645—81.

[49] Mega JL, Close SL, Wiviott SD, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. Circulation 2009;119:2553—60.

[50] Varenhorst C, James S, Erlinge D, et al. Genetic variation of CYP2C19 affects both pharmacokinetic and pharmacodynamic responses to clopidogrel but not prasugrel in aspirin-treated patients with coronary artery disease. Eur Heart J 2009;30:1744—52.

[51] Cannon CP, Husted S, Harrington RA, et al. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate-receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. J Am Coll Cardiol 2007;50:1844—51.

[52] Gerson LB. Proton pump inhibitors and potential interactions with clopidogrel: an update. Curr Gastroenterol Rep 2013;15:329.