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’événements indésirables chez des patients traités par clopidogrel : méta-analyse de 23 035 sujets

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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).

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

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.

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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, genotyping 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, TLR, TVR, 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.

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] (I² = 67%, P < 0.0001) 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
Table 1  Main characteristics of all the studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Study population</th>
<th>Age (years)</th>
<th>Carriers/non-carriers (n/n)</th>
<th>Clopidogrel dose (LD→MD)</th>
<th>Follow-up (months)</th>
<th>Endpoints</th>
<th>Genotyping method</th>
<th>Genetic variant</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nishio et al. [18]</td>
<td>2012</td>
<td>Japan</td>
<td>PCI</td>
<td>69.8</td>
<td>100/60</td>
<td>300 mg → 75 mg/day</td>
<td>21.5</td>
<td>Death, ST, MI, TLR</td>
<td>TaqMan PCR</td>
<td>*2, *3</td>
<td>9</td>
</tr>
<tr>
<td>Peng et al. [20]</td>
<td>2013</td>
<td>China</td>
<td>CAD</td>
<td>64.9</td>
<td>271/235</td>
<td>300 mg → 75 mg/day</td>
<td>12</td>
<td>Non-fatal MI, death, stroke, revascularization</td>
<td>TaqMan PCR</td>
<td>*2</td>
<td>9</td>
</tr>
<tr>
<td>Trenk et al. [37]</td>
<td>2008</td>
<td>Germany</td>
<td>Elective PCI</td>
<td>66.3</td>
<td>245/552</td>
<td>600 mg → 75 mg/day</td>
<td>12</td>
<td>RPA, death, non-fatal MI</td>
<td>TaqMan PCR</td>
<td>*2</td>
<td>9</td>
</tr>
<tr>
<td>Harmsze et al. [30]</td>
<td>2010</td>
<td>Netherlands</td>
<td>PCI</td>
<td>62.7</td>
<td>193/403</td>
<td>NA</td>
<td>12</td>
<td>ST</td>
<td>PCR</td>
<td>*2, *3</td>
<td>8</td>
</tr>
<tr>
<td>Tang et al. [22]</td>
<td>2012</td>
<td>China</td>
<td>PCI</td>
<td>58.9</td>
<td>384/286</td>
<td>300 mg → 75 mg/day</td>
<td>12</td>
<td>Cardiovascular death, MI, TVR, ST</td>
<td>TaqMan PCR</td>
<td>*2, *3, *17</td>
<td>9</td>
</tr>
<tr>
<td>Bouman et al. [15]</td>
<td>2011</td>
<td>Germany</td>
<td>CAD + PCI</td>
<td>61.2</td>
<td>37/75</td>
<td>600 mg → 75 mg/day</td>
<td>18</td>
<td>ST</td>
<td>TaqMan PCR</td>
<td>*2</td>
<td>9</td>
</tr>
<tr>
<td>Sawada et al. [26]</td>
<td>2011</td>
<td>Japan</td>
<td>PCI</td>
<td>69.6</td>
<td>42/58</td>
<td>300 mg → 75 mg/day</td>
<td>18.2</td>
<td>ST, death, MI, TVR</td>
<td>TaqMan PCR</td>
<td>*2</td>
<td>7</td>
</tr>
<tr>
<td>Pare et al. [33]</td>
<td>2010</td>
<td>Canada</td>
<td>NSTE-ACS</td>
<td>63.8</td>
<td>650/1880</td>
<td>300 mg → 75 mg/day</td>
<td>12</td>
<td>Death, non-fatal MI</td>
<td>TaqMan PCR</td>
<td>*2, *3</td>
<td>9</td>
</tr>
<tr>
<td>Yamamoto et al. [13]</td>
<td>2010</td>
<td>Japan</td>
<td>Stable CHD</td>
<td>68.6</td>
<td>62/36</td>
<td>300 mg → 75 mg/day</td>
<td>12</td>
<td>Death, non-fatal MI</td>
<td>PCR</td>
<td>*2, *3</td>
<td>8</td>
</tr>
<tr>
<td>Giusti et al. [29]</td>
<td>2009</td>
<td>Italy</td>
<td>ACS + PCI</td>
<td>NA</td>
<td>247/525</td>
<td>600 mg → 75 mg/day</td>
<td>6</td>
<td>Death, non-fatal MI</td>
<td>PCR</td>
<td>*2</td>
<td>9</td>
</tr>
<tr>
<td>Collet et al. [28]</td>
<td>2009</td>
<td>France</td>
<td>MI</td>
<td>40.1</td>
<td>73/186</td>
<td>NA → 75 mg/day</td>
<td>&gt; 48</td>
<td>Death, non-fatal MI</td>
<td>TaqMan PCR</td>
<td>*2</td>
<td>9</td>
</tr>
<tr>
<td>Shuldiner et al. [34]</td>
<td>2009</td>
<td>America</td>
<td>Elective PCI</td>
<td>65.1</td>
<td>67/158</td>
<td>600 or 300 mg → 75 mg/day</td>
<td>12</td>
<td>Cardiovascular death, MI, urgent revascularization MI, stroke, ST, death</td>
<td>SNPlex&lt;sup&gt;a&lt;/sup&gt;</td>
<td>*2</td>
<td>9</td>
</tr>
<tr>
<td>Wallentin et al. [38]</td>
<td>2010</td>
<td>America, Europe</td>
<td>ACS</td>
<td>62.5</td>
<td>1388/3516</td>
<td>600 or 300 mg → 75 mg/day</td>
<td>12</td>
<td>Cardiovascular death, MI, stroke</td>
<td>TaqMan PCR</td>
<td>*2,*8,*17</td>
<td>8</td>
</tr>
<tr>
<td>Tiroch et al. [36]</td>
<td>2010</td>
<td>Germany</td>
<td>Acute MI</td>
<td>64.8</td>
<td>248/680</td>
<td>600 mg → 75 mg/day</td>
<td>12</td>
<td>TLR, death, MI</td>
<td>TaqMan PCR</td>
<td>*2, *17</td>
<td>9</td>
</tr>
<tr>
<td>Mega et al. [32]</td>
<td>2009</td>
<td>America, Europe</td>
<td>ACS + PCI</td>
<td>60.1</td>
<td>395/1064</td>
<td>300 mg → 75 mg/day</td>
<td>15</td>
<td>Cardiovascular death, MI, stroke</td>
<td>PCR</td>
<td>*2</td>
<td>9</td>
</tr>
<tr>
<td>Sibbing et al. [35]</td>
<td>2009</td>
<td>Germany</td>
<td>CAD + PCI</td>
<td>66.5</td>
<td>680/1805</td>
<td>600 mg → 75 mg/day</td>
<td>1</td>
<td>ST</td>
<td>TaqMan PCR</td>
<td>*2</td>
<td>8</td>
</tr>
<tr>
<td>Simon et al. [21]</td>
<td>2009</td>
<td>France</td>
<td>Acute MI</td>
<td>66.2</td>
<td>617/1561</td>
<td>300–900 mg → 12 75 mg/day</td>
<td>12</td>
<td>Death, non-fatal MI</td>
<td>SNPlex&lt;sup&gt;a&lt;/sup&gt;</td>
<td>*2,*5,*17</td>
<td>8</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Country</td>
<td>Study population</td>
<td>Age (years)</td>
<td>Carriers/non-carriers (n/n)</td>
<td>Clopidogrel dose (LD → MD)</td>
<td>Follow-up (months)</td>
<td>Endpoints</td>
<td>Genotyping method</td>
<td>Genetic variant</td>
<td>NOS</td>
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<tr>
<td>Malek et al.</td>
<td>2008</td>
<td>Poland</td>
<td>ACS + PCI</td>
<td>60.0</td>
<td>21/84</td>
<td>300 or 600 mg → 75 mg/day</td>
<td>12</td>
<td>Death, MI</td>
<td>TaqMan PCR</td>
<td>*2</td>
<td>8</td>
</tr>
<tr>
<td>Tang et al.</td>
<td>2011</td>
<td>China</td>
<td>CHD + PCI</td>
<td>58.0</td>
<td>137/130</td>
<td>300 mg → 75 mg/day</td>
<td>12</td>
<td>Death, angina recurrence, MI, urgent revascularization, ST, death, MI, ischaemic stroke, bleeding Death, non-fatal MI, ST, TVR, TLR</td>
<td>MALDI-TOF MS</td>
<td>*2</td>
<td>9</td>
</tr>
<tr>
<td>Luo et al.</td>
<td>2011</td>
<td>China</td>
<td>CHD + PCI</td>
<td>70.8</td>
<td>802/936</td>
<td>300 mg → 75 mg/day</td>
<td>6</td>
<td>ST, death, MI, ischaemic stroke, bleeding Death, non-fatal MI, ST, TVR, TLR</td>
<td>TaqMan PCR</td>
<td>*2</td>
<td>9</td>
</tr>
<tr>
<td>Oh et al.</td>
<td>2011</td>
<td>Korea</td>
<td>PCI</td>
<td>60.8</td>
<td>1011/1135</td>
<td>300 or 600 mg → 75 mg/day</td>
<td>12</td>
<td>ST, death, MI, ischaemic stroke, bleeding Death, non-fatal MI, ST, TVR, TLR</td>
<td>TaqMan PCR</td>
<td>*2</td>
<td>9</td>
</tr>
</tbody>
</table>

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; TVR: target vessel revascularization.

* Applied Biosystems, Foster City, CA, USA.
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 (I² = 68%; P = 0.0002), no statistical heterogeneity was found in the Asian group (I² = 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, I² = 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 (I² = 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).
Cytochrome CYP2C19 polymorphism and adverse events

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.
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 blocks 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.
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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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.

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