Nonresponders to clopidogrel: pharmacokinetics and interactions involved

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**Importance of the field:** The use of clopidogrel and aspirin has become standard therapy in patients with acute coronary syndromes and stent implantation. However, concern arises because about 25% of subjects are nonresponders to clopidogrel. This nonresponsiveness is associated with a threefold increase in adverse outcomes. Clopidogrel resistance is multifactorial, but genetic polymorphisms in clopidogrel's metabolic activation (e.g., cytochrome P450 2C19) and drug–drug interactions at this level (e.g., between proton pump inhibitors (PPIs) and clopidogrel) are both associated with decreased clopidogrel efficacy. Despite all PPIs being potent inhibitors of CYP2C19, evidence about their clinical impact is controversial.

**Areas covered in this review:** Pharmacogenomic and pharmacokinetic aspects of clopidogrel nonresponsiveness were considered in detail.

**What the reader will gain:** The reader will gain an exhaustive review of the current state of the controversial issues regarding genetic polymorphisms and drug–drug interactions affecting clopidogrel efficacy.

**Take home message:** It is important to consider clopidogrel resistance in some patients and establish strategies to handle this problem (e.g., genotyping, platelet aggregability tests, new antiplatelet drugs). The combined use of PPIs and clopidogrel is at present regulated by the FDA and EMEA; however, the risk/benefit balance should be made for each patient individually.

**Keywords:** clopidogrel, interactions, nonresponders, pharmacogenomic, pharmacokinetic


1. Introduction

Since the publication of the results of the CURE [1] and PCI-CURE [2] trials, a true revolution has come in the management of antiplatelet therapy for acute coronary syndromes (ACS). These trials provided the initial evidence supporting the efficacy of dual antiplatelet therapy of aspirin and clopidogrel in reducing major cardiovascular events and stent thrombosis in patients with non-ST elevation ACS and for those treated with coronary percutaneous intervention (PCI). Additional research led to the use of dual antiplatelet therapy in patients with ST-elevation ACS irrespective of the reperfusion strategy adopted [3,4]. The effectiveness of combination therapy and its safety was also demonstrated [5], and it became the standard of care for patients with ACS or those submitted to stent implantation [6,7]. However, despite the amount of evidence favoring the use of clopidogrel, there still remains a variable proportion of patients who suffered cardiovascular events under such treatment [8]. In a recent meta-analysis of 3960 patients from 15 trials (including randomized or observational prospective studies in which clopidogrel activity had been measured by light transmission aggregometry), Combescure et al. [9] estimated that the presence of clopidogrel
3. Clopidogrel pharmacokinetics and pharmacogenomics

3.1 An overview of clopidogrel pharmacokinetics

After its absorption in the intestine, clopidogrel needs to be activated in the liver. This biotransformation process involves many mono-oxygenases of the cytochrome P450 system [11]. As shown in Figure 1, the first oxidative reaction involves CYP1A2, CYP2B6 and CYP2C19 enzymes and leads to the production of 2-oxo-clopidogrel, an inactive intermediary. Kazui et al. [12] recently demonstrated that CYP2C19 makes the key contribution to this oxidative phase. The following step is the conversion of 2-oxo-clopidogrel into its active thiol metabolite (R130964). In this case, the main contributor is CYP3A4, followed by CYP2C19 (Figure 1). According to these data, any modification in CYP2C19 and, to a lesser extent, in CYP3A4 or 3A5 functioning will influence the conversion rate of clopidogrel into its active metabolite. This phenomenon, in which the concentration of the active metabolite relies on the activity of a single key metabolic pathway, is considered a clear example of the so-called 'high-risk pharmacokinetic profile' [13] and would have clinical relevance, as described below.

Interestingly, clopidogrel is a thienopyridine derivative containing an asymmetric carbon, which results in the existence of two enantiomers (R and S), of which the S-enantiomer is the active compound [14-16]. As required by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [17], the content of the inactive R-enantiomer must be carefully controlled in bulk substance and drug products. Also, according to the ICH guideline on impurities in new drug products [17], the level of impurities in the product should be carefully controlled, and the upper level of these impurities should be determined and supported by adequate data in the registration application. In a study comparing the purity of 18 clopidogrel copies with the original branded product, Gomez et al. [18] found high levels of impurities in the copies. More than 60% of the copies contained more than fourfold the amount of hydrolysis product or R-enantiomer compared with the reference product. Because the R-enantiomer is devoid of anti-aggregatory activity [14,19], it makes sense that evaluation of the S-enantiomer should be required in studies of the bioequivalence of clopidogrel formulations. For the same reason, the active metabolite of clopidogrel should be measured. The impact of these potentially confounding factors in these studies is unknown, and the relevance of this phenomenon in studies addressing nonresponsiveness to clopidogrel should be addressed.

3.2 Pharmacogenomics of clopidogrel nonresponse

It is difficult to assess the prevalence of clopidogrel unresponsiveness, defined by the lack of the inhibitory effect over platelets. However, in a meta-analysis including 4564 patients with coronary heart disease, Sofi et al. [20] reported a

nonresponse was associated with a threefold increase in the risk of recurrent ischemic events (relative risk (RR) = 3.53; 95% CI 2.39 – 5.20). The mechanism underlying the poor response to clopidogrel is still a matter of research and debate. The categorization of a patient as a nonresponder case is essentially based on biochemical indicators and tests that evaluate the extent of platelet inhibition after clopidogrel treatment. There are many definitions and methods to test clopidogrel response variability [8]. As stated by Angiolillo et al. [10], this variability is multifactorial in essence, comprising genetic (single-nucleotide polymorphisms in genes related to the drug’s pathway), cellular (expression of receptors for clopidogrel, platelet turnover) and clinical factors (diabetes, chronic renal failure, age, sex). In this review we examine some of these mechanisms.

Clopidogrel is a prodrug that needs to be activated to inhibit platelets. This has led to an large increase in information related to pharmacokinetic factors implied in clopidogrel metabolism and effects in recent years. Therefore, we focus on the pharmacokinetic issues that may affect clopidogrel efficacy.

2. Methods

A Medline search of published papers including pharmacokinetic, pharmacodynamic and pharmacogenomic information related to clopidogrel and mechanisms for clopidogrel resistance was done. Terms included in the primary search (up to December 2009) were: clopidogrel, proton pump inhibitors, pharmacokinetics and pharmacogenomics. All abstracts were reviewed and selected articles were retrieved. A secondary search was carried out from references of articles from the first search. Information from abstracts and presentations at the 2010 American College of Cardiology scientific sessions was also included. Relevant information on these aspects was registered and compiled.
frequency of 26.4% of clopidogrel unresponsiveness. This author reports that, after 1 year of follow-up, residual platelet activity was associated with a fivefold increase in the risk of death or thrombotic recurrences. These figures are similar to those found by Combescure et al. [9] in their meta-analysis of 3290 patients, in which on average 25% of subjects revealed nonresponse to clopidogrel. As mentioned before, one of the key hypotheses to explain this phenomenon resides in the genetically determined modifications in the pharmacokinetic profile of clopidogrel. Because CYP2C19 is involved in both reactions that lead to active clopidogrel, it is a key player in drug response variability. In general terms, loss-of-function variants of CYP2C19 (2C19*2 and 2C19*3) account for more than 95% of poor metabolism in clinically relevant medications [21]. Despite it being a controversial issue, it is estimated that 2–15% of Caucasians [22], 4% of Blacks, and 10–25% of Southeast Asians exhibit these poor metabolism variants [23]. The rationale for this line of research is shown in Figure 2. Regarding the influence of CYP2C19 loss-of-function polymorphisms on clopidogrel response, Hulot et al. [24] reported that healthy subjects heterozygous for the 2C19*2 variant had less inhibitory response to clopidogrel, using two different tests to assess platelet function. The next challenge was to demonstrate the link between polymorphisms and suboptimal platelet inhibition in patients under clopidogrel treatment. This hypothesis was tested by Giusti et al. [25] in a sample of 1419 patients with ACS under treatment with clopidogrel. In this study, carriers of the loss-of-function allele had more residual platelet activity than other patients. Carriers of the CYP2C19*2 allele had higher platelet aggregation levels than noncarriers (p = 0.001). These authors also found that this genotype was an independent predictor of response variability to clopidogrel.

How much of this variability in response is attributable to genetic polymorphisms of the CYP2C19 is still a difficult question to answer. Shuldiner et al. [26] identified some genetic variants related to ex vivo clopidogrel response (assessed by aggregometry) in 429 apparently healthy Amish persons. Because genetic polymorphisms are heritable, the inclusion of an Amish community, in which all individuals
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Figure 2. Relationship between genomic polymorphism in clopidogrel biotransformation and its efficacy and effectiveness. 
CV: Cardiovascular; CYP: Cytochrome P450.

are highly related, seems to offer an optimal approach to test this topic. Performing a genome-wide association study, these authors found a cluster of 13 single nucleotide polymorphisms, near the coding region for CYP2C19, which are associated with a reduced response to clopidogrel. Amish persons homozygous for CYP2C19*2 (2.1% of the population) had the poorest response to clopidogrel. Subjects with 0, 1 and 2 copies of this allele had 40.7, 47.1 and 65.4%, respectively, of reduction in ADP-induced platelet aggregation. It was estimated that the presence of the CYP2C19*2 genotype accounted for 12% of the variability in the clopidogrel response. These findings were verified in an independent cohort of patients who underwent programmed percutaneous coronary intervention (PCI) in whom the presence of the CYP2C19*2 polymorphism was associated with a greater residual platelet activity, and, perhaps more important, to an increased risk of cardiovascular ischemic event or death at 1 year of follow-up (hazard ratio (HR) = 2.42, 95% CI 1.69 – 8.05, p = 0.0005) and stent thrombosis (HR = 6.02, 95% CI 1.81-20.04; p = 0.0009) in carriers than in noncarriers. One of the limitations of this study is that it focused on only one variant of single nucleotide polymorphism. The study by Simon et al. [29] evaluated this problem. These authors studied 2208 patients admitted for acute myocardial infarction to the French registry FAST-MI. All subjects received clopidogrel and were followed up for 1 year after the index event. Samples were tested for single nucleotide polymorphisms at genes ABCB1 (that modulate clopidogrel absorption), P2RY12 and ITGB3 (both related to the mechanism of action), CYP3A5 and CYP2C19. Two ABCB1 polymorphisms were associated with an increased risk of cardiovascular events (HR = 1.72, 95% CI 1.20 – 2.47). An interesting finding was an elevated event rate (death, nonfatal myocardial infarction, or stroke) observed in carriers of CYP2C19 loss-of-function polymorphisms *2, *3, *4 and *5 (HR = 1.98, 95% CI 1.10 – 3.58), especially in those subjects homozygous for such polymorphisms. In the subgroup of carriers of such variants who underwent PCI, the outcome was much worse (HR = 3.58, 95% CI 1.71 – 7.51). No association was observed with other assessed polymorphisms.

Another study that contributed to the topic was carried out by Mega et al. [30], who investigated the complete pathway that goes from CYPs’ genetic polymorphism, through active clopidogrel levels and platelet function, to their clinical impact. In 162 healthy subjects treated with clopidogrel, they initially assessed the association between genetic variants of all CYPs involved in clopidogrel metabolism (1A2, 2B6, 2C9, 2C19, and 3A5), plasma levels of active clopidogrel and platelet inhibition. An inverse relationship for loss-of-function polymorphism and active clopidogrel levels was observed for CYP2C19 and, to a much lesser extent, CYP2B6. According to these data, patients were classified as ‘ultrarapid’, ‘extensive’, ‘intermediate’ and ‘poor’ metabolizers if they had at least one copy of the CYP2C19 loss-of-function allele. Therefore, following a gradient pattern across the metabolizer type, the lower activated clopidogrel concentration had the higher residual platelet reactivity. The second phase of the trial involved the
genotyping of DNA samples from 1477 patients with ACS, participants of the TRITON-TIMI38 [31] trial who were assigned to clopidogrel. Cardiovascular outcomes were measured in subject carriers and noncarriers of the CYP2C19 loss-of-function variant. At 1.5 years of follow-up, carriers had significantly more ischemic events (death from cardiovascular cause, myocardial infarction or stroke) than noncarriers (HR = 1.53, 95% CI 1.07 – 2.19). Similar results were observed for stent thrombosis (HR = 3.09, 95% CI 1.19 – 8.00).

As mentioned before, the other CYPs involved in clopidogrel activation are CYP3A4 and CYP3A5. CYP3A4, 3A5 accounts for ~50% of the CYP3A system activity in the liver [32]. Evidence regarding the influence of CYP3A single nucleotide polymorphisms over clopidogrel efficacy and effectiveness is contradictory. Small studies have revealed a link between clopidogrel, loss-of-function polymorphisms, residual platelet activation and cardiovascular events. In a two-phase study, Suh et al. [33] selected 32 healthy subjects and genotyped them for CYP3A5. After treatment with clopidogrel they compared platelet aggregation in carriers and noncarriers of the loss-of-function allele CYP3A5*3. It was found that carriers had more impaired platelet function than noncarriers. In a second phase, 348 patients submitted for PCI and stent implantation, who had been treated with clopidogrel, were genotyped for these variants. After a 6-month follow-up period it was observed that carriers had a lower cardiovascular events rate (cardiovascular death, myocardial infarction, nonhemorrhagic stroke) compared with noncarriers. However, these results are inconsistent, and other authors did not reach similar conclusions [24,30,34]. Regarding CYP3A4 polymorphisms, studying 82 patients under clopidogrel, Angiolillo et al. [35] observed that carriers of the IVS10+12G>A polymorphism displayed a higher platelet reactivity than noncarriers. Again, these findings are inconsistent and other publications suggested different results [25,34]. Therefore, the evidence that supports the influence of CYP3A4/5 polymorphisms on clopidogrel pharmacokinetics or pharmacodynamics is inconclusive. The information is also controversial for the rest of the CYPs variants involved in clopidogrel metabolism [36].

In summary, the available evidence supports some CYP2C19 polymorphisms on clopidogrel efficacy and effectiveness. As it can be easily understood, the translation of such information into the clinical setting is difficult to practice. As it was pointed out by Storey [37], in an acute setting (e.g., in a case of an ST-evation ACS), genotyping of patients in order to adjust therapy (in a yet undefined way) is not an option, mainly because any delay in reperfusion therapy would represent a reduction in myocardial salvage and survival. Despite the recent availability of ‘point-of-care’ devices to assess platelet function, in patients with ST-segment elevation myocardial infarction they are not a valid alternative because it would be necessary to wait 6 – 12 h from the administration of clopidogrel to evaluate its response. However, in patients with non-ST-elevation ACS in a nonurgent condition, these devices could be an option to genotyping [20]. Finally, there are an increasing number of new drugs available as alternatives to clopidogrel for such patients. By contrast, for patients to be submitted to a programmed PCI, it could be useful to know beforehand its loss-of-function polymorphism carrier condition. But, even in these cases, more research is also required to assess the effectiveness of such approach.

### 3.3 Pharmacokinetic drug–drug interactions and clopidogrel

Because the CYP450 system accounts for at least 50% of the metabolism of the most common drugs used in practice [21], it is logical to expect that drugs metabolized through this pathway are susceptible to drug–drug interactions. In some cases the problem relies on the coadministration of drugs that compete for the same metabolic pathway. For many years it was believed that the main CYP involved in clopidogrel activation was CYP3A4/5. Therefore, it was considered necessary to explore if cotreatment with drugs such as those listed in Table 1 [38] could affect clopidogrel activation. According to these data, Lau et al. [59] investigated the effect of the coadministration of clopidogrel and atorvastatin (a drug that could probably compete with clopidogrel at the level of CYP3A4 metabolism) on their pharmacokinetics. This study also has clinical relevance because this combination represents a very frequently used association as most of the patients who have coronary artery disease also exhibit hypercholesterolemia. In a sample of 44 patients submitted to PCI and stent placement, the authors treated 19 patients with clopidogrel alone, 9 with clopidogrel and pravastatin (a statin devoid of CYP metabolism) and 16 with clopidogrel and atorvastatin. Platelet aggregation was higher in the atorvastatin plus clopidogrel group. No differences were found between clopidogrel alone and clopidogrel plus pravastatin. Also, it was observed a dose-dependent pattern in residual platelet reactivity after testing for different doses of atorvastatin. Despite the internal consistency of this study and the concern that it provoked in the medical community, many other studies have refuted such findings. To investigate the potential clinical impact of this interaction, a post hoc analysis of the CREDO trial (clopidogrel for the reduction of events during observation), which randomized 2116 patients who underwent PCI to clopidogrel pretreatment followed by 1 year’s treatment or no pretreatment and 1 month’s treatment, was carried out. A total of 1001 patients received CYP3A4 metabolized statins (atorvastatin, simvastatin, lovastatin and cerivastatin). There were no differences in clinical end points (death, myocardial infarction or stroke) after 1 year of follow-up [40]. Finally, in one study that prospectively included a cohort of 1001 patients submitted for cardiac catheterization, Hochholzer et al. [41] observed no among-treatment effect when clopidogrel is combined with different statins metabolized by CYP3A4 (atorvastatin, fluvastatin, simvastatin and lovastatin) over residual platelet reactivity.
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Table 1. Selected substrates, inhibitors and inducers of cytochrome P450 3A4 and 2C19.

<table>
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<tr>
<th>Substrates</th>
<th>Inhibitors</th>
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<td>3A4</td>
<td>Diltiazem</td>
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<td>Nifedipin</td>
<td>Phenytoin</td>
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<td>Alprazolam</td>
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<td>Atorvastatin</td>
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<td>Clarithromycin</td>
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<td>Sildenafil</td>
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<td>Losartan</td>
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<td>2C19</td>
<td>Diazepam</td>
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<td>Carisoprodol</td>
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<td>Citotidine</td>
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<td>Ticlopidine</td>
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From [21] and [38].

In recent years drug interactions involving CYP2C19 have received a lot of attention. As shown in Table 1, many drugs commonly used in clinical practice are metabolized by this CYP member. However, the most remarkable drug–drug interaction with clopidogrel is the one that involves proton pump inhibitors (PPIs). The frequency of the use of PPIs in practice is increasing over time, but the impact of their interaction with clopidogrel is still a subject for debate. Because the use of clopidogrel and aspirin in combination was associated with an increased risk of gastrointestinal bleeding [42], the use of PPIs became more and more frequent in order to prevent this complication, especially in patients treated for long periods of time. In 2008, the American College of Cardiology, the American Heart Association and the American College of Gastroenterology published an expert consensus document addressing the reduction of gastrointestinal risks associated with the use of antiplatelets [43]. In that document the use of PPIs in patients under dual antiplatelet therapy (aspirin plus clopidogrel) is clearly recommended. In a recently published retrospective cohort study using data from 8205 patients who were treated with clopidogrel after discharge for ACS, it was observed that 63.9% of subjects were also prescribed with a PPI [44]. As shown in Table 1, all of the available PPIs inhibit CYP2C19 to a certain degree and, consequently, they could probably affect clopidogrel performance. However, at least in vitro, not all PPIs inhibit CYP2C19 activity to the same extent, as Li et al. reported [45]. In this study, the maximal inhibition in the CYP2C19 mediated by S-Mephenytoin and 4′hydroxilation was observed with omeprazole (Figure 3). On the other hand, pantoprazole seemed to affect CYP to a lesser extent. A critical issue for practice is that omeprazole is an over-the-counter drug in many countries and the magnitude of the epidemiological impact is difficult to assess.

The first clue that gave support to this hypothesis was a study by Gilard et al. [46], who observed higher levels of residual platelet reactivity in 105 patients treated with clopidogrel plus omeprazole. The same group validated their findings in a randomized, double-blind, placebo-controlled trial including 124 patients treated with clopidogrel, who underwent stent implantation and were assigned to omeprazole or placebo [47]. After 7 days of treatment, platelet reactivity was significantly higher in the omeprazole group. In the same way, O'Donoghue et al. [48] studied 99 patients from the PRINCIPLE-TIMI 44 trial (prasugrel in comparison to clopidogrel for inhibition of platelet activation and aggregation; TIMI44). These authors observed that patients who underwent treatment with a PPI had significantly lower platelet inhibition than those not receiving such drugs.

To evaluate the clinical impact of this drug–drug interaction, Juurlink et al. [49] did a retrospective, population-based, nested case-control study. Using a database of Ontario residents they identified 13,636 patients, aged > 66 years, who were prescribed with clopidogrel after acute myocardial infarction. Cases were defined as patients who died or suffered a recurrent myocardial infarction 90 days after discharge. Controls were selected from the same population but had not been readmitted for acute myocardial infarction. Based on prescription records, the authors defined the exposure to PPIs in the population. After several analyses it was concluded that the use of PPIs in addition to clopidogrel was associated with recurrence in myocardial infarction at 3 months after the index event (odds ratio (OR) = 1.27, 95% CI 1.03 – 1.57). The use of pantoprazole was not associated with reinfarction in the short-term (OR = 1.02, 95% CI 0.70 – 1.47), but the use of other PPIs seemed to be involved in such an interaction (OR = 1.40, 95% CI 1.10 – 1.77). Similar findings were also published by Ho et al. [50], who analyzed prescription data from 8205 patients with ACS receiving clopidogrel in a retrospective cohort study. Two-thirds of patients were also prescribed with PPIs at discharge. With the aim of assessing these drug–drug interactions, a nested case-control study was performed. In the multivariable analysis, it was observed that PPI use was associated with an increased risk of death or readmission due to ACS (OR = 1.25, 95% CI 1.11 – 1.41) compared with non-users after a median follow-up of 521 days. Analyzing only the cohort of patients prescribed with PPI and clopidogrel (n = 5244), it was observed that those who discontinued PPIs for a period of > 14 days had a significantly lower event rate than for subjects who continued on PPI therapy (OR = 1.27, 95% CI 1.10 – 1.46). These findings indicate that the addition of a PPI may attenuate the effectiveness of clopidogrel. Because the use of a PPI could be a marker of comorbidity and, therefore, act as a conditioning factor of adverse outcomes, the investigators adjusted the analysis according to the history of
gastrointestinal bleeding. They observed that, independently of previous gastrointestinal bleeding history, the association between PPI use and worst clinical outcome still remained significant.

Nevertheless, there are many authors that describe no clinical impact of the cotreatment of clopidogrel and PPIs. Neutral results were observed by Siller-Matula et al. [50] in a nonrandomized trial (authors do not declare how the intervention was assigned) of 300 subjects treated with clopidogrel for PCI, with no differences in platelet aggregation between subjects treated with clopidogrel alone or plus pantoprazole, or esomeprazole. This could be evidence favoring a differential inhibitory effect on CYP2C19 with distinct PPIs. O’Donoghue et al. [48] analyzed the data from 6795 patients allocated to clopidogrel in the TRITON-TIMI 38 trial. In this study, 4529 patients (33%) also received a PPI at the time of randomization. The investigators found no association between the use of PPIs and clopidogrel at randomization and the occurrence of cardiovascular death, myocardial infarction or stroke (HR = 0.94, 95% CI 0.80 – 1.11) [48] during the follow-up period. Similar results were recently reported by Ray et al. [51] in a retrospective database analysis of 20,596 patients with ACS (13,003 with clopidogrel alone and 7593 with clopidogrel plus a PPI). There was no association between PPI use and fatal or nonfatal myocardial infarction, sudden cardiac death, stroke, or cardiovascular death (HR = 0.99, 95% CI 0.82 – 1.19) after a 1-year follow-up period.

There is a state of debate across the medical community because of the contradictory evidence on this issue. From the regulatory perspective, a recent warning delivered by the EMEA [52] and the FDA [53] shows the importance assigned by the authorities to this topic. In May 2009, the EMEA recognized that some PPIs could affect clopidogrel activation and recommended some modifications in clopidogrel labeling to advise doctors and patients and to discourage the use of this association unless absolutely necessary [52]. In November 2009, the FDA recommended that the concomitant use of omeprazole or esomeprazole with clopidogrel be avoided [53]. Box 1 summarizes the FDA recommendations on this topic.

Despite the recommendations provided by the different regulatory authorities, it is relevant to the scientific community to understand in a more comprehensive way this complex interaction. In the editorial accompanying O’Donoghue et al.’s article [48], Sibbing and Kastrati [54] presented the problem as a matter of fact or fiction. According to them, it must be highlighted that clinical evidence comes from very different sets of patients. On the one side we have population-based studies, which give information from unselected populations with higher prevalence of clinical factors associated with less clopidogrel response (i.e., chronic renal disease, diabetes mellitus, BMI). On the other hand, O’Donoghue et al. [48] analyzed subjects from a randomized, controlled trial who are certainly healthier than those from nonselected populations. It should be noticed that in this study 40.7% of recruited subjects using PPI were on pantoprazole. The results of the COGENT trial also support the lack of interaction. Presented at the Late Breaking Clinical Trials Sessions during the Transcatheter Cardiovascular Therapeutics 2009 meeting, Bhatt’s [55] study randomized patients with ACS or stent implantation to clopidogrel alone or a tablet with a fixed-dose combination of clopidogrel 75 mg and omeprazole 20 mg. Although the study was interrupted with almost 70% of the calculated sample of 5000 subjects, it was observed that the risk of cardiovascular events was similar in both arms of the study with a conclusive benefit on gastrointestinal events favoring the association of a PPI.

<table>
<thead>
<tr>
<th>CYP2C19 inhibition constant</th>
<th>S-Mephenytoin</th>
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<tbody>
<tr>
<td>Reaction</td>
<td>Omeprazole</td>
<td>Esomeprazole</td>
<td>Lansoprazole</td>
<td>Pantoprazole</td>
<td>Rabeprazole</td>
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<tr>
<td>S-Mephenytoin</td>
<td>6.2 ± 0.8 µM</td>
<td>8.6 ± 1.0 µM</td>
<td>0.45 ± 0.07 µM</td>
<td>69.4 ± 9.2 µM</td>
<td>21.3 ± 2.8 µM</td>
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<td>4’ hydroxilation</td>
<td>2.4 ± 0.05 µM</td>
<td>7.9 ± 0.5 µM</td>
<td>0.74 ± 0.09 µM</td>
<td>15.3 ± 1.1 µM</td>
<td>18.8 ± 1.3 µM</td>
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Figure 3. Inhibitory constants for CYP2C19 S-Mephenytoin and 4’hydroxilation using different proton pump inhibitors in human liver microsomes. From [45].
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Box 1. FDA recommendation for the use of concomitant medication in clopidogrel-treated subjects.

<table>
<thead>
<tr>
<th>Information supports avoidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPIs</td>
</tr>
<tr>
<td>Omeprazole</td>
</tr>
<tr>
<td>Esomeprazole</td>
</tr>
<tr>
<td>Other drugs</td>
</tr>
<tr>
<td>Cimetidine</td>
</tr>
<tr>
<td>Fluconazole</td>
</tr>
<tr>
<td>Ketoconazole</td>
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<tr>
<td>Etravirine</td>
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<tr>
<td>Felbamate</td>
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<tr>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Fluvoxamine</td>
</tr>
<tr>
<td>Voriconazole</td>
</tr>
<tr>
<td>There is no evidence of interaction</td>
</tr>
<tr>
<td>Ranitidine</td>
</tr>
<tr>
<td>Famotidine</td>
</tr>
<tr>
<td>Nizatidine</td>
</tr>
<tr>
<td>There is no evidence to give a recommendation</td>
</tr>
<tr>
<td>Balance risk/benefit in each patient</td>
</tr>
<tr>
<td>Pantoprazole</td>
</tr>
<tr>
<td>Rabeprazole</td>
</tr>
</tbody>
</table>

From [53].

The lack of any clinically relevant interaction between PPIs and clopidogrel was also seen in the abovementioned study by Ray et al. [51]. However, it is important to highlight that, in the later study, 62% of the patients with a PPI were on pantoprazole. This fact should have been taken into account at the time to interpret the conclusions of the evidence showed. In the accompanying editorial of Grinswold et al. [56], it was concluded that, despite the consistency of the methodology used by the authors, the question still remains undefined. More recently, during the 2010 American College of Cardiology scientific sessions, Harjai et al. [57] reported in a retrospective population-based registry of patients submitted for PCI that there was no association between PPI use (28% of patients included in the registry) and myocardial infarction, target vessel revascularization or stroke at 5-year follow-up. These authors also did a propensity-adjusted multivariable analysis to assess interaction in the subset of patients taking omeprazole or esomeprazole which represented 12% of the original cohort. Surprisingly, there was a lower incidence of cardiovascular events in the group treated with PPI compared with non-PPI subjects (3.9 vs 6.1%, respectively). Regarding this study, it is important to underline that, although the use of propensity scores is a consistent way to handle unbalanced groups in observational studies [58], the reduced size of the analyzed sample implies a clear limitation to ruling out PPI and clopidogrel interaction.

Another relevant question regarding the potential interaction between clopidogrel and PPI is about the timing of drug administration. Some experts have suggested that the lessened clopidogrel efficacy attributed to PPI coadministration could be overcome by separating both pills by 12 h. This strategy has no supporting evidence and, as was stated by Depta and Bhatt [59], is contradictory to some ex vivo data.

In summary, there is evidence provided from basic and clinical studies that supports the hypotheses that not all PPIs equally affect clopidogrel efficacy and effectiveness. These studies would indicate that pantoprazole probably has least effect on clopidogrel and also point out that the presence of comorbidities potentially related to ‘platelet resistance’ could potentiate the adverse impact of PPIs in general on clopidogrel-treated patients. Perhaps, as we suggested in Figure 4, in patients similar to those included in randomized, controlled trials, with less prevalence of conditions related to clopidogrel resistance (e.g., less age, body mass index and chronic renal failure), the addition of a PPI to clopidogrel does not imply any change in clinical outcome. In the same way, in patients more representative of general nonselected populations (like those analyzed in registries), this drug-drug interaction could really lead to an adverse cardiovascular outcome.

4. Expert opinion

Regarding the pharmacogenomic evidence presented, the influence of some selected polymorphisms on clopidogrel activation is well established. In particular, the role of CYP2C19 loss-of-function alleles was highlighted as clinically relevant. A consequence of this were the modifications to clopidogrel labeling in May 2009 (an FDA request), adding information on this topic [60]. However, there is no accepted way to handle this phenomenon in clinical practice. With respect to relevant pharmacokinetic interactions, a key issue surrounds the debate on the concomitant use of PPIs and clopidogrel. An explanation for the contradictory results of studies on this topic could be related to the type of PPI evaluated (pantoprazole seems to be the ‘safest’ in view of its lack of relevant interaction with the CYP family) and the type of population on which the combination of drugs were tested (‘real-life’ patients in the population-based studies vs ‘selected’ patients from the randomized, controlled studies). Despite the ongoing debate in the medical community, regulatory authorities have declared that the use of omeprazole or esomeprazole should be avoided in these patients, and that other PPIs should be used after a risk/benefit analysis.

Because many patients will still be treated with clopidogrel and would need concomitant protection to reduce the risk of gastrointestinal bleeding, it is important for treating physicians to have more information on this topic. The use of statistics to solve problems in processing data from observational studies should be complemented with rational design in retrospective studies. However, in recent years many new antiplatelet compounds have arisen as alternatives to clopidogrel. The approval of prasugrel, a new
P2Y12 inhibitor, was the first step on this pathway. This drug, which is hydrolyzed by esterases and activated in the liver by CYPs 3A4, 2B6, and to a lesser extent by 2C9 and 2C19, would not have clinically significant drug-drug interactions [61,62] and demonstrates a reduction in the rate of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke in patients with ACS [33]. The other molecule that is about to obtain FDA approval is ticagrelor, a non-thienopyridine reversible and direct antagonist of P2Y12 receptor which requires no metabolic activation and has recently demonstrated reduction in cardiovascular death, myocardial infarction or stroke without a rise in bleeding rate at 1-year follow-up [63].

Nevertheless, more information on efficacy and safety of these alternatives will be required to make a more appropriate and balanced comparative analysis with regards to the well-established clopidogrel-based antiplatelet therapies.

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**Declaration of interest**

The authors state no conflict of interest and have received no payment in preparation of this manuscript.
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Bibliography

Papers of special note have been highlighted as either of interest (●) or of considerable interest (★★) to readers.


** This article revealed the relationship between CYP2C19 polymorphism and variability in clopidogrel response assessed by platelet function.


** This article showed, in a huge sample of subjects, that polymorphisms were independently associated with worst clopidogrel response.


** This article determined an association between CYP2C19 polymorphisms, reduced clopidogrel activity on platelet aggregation and worst clinical outcomes in a real-world population using a genome-wide association approach.


** This article revealed that the loss-of-function alleles of CYP2C19 determined the adverse prognosis in a reduced sample of nonselected patients with STEMI.


** This consensus gave rationale to the broad use of PPIs as a gastrointestinal bleeding prophylaxis in patients treated with a dual antiplatelet regime.
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44. Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. JAMA 2009;301:937-44

** This is one of the most important examples of population-based research that raised concern about the clinical impact of the use of PPI plus clopidogrel.


** This is the basic-science evidence that supported the differential inhibitory effect of many PPIs on CYP2C19 activity.


** This is the only randomized-controlled trial that assessed the topic of the lack of efficacy of clopidogrel in omeprazole-treated patients.


** This article observed no clinical association between PPI use and clopidogrel using data from a randomized, controlled trial population.


** This is the first population-based study that reported worst clinical outcomes in patients co-treated with clopidogrel and PPIs and suggested that pantoprazole had no such effect.


** This study, despite stating that there are no clinically relevant interaction between PPIs and clopidogrel, revealed that two-thirds of the patients were treated with pantoprazole, which is the PPI with less inhibitory effect on CYP2C19 activity.


** This is the statement released for Europe.


** This is the statement released by the FDA and gives clear recommendations about concomitant treatments in clopidogrel-treated subjects.

54. Sibbing D, Kastrati A. Risk of combining PPIs with thienopyridines: fact or fiction? Lancet 2009;374:952-4

** This editorial provided an interesting approach about the discrepancies observed in studies regarding PPI and clopidogrel use.


** This trial, despite the fact of its premature interruption, gives important information about the lack of adverse cardiovascular influence of the coadministration of clopidogrel and omeprazole in the setting of a randomized trial to evaluate the efficacy and safety of a fixed-dose combination of clopidogrel 75 mg and omeprazole 20 mg. It also provided evidence supporting the use of PPIs to prevent gastrointestinal bleeding in patients under dual antiplatelet therapy.


** This paper gives a practical approach to the question about association of PPIs and clopidogrel. It also provided recommendations for the management in this setting.


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