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Results of genotype-guided antiplatelet therapy in patients who undergone percutaneous coronary intervention with stent

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ABSTRACT

Background: Clopidogrel has provided beneficial effects in acute coronary syndrome and percutaneous coronary intervention. Different polymorphisms have been associated with differences in clopidogrel response. The aim of this study was to check if CYP2C19/ABCB1-genotype-guided strategy reduces the rates of cardiovascular events and bleeding.
Methods: This experimental study included patients undergoing percutaneous coronary intervention with stent. The prospective genotype-guided strategy (intervention group) was compared against a retrospective non-tailored strategy (control group). Primary efficacy endpoint was the composite of cardiovascular death, acute coronary syndrome or stroke during 12 months after intervention. Secondary endpoint was to compare the efficacy of the different antiplatelet therapies used in genotyping conditions.
Results: The study included 719 patients undergone stent, more than 86% with acute coronary syndrome. The primary endpoint occurred in 32 patients (10.1%) in the genotyping group and in 59 patients (14.1%) in the control group (HR 0.63, 95% CI (0.41–0.97), p = 0.037). There was no difference in The Thrombolysis in Myocardial Infarction major and minor bleeding criteria between the two groups (4.1% vs. 4.7%, HR = 0.80, 95% CI (0.39–1.63), p = 0.55). In intervention group, there was no difference in the rate of events in patients treated with clopidogrel versus patients treated with other antiplatelet treatments (9.1% vs 11.5% p = 0.44), or bleeding (3.7% vs 4.6%, p = 0.69).
Conclusions: The genotype-guided strategy could reduce the rates of composite of cardiovascular events and bleeding during 12 months after percutaneous coronary intervention compared to a non-genotype-guide strategy.

1. Introduction

Clopidogrel is an antiplatelet drug used in the treatment of acute coronary syndrome (ACS) and those patients who are implanted with stent after percutaneous coronary intervention (PCI), in combination with acetylsalicylic acid [1]. However, despite clopidogrel treatment, a significant number of patients show increased incidence of recurrent atherothrombotic events.

Multiple mechanisms have been proposed for the variable response to clopidogrel, particularly when patients undergo PCI [2]. In the last years, different genetic polymorphisms have been associated with differences in response to clopidogrel. However, variability within the *CYP2C19* and *ABCB1* polymorphisms showed the higher level of evidence in loss of antiplatelet effect [3–7]. Intestinal absorption of the prodrug clopidogrel is limited by multidrug resistance protein 1 (MDR1, also named P-glycoprotein), which is an intestinal efflux pump that is encoded by the *ABCB1* gene. It has been shown that *ABCB1* C3435T polymorphism in *ABCB1* gene influences oral bioavailability of clopidogrel and prognosis of patients with ACS [8]. The peak plasma concentration and the total area under the plasma concentration time curve of clopidogrel and its active metabolite have been

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demonstrated to be significantly lower among homozygous variant allele carriers (*ABCB1* 3435 TT) compared with hetero or homozygous wild-type carriers (*ABCB1* 3435 CT or CC respectively) [8]. Subsequently, the majority of the prodrug is inactivated by esterases. The remainder of the prodrug undergoes activation in the liver by hepatic cytochrome isoenzymes. The *CYP2C19* gene is important in clopidogrel response because the conversion to its active metabolite depends partially on this enzyme. Loss of function (LOF) *CYP2C19* alleles, mainly *CYP2C19**2* variant, have been associated with lower levels of active clopidogrel metabolite, diminished platelet inhibition and higher rates of cardiovascular events [9].

Therefore, variations within the *CYP2C19* and *ABCB1* genes seem to be consistent genetic determinant of clopidogrel failure. In a genetic substudy of TRITON-TIMI 38 trial published by Mega et al. [3], they genotyped a subset of ACS undergone PCI patients who provided samples for genetic analysis with the aim of assessing the contribution of the *ABCB1* 3435 C > T polymorphism in the context of *CYP2C19* status. The results showed that in patients with ACS who underwent stent and treated with clopidogrel, both variants were significant independent predictors of cardiovascular death, ACS or stroke; those patients who were either carrier of LOF alleles (*CYP2C19* and/or *ABCB1*) had double rate of cardiovascular events than patients who did not carry at-risk genotypes in either gene. Similarly, patients who did not carry at-risk genotypes in either gene showed similar rate of cardiovascular events as those patients treated with prasugrel [3].

These results were later replicated in other genetic substudy of the PLATO trial [10], where patients without any LOF *CYP2C19* allele and not high-expression ABCB1 phenotype had no difference outcome between clopidogrel and ticagrelor.

The efficacy of prasugrel and ticagrelor seems not to be influenced by *CYP2C19* neither *ABCB1* polymorphisms [3,10].

However, compared with clopidogrel, prasugrel and ticagrelor increased the risk of bleeding [11,12]. Prasugrel increased the risk of major bleeding not related to revascularization procedures and fatal bleeding [11] and ticagrelor increased the risk of minor and major bleeding not related with coronary bypass and an increased frequency of fatal intracranial hemorrhage was observed [12].

Therefore, there is a great interest in investigating the potential benefits of personalized strategies that would focus the use of new P2Y12 inhibitors to patients at high risk for poor response to clopidogrel.

The aim of this study is to check if *CYP2C19/ABCB1* genotype-guided strategy in which the choice of antiplatelet therapy is based on the genetic test, reduces the rates of cardiovascular events and bleeding compared to a non-tailored strategy in patients who undergone PCI with stent.

2. Material and methods

2.1. Patients and treatment

This is a non-randomized experimental study including coronary artery disease patients following PCI undergone stent and requiring dual antiplatelet therapy during 1–12 months. The prospective *CYP2C19/ABCB1* genotype-guided strategy (intervention group, n = 317) was compared against a retrospective non-tailored strategy (control group, n = 402) (Fig. 1). The inclusion criteria were: 1) Patients older than 18 years old with diagnostic of coronary artery disease, 2) Performed PCI with stent implantation and 3) Signed informed consent to participate in the study.

The exclusion criteria were: 1) patients requiring oral anticoagulation or 2) presenting contraindication for taking acetylsalicylic acid/clopidogrel/prasugrel/ticagrelor or 3) with high risk of bleeding. The complete design, recruitment and follow-up of the study are published in [13].

Patients included in the intervention group were recruited from April 2012 to September 2013; patients included in the control group were recruited from April 2010 to March 2012, both in San Cecilio University Hospital, Granada, Spain.

At the time of admission, in the intervention group, patients were treated as standard care at discretion of attending physician. The genetic test was performed as soon as possible after admission and the result was reported in 24–48 h. Then, patients who carried 1 or more *CYP2C19* LOF alleles (*CYP2C19**2, *3) and/or *ABCB1* TT polymorphism received prasugrel or ticagrelor (the last one was approved during the study) whereas non-carriers patients received clopidogrel. In the retrospective group, patients received treatment based on the routine clinical practice.

The study protocol was approved by the Ethics Committee of San Cecilio University Hospital. Informed written consent from all participants was obtained in accordance with the tenets of the Declaration of Helsinki. The authors confirm that this study has been registered in Eudra CT (Eudra CT: 2016-001294-33).

2.2. Clinical evaluation

Primary efficacy endpoint was the composite of cardiovascular death, ACS, or stroke during 12 months after PCI. Secondary endpoint was to compare the efficacy of the different antiplatelet therapies used in genotyping conditions. We also studied the rate of definite stent thrombosis [14] and the need for urgent revascularization not related to stent thrombosis. Safety endpoints included TIMI major or minor bleeding not related to coronary artery bypass grafting. Analysis was made by intention-to-treat during the first year under dual antiplatelet therapy.

The efficacy and safety endpoints occurring during 1-year follow-up were recorded by the investigators using hospital patient files, pharmacy records, and patient questionnaires. Patients were asked to fill out a questionnaire every 3 months after PCI, to obtain information about changes in antiplatelet drug use, comedication, drug compliance, and adverse or endpoint events.

2.3. CYP2C19*2, CYP2C19*3 and ABCB1 genotyping

For genotyping, DNA was isolated from saliva using standard procedures. Buccal mucosa cells collection and DNA extraction procedures were carried out according to the method detailed in Freeman et al. [15], a non-organic (proteinase K and salting out) protocol with some modifications described by Gomez-Martín A. et al. [16].

The *CYP2C19**2* (rs4244285), *CYP2C19**3* (rs4986893) and *ABCB1* (rs1045642) single-nucleotide polymorphisms (SNPs) were genotyped by triplicate using TaqMan® allelic discrimination assay (Life Technologies, Foster City, CA, USA), two replicates were performed in the Genomics Unit of GENYO and a third test was carried out in San Cecilio

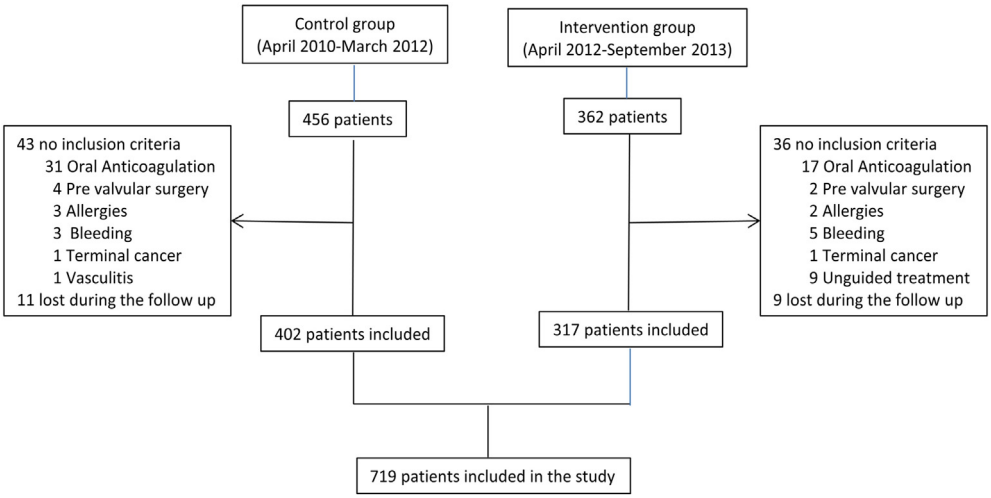

Fig. 1. Study profile.