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Routine CYP2C19 Genotyping to Adjust Thienopyridine Treatment after primary PCI for ST-elevation Myocardial Infarction: Results of the GIANT study

Running title: Routine CYP2C19 genotyping to adjust antiplatelet therapy

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[@DrHulot](https://twitter.com/DrHulot) [PARCC](https://www.parcc.fr) Anti-platelet therapy adjustment guided by CYP2C19 genotyping can be done in <7 days in STEMI patients with saliva DNA analysis.

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Abstract:

Objectives. To evaluate prospectively the clinical impact of routine transmission of *CYP2C19* genotype in the management of acute ST-elevation myocardial infarction (STEMI) with primary PCI.

Background. Response to clopidogrel widely differ between patients, notably because of *CYP2C19* genetic polymorphisms.

Methods. *CYP2C19* genotype (6 alleles) was determined centrally and communicated within 4.1 ± 1.9 days of primary PCI in 1,445 STEMI patients recruited in 57 centers in France. *CYP2C19* metabolic status was predicted from genotype and served to adjust thienopyridine treatment. The primary endpoint was differences in 12-month outcomes (death, myocardial infarction and stent thrombosis) between patients with wild-type genotype or gain-of-function allele (Class 1, N= 1118) and patients with loss-of-function (LOF) allele (Class 2, N= 272) who received optimized thienopyridine treatment.

Results. The detection of LOF allele resulted in adjustment of P2Y₁₂ inhibition in 85% of patients with a significantly higher use of prasugrel or double dose clopidogrel. The primary endpoint did not differ class 1 vs. class 2 patients (3.31% vs. 3.04% respectively, $p=0.82$). In contrast, carriers of LOF alleles without treatment adjustment had a significantly worse outcome (15.6%, $p<0.05$). Bleeding rates were not different between groups.

Conclusion. In a real-world setting, a complete *CYP2C19* genotype can be mostly determined in <7 days using a saliva DNA analysis collected during the in-hospital phase of STEMI patients treated with primary PCI. Genotype information led to stronger platelet inhibition treatment in

the vast majority of LOF carriers and to similar clinical outcomes than in patients carrying a wild genotype or a gain-of-function allele.

Keywords: STEMI; clopidogrel; CYP2C19; genetics; real-life setting

Condensed abstract

Previous retrospective studies have shown an association between *CYP2C19* loss of function (LOF) allele, present in up to 30 % of patients, and a higher risk of MACE after acute coronary syndrome or percutaneous intervention. The present study showed the feasibility of routine *CYP2C19* genotyping in a cohort of all-comer STEMI patients treated with primary PCI. This technique allowed appropriate treatment adjustment in a vast majority of LOF patients with a significantly beneficial impact on the one-year rate of clinical composite endpoint compared to unadjusted LOF patients and no differences compared to patients with a wild or gain of function genotype.

List of abbreviations:

ACS : Acute coronary syndrome

AMI: Acute myocardial infarction

CYP2C19: cytochrome P450 2C19

GOF: gain-of-function

HPR: high platelet reactivity

LOF: loss-of-function

MACCE: Major adverse cardiac and cerebrovascular events

PCI: percutaneous coronary intervention

Introduction

Inhibition of the P2Y₁₂ platelet receptor is a major objective in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI)(1,2). Clopidogrel is a second- generation P2Y₁₂ irreversible inhibitor which requires enteric metabolism and 2-step hepatic transformation in order to produce its active metabolite(3). Several cytochromes are involved in this oxidative process but the most important is CYP2C19. CYP2C19 activity depends on genetic polymorphisms and loss of function (LOF) alleles (notably *CYP2C19*2* and *CYP2C19*3*) are present in 15% to 30% of the population according to ethnicity(4). Evidence suggests that such patients are at higher risk of ischemic events after an ACS or a PCI(5-12). Such a higher risk is explained by a significant reduction in clopidogrel bioactivation leading to a subsequent high platelet reactivity (HPR)(13). Prasugrel and ticagrelor are high intensity P2Y₁₂ inhibitors and do not dependent upon CYP2C19 activity but a systematic switch to these drugs is associated with a higher bleeding risk. Conversely, *CYP2C19* gain-of-function alleles (GOF, such as *CYP2C19*17*) are present in 5% to 20% of the population and can be linked to an increase in biological activity with a controversial impact on increased response to clopidogrel and bleeding risks(14-16).

Recent observational(17) and randomized studies(18-20) have shown that *CYP2C19* genotype-guided strategy for selection of oral P2Y₁₂ inhibitors can reduce the increased thrombotic risk observed in *CYP2C19* LOF carriers while limiting the incidence of bleeding associated with a systematic use of potent P2Y₁₂ inhibitors. In these studies, *CYP2C19*2* and 3 genotype was determined with point-of-care genetic testing or with on-site genetic analyzers which allowed a rapid (<24h in most cases) genotype assessment and drug adjustment(19-21). These techniques are however not accessible to all cardiology centers and it is currently unclear if the use of a

routine *CYP2C19* genotyping to tailor P2Y12 inhibitors in a real-world situation will be associated with a similar benefit. In addition, more extensive genetic techniques are required to screen for a more comprehensive set of *CYP2C19* LOF (*2 to *6) and GOF (*17) alleles(22), thus providing a better prediction of *CYP2C19* metabolic activity(23).

The objective of the Genotyping Infarct patients to Adjust and normalize Thienopyridine treatment (GIANT, NCT01134380) study was to prospectively assess the clinical impact of a routine transmission to the cardiology team, in charge of STEMI patients treated with primary PCI and coronary stent, of the *CYP2C19* metabolic status, predicted on *CYP2C19* genotype based on 6 screened alleles and using a simple non-invasive saliva sampling, and of potential adjustment and optimization of thienopyridine treatment according to pre-specified recommendations. Our main hypothesis was that a routine *CYP2C19* genotyping and genotype-guided adjustment for higher intensity thienopyridine treatment in *CYP2C19* LOF carriers reduces the high rate of ischemic events observed in these patients when treated with clopidogrel as compared to patients with *CYP2C19* wild-type genotype or gain-of-function allele.

Methods

Additional information are available in the supplemental material.

Trial design and patients

The GIANT study was a prospective, multi-center, observation study performed at 57 sites in France (supplemental data, annex 1). The protocol was approved by ethics committee and national authorities and all enrolled patients provided informed and signed consents to participate the study and to genetic analyses. The population consisted of all patients presenting

with STEMI of less than 24-hour onset and admitted for primary PCI. A complete *CYP2C19* genetic profiling was performed in the study patients. The genotyping results were communicated to the study investigators for potential adjustment and optimization of thienopyridine treatment according to running recommendations at the time of the recruitment period.

Genotyping methods

Saliva DNA collectors (Oragene DNA, Dnagenotek) were shipped to a central lab (La Pitié Salpêtrière, Paris, France) for DNA extraction and genetic analysis. Screening for *CYP2C19* loss of function (*2, *3, *4, *5 or *6) and gain of function (*17) alleles were performed using commercially available Taqman allelic discrimination assays (ThermoFisher scientific, Waltham, MA, USA) on a 7900HT sequence detection system (Applied Biosystems, Courtaboeuf, France) as previously described(24). These genotype results were then used to classify patients into 4 different groups predicting *CYP2C19* metabolic activity as shown in Table 1. The prediction was based on available scientific information at the time of the study(23). Notably, carriers of the GOF *17 alleles were considered as rapid metabolizers. In addition, because of the lack of definitive evidence at the time the study was performed, compound carriers of both a GOF and LOF alleles (i.e. *2 / *17, *3 / *17 and *4 / *17) were considered as normal metabolizers.

Adjustment

The study site received the predicted *CYP2C19* metabolic status for each patient and patient treatment was adjusted according to the clinical pharmacogenetics implementation consortium guidelines for cytochrome 2C19 genotype and clopidogrel therapy(23). It was recommended on the basis of the results that the very slow metabolizers should be treated with prasugrel, the slow

metabolizers with either prasugrel or a double dose of clopidogrel. The remaining groups were treated according to the investigator's preference. Patients with normal and rapid CYP2C19 metabolic status (corresponding to wild genotype or gain-of-function allele) were defined as Class 1 and patients with reduced CYP2C19 metabolic activity (i.e., carriers of LOF allele) who received high intensity thienopyridine treatment were defined as Class 2. Lastly, patients with reduced CYP2C19 metabolic activity (i.e., carriers of LOF allele) but who did not receive a high intensity thienopyridine treatment as recommended were defined as Class 3.

Objectives

The primary objective was to demonstrate that the rate of ischemic events observed in *CYP2C19* LOF carriers detected by a routine genotype and receiving an adjusted higher intensity thienopyridine treatment is similar to the one observed in patients with *CYP2C19* wild-type genotype or gain-of-function allele and receiving a standard thienopyridine treatment. The primary endpoint was difference in 12-month outcomes (including death, myocardial infarction and stent thrombosis) between Class 1 and Class 2 patients . The secondary endpoint involved the difference in 12-month MACCE between and the major bleeding complications (based on the criteria used in the STEEPLE clinical trial(25)) at 12 months between groups.

Data Management and sample size

All data were entered into an eCRF (Clinigrid, Paris, France). Independent monitoring and data management were carried out by the Cardiovascular European Research Center, Massy, France. All outcomes were adjudicated by an independent committee (supplemental data, annex 1).

The primary endpoint was used to define the cohort size according to historical rates in previous French studies. The 'loss of function' cohort required 330 patients to detect a difference with non-slow responders with an 80% power and alpha error of 5% (based on a superiority design). As loss of function represented 28% of screened patients in prior genotyping studies, the final size of the global cohort was 1500 patients after taking into account an estimation of follow-up loss. Patients were first analyzed by per-protocol analysis, taking into account Class 1 patients and Class 2 patients but excluding Class 3 patients (patients with reduced CYP2C19 metabolic activity but who did not receive a high intensity thienopyridine treatment as recommended by the protocol). Class 3 patients were then compared to Class 1 and 2 patients in a secondary analysis.

Results

A total of 1,499 patients were included in 57 centers in France from June 2010 to through January 2012. After adjustment for major protocol deviations, the final analysis was carried out in 1,445 patients (Figure 1). *CYP2C19* genotyping was successfully achieved for 1437 (99.4%) patients and *CYP2C19* metabolic status was communicated in 4.1 ± 1.9 days after the PCI procedure, with a delay of shipment of the saliva samples to the central genetic laboratory of 3.8 ± 1.7 days. Only 18.4% received the genotyping results in the first 48 hours after PCI but 93.6% of patients received their results within 7 days.

Based on the results of genotype profiling (Table 2 and Figure 1), the patients were divided into three different classes according to *CYP2C19* genotype and predicted metabolism status and subsequent antiplatelet therapy adjustment. Class 1 was composed of 1,118 patients with wild-type genotype (47.3%) or gain-of-function allele (30%) and with respectively a predicted normal or rapid *CYP2C19* metabolism status. Out of the remaining 319 patients whose genotype indicated slow and

very slow metabolism status (20.3% and 1.7% respectively) and a resistance to clopidogrel, 272 (85%) patients in whom treatment was adjusted or already optimal according to the genotype was considered as Class 2 (Figure 1). Class 3 was composed of 46 patients with slow and very slow metabolism status but who did not receive a high intensity thienopyridine treatment and were thus not appropriately adjusted (Supplemental Table 1).

The baseline characteristics and procedural data of the classes 1 and 2 study patients are shown in Table 3 and were well-balanced between groups. Pre- and post-genotyping antiplatelet treatments are described in Table 4. After the genotype results were provided, there was a significantly higher prescription of clopidogrel high dose (150mg/d) or prasugrel in class 2 patients.

Primary endpoint: As shown in Figure 2, class 2 patients (slow and very slow metabolizers in whom thienopyridine treatment was adjusted) had similar 12-month rates of death, MI or stent thrombosis than the ones observed in class 1 patients (3.04% in class 1 vs. 3.31% in class 2, Hazard ratio: 1.10, 95% CI [0.49-2.44], $p=0.82$ by log-rank test). Reciprocally, the 46 slow/very slow responders with a non-adjusted or inappropriate treatment (Class3) had significantly higher rates of death, MI or stent thrombosis compared to Class 2 patients (15.6%, $p<0.05$ as compared to class 1 or class 2). The seven outcomes in class 3 patients correspond to 4 deaths and 3 MI or stent thrombosis.

Secondary endpoints: Class 2 patients had a similar rate of MACCE at 12 months compared with patients in class 1 as shown in Table 5. The overall rate of major bleeding was low (1.9%) and no differences were observed between the classes of patients. Similar results were observed when considering both major and minor bleedings (3.58% in class 1 vs. 3.31% in class 2, $p=NS$).

Additional analyses:

There was no significant difference in the occurrence of MACCE at 12 months according to the CYP2C19 metabolism status (2.53% in rapid, 3.36% in normal, 2.80% in slow and 9.09% in very slow metabolizers, $p=0.34$). Similar results were observed for major and minor bleedings (3.22% in rapid, 3.65% in normal, 3.60% in slow, $p=0.92$). No bleedings were observed in very slow metabolizers.

We then perform additional analyses to further characterize the influence of the GOF *CYP2C19**17 allele. We first observed that none of the 65 patients with the *17 / *17 genotype presented a MACCE over the 12-month follow-up period as compared to 2.98% in *1 / *17 carriers, 3.00% in compound carriers of both a GOF and LOF alleles (*2 / *17) and 3.42% in patients with the *1 / *1 wild-type genotype. The rates of major and minor bleeding rates were however similar over these genotypes (3.07% in *17 / *17, 3.25% in *1 / *17, 3.00% in *2 / *17 and 3.76% in *1 / *1, $p=0.96$).

We finally performed a sensitivity analysis by considering the 100 compound carriers of both a GOF and LOF alleles (*2/*17, *3/*17 and *4/*17) as slow metabolizers instead of normal metabolizers as initially planned (Table 2). This reclassification did not change our primary results and the primary endpoint was not statistically different between groups (Hazard ratio : 1.12, 95%CI [0.55-2.29], $p=0.73$ by log-rank test).

Sub-group analysis:

Sub-group analysis did not show any significant differences associated with gender or AMI localization regarding the occurrence of MACCE between the study groups.

The occurrence of outcomes was not different in the 44 Class 2 patients who were adjusted to clopidogrel high-dose (150 mg/d) vs. the 225 Class 2 patients adjusted to prasugrel: 4.54% vs. 3.11% for the primary endpoint, $p=0.63$; 11.36% vs. 9.78% for MACCE, $p=0.75$ and 2.27% vs. 2.22% for major bleeding, $p=0.98$.

Discussion

In this study, we found that 1/ in a real-world setting, a complete *CYP2C19* genotype can be determined in ≤ 7 days in a vast majority of patients using a saliva DNA analysis collected during the in-hospital phase of STEMI management; 2/ the detection of loss-of-function alleles and prediction for a reduced *CYP2C19* metabolism in 22% of patients allows the adjustment of P2Y₁₂ inhibition leading to use of prasugrel or double dose clopidogrel in 85% of patients; 3/ the one-year clinical outcome of those patients with reduced *CYP2C19* metabolism and high intensity thienopyridine therapy does not differ from that of patients with a normal or rapid *CYP2C19* metabolism; and 4/ reciprocally, the remaining 15% of patients with reduced *CYP2C19* metabolism without appropriate adjustment of P2Y₁₂ inhibitors display a significantly worse prognosis.

To the best of our knowledge, this is the first real-world, large-scale, observational and prospective study that evaluated the role of a pragmatic strategy to determine *CYP2C19* genotype and tailor antiplatelet therapy after primary PCI (Central Illustration). Our study provides an important information by showing that adjustment of antiplatelet treatment on the basis of *CYP2C19* genotype can be performed in the week following MI and primary PCI which appears

to blunt the risk of ischemic events associated with the *CYP2C19* LOF alleles, which was found similar to the risk of patients without *CYP2C19* LOF alleles. Our results thus extend the previous demonstration that a rapid (<24h) *CYP2C19*-genotype-guided strategy for selection of P2Y12 inhibitor can reduce high-on-treatment platelet reactivity (RAPID GENE study(19)) and ischemic events (PHARMCLO(20) and POPULAR GENETICS(18) studies) in *CYP2C19**2 carriers. Indeed, in these three studies, *CYP2C19* genotype was principally achieved with point-of-care genetic testing which provided results in 1 to 2 hours(18-21) and consequently led to an adjusted antiplatelet therapy in the first day after genotyping(18). An important proportion of recurrent ischemic events occur in the immediate days following MI and PCI and a more rapid genotyping could therefore indicate a more rapid therapy adjustment during this high-risk period. However, the acute management of MI typically includes higher loading doses or the use of more potent and *CYP2C19*-independent P2Y12 inhibitors(1). Reciprocally, numerous studies evaluating the impact of *CYP2C19**2 or other LOF alleles on clinical outcomes after myocardial infarction, ACS or PCI, found an association with higher long-term MACE or stent thrombosis rates in patients chronically treated with clopidogrel 75 mg/day(6,8,12). This is in line with our results which showed that the carriers of *CYP2C19* LOF alleles but without antiplatelet therapy adjustment had a 15.6% rate of death/MI/stent thrombosis at one year versus 3.3% for the adjusted population ($p<0.05$) or 3.04% for the gain-of-function or wild genotype population. The similar outcomes between class 1 (rapid / normal metabolizers) and class 2 (slow / very slow with drug adjustment) patients suggest a potential benefit associated with the use of more potent P2Y12 inhibitors in *CYP2C19* LOF carriers. This adjustment was mainly based on an increased use of prasugrel from 55.9% to 82.7%. Overall, our results suggest that *CYP2C19* genotype can be performed in the days following MI in order to appropriately select chronic treatment with P2Y12

inhibitors and this strategy is associated with a reduction of ischemic events in *CYP2C19* LOF carriers.

In the GIANT study, we performed a more comprehensive assessment of 6 *CYP2C19* alleles. Even if the *CYP2C19**2 allele is the most frequent LOF allele, other rare alleles are also associated with reduced *CYP2C19* activity(4). By screening 4 additional LOF alleles (*3, 4, 5 and 6) we found 17 carriers that would have been wrongly considered as normal metabolizers with a single screening of *CYP2C19**2. Because of the low frequency of these alleles, it is however impossible to ascertain that the *CYP2C19*-genotype guided strategy is associated with a beneficial effect in these few patients as in *CYP2C19**2 carriers. This would deserve further investigations in larger cohorts of patients. In addition, the *CYP2C19**17 allele is associated with an increased *CYP2C19* activity and controversial impact of the response to clopidogrel. Some studies have suggested an increased bleeding risk in these patients as a result of a higher response to clopidogrel(16,23,26). In this study, these patients were identified as rapid metabolizer which however did not trigger specific recommendation for drug adjustment. Additional analyses did not reveal a significant influence of *17 allele on the results, even if we found that none the 65 *17 / *17 carriers had a MACCE during the 12-month follow up. Lastly, compound carriers of both the *2 LOF and *17 GOF alleles were considered as normal metabolizer in our study. This classification was based on available evidence at the time when this study was performed, but new evidence suggests that these patients could present with a reduced *CYP2C19* activity(27). In our study, we however did not see any particular differences in the rate of MACE or bleedings in these 98 (6.8%) patients. Reciprocally, the primary endpoint was not affected by the reclassification of these compound carriers as slow metabolizers. Further studies are now needed to better specify the optimal adjustment strategy in these patients with less frequent *CYP2C19* genotypes.

The recent POPULAR-GENETICS study(18) has suggested that *CYP2C19*-genotype guided strategy for the selection of P2Y12 inhibitor resulted in lower incidence of bleeding in the genotype-guided group as compared to standard treatment. We did not observe such a result on our study, however with a lower rate of major and minor bleeding events in our patients. This could be due the differences in the criteria used to define bleeding events between studies or to difficulties to identify minor bleeding events that did not require hospitalization in our study. Nevertheless, the lower use of more potent P2Y12 inhibitors as long-term antiplatelet therapy in patients that are predicted as good responders to clopidogrel 75 mg/d (class 1 in our study) would likely be associated with a reduction in bleeding events. Recent registries have shown that a majority of patients still receive clopidogrel in the management of acute myocardial infarction, such as in the recent TASTE, SCAAR registry-based trial, where 66% of the patients received clopidogrel, 28.5% ticagrelor and the remaining patients were treated with prasugrel(28).

The respective role of genotyping versus phenotyping assessment to guide P2Y12 inhibition has a subject of debate(29). GRAVITAS, ARCTIC, ANTARTIC and TRIGGER-PCI (30-33) are the most important of several randomized trials which have evaluated the benefits of a tailored approach based on a systematic evaluation of platelet reactivity. None of these studies has succeeded in validating the role of phenotyping testing. Conversely, genotype evaluation could appear as a more complex and time-consuming approach, but our results indicate that the delay to obtain *CYP2C19* genotyping from a genetic laboratory does not impact the benefit of genotype-guided adjustment. Our results, combined with other observational and randomized trials, indicate that management of MI patients could be improved by a systematic implementation *CYP2C19* genotype-guided strategy.

Study limitations

The absence of randomization, either at the time of primary PCI to obtain a control group of patients without genotyping, and/or after genotyping to set up a balanced control group of untailored treatment in LOF carriers, limits the impact of the findings but has permitted the implementation of a genotyping strategy in an all-comer population of primary PCI in more than 50 centres. As a complementary analysis, we reported a higher rate of clinical events in Class 3 patients but the reason for disrespecting the genotype adjustment was left to the physician's discretion and is potentially linked to the identification of different characteristics in these patients. In addition, an important proportion of patients were initially treated with clopidogrel where current guidelines rather support the use of more potent thienopyridines (prasugrel or ticagrelor) in the acute management of STEMI. The relevance of *CYP2C19* genotype in STEMI patients receiving prasugrel or ticagrelor as initial pharmacotherapies remain to be determined, especially in the context of early de-escalation of antiplatelet treatment after the acute phase as established in the TROPICAL-ACS study(29,34). Finally, an adjustment strategy was recommended according to the genotype but was finally decided by the prescribing physician. Therefore, our study was not designed to directly evaluate and compare optimal adjustment strategies. A small proportion of LOF carriers (16.2%) were adjusted to clopidogrel high dose (150 mg/d), a strategy that has been shown not to be as effective as prasugrel or ticagrelor to reduce on-treatment high platelet reactivity. However, we did not observe increased rates of outcomes in patients adjusted to clopidogrel 150 mg/d compared to patients adjusted to prasugrel 10mg/d. Similarly, 43.6% of normal and rapid *CYP2C19* metabolizers received prasugrel 10 mg/d and our study was not designed to evaluate de-escalation to clopidogrel 75 mg/d in those patients.

Conclusion

In a real-world setting, a complete *CYP2C19* genotype can be determined in <7 days in a vast majority of patients using a saliva DNA analysis collected during the in-hospital phase of patients with an acute myocardial infarction treated with primary PCI. Genotype information led to stronger platelet inhibition treatment in the vast majority of LOF carriers and finally to a similar clinical outcome than in patients carrying a wild genotype or a gain-of-function allele.

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Clinical perspectives:**What's known?**

Response to clopidogrel widely differ between patients, notably because of *CYP2C19* genetic polymorphisms. Patients with *CYP2C19* loss of function (LOF) alleles have a higher risk of MACE after acute coronary syndrome or percutaneous intervention but *CYP2C19* genotyping is not performed in daily practice.

What's new?

In a real-world setting, a complete *CYP2C19* genotype can be determined in <7 days in a vast majority of patients using a saliva DNA analysis collected during the in-hospital phase of patients with an acute myocardial infarction treated with primary PCI. Genotype information led to stronger platelet inhibition treatment in the vast majority of LOF carriers and finally to a similar clinical outcome than in patients carrying a wild genotype or a gain-of-function allele.

What's next?

The implementation of a pragmatic strategy to determine *CYP2C19* genotype and tailor antiplatelet therapy after primary PCI should be evaluated.

Figure legends:

Figure 1. Study Flow Chart

Figure 2: Primary Endpoint (Kaplan-Meier survival curves)

Central Illustration. A pragmatic strategy to genotype CYP2C19 in STEMI/PCI patients and adjust thienopyridine therapy in loss-of-function carriers

Figure 1

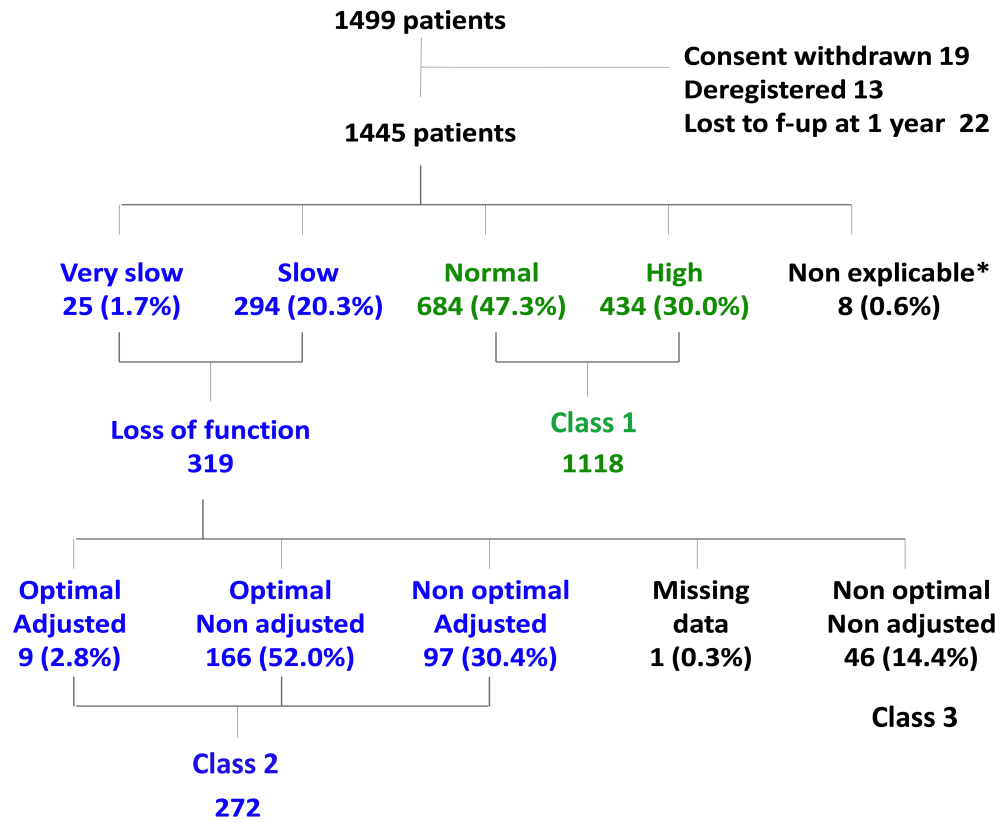
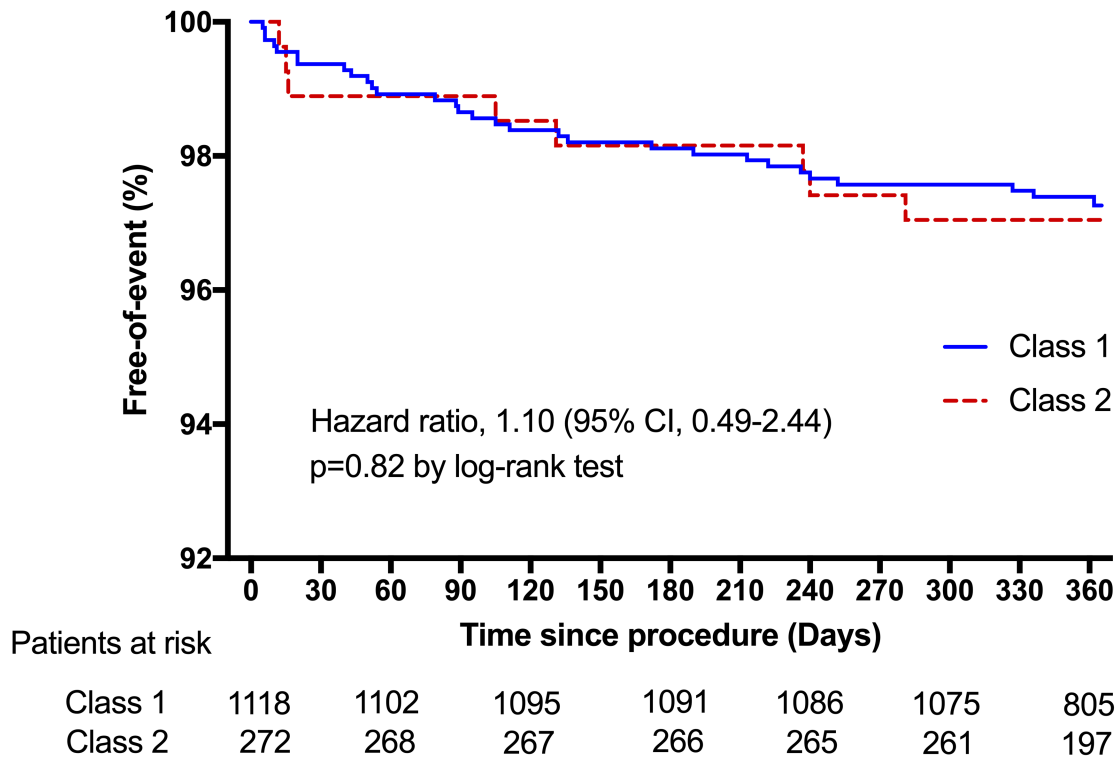


Figure 2



Central Illustration

In-hospital saliva
sampling in 1499
STEMI / PCI patients



CYP2C19 routine
genotyping
(6 variants)



Results in
 4.1 ± 1.9 days
after the PCI
(94% \leq 7 days)



22% slow
responders
85 % adjustment
of thienopyridines



1-year rate of death, MI or stent thrombosis

