# Effect of *CYP2C19* and *ABCB1* single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial

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*Lancet* 2010; 376: 1320–28

Published Online August 29, 2010 DOI:10.1016/S0140-6736(10)61274-3

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## Summary

**Background** In the PLATO trial of ticagrelor versus clopidogrel for treatment of acute coronary syndromes, ticagrelor reduced the composite outcome of cardiovascular death, myocardial infarction, and stroke, but increased events of major bleeding related to non-coronary artery bypass graft (CABG). *CYP2C19* and *ABCB1* genotypes are known to influence the effects of clopidogrel. In this substudy, we investigated the effects of these genotypes on outcomes between and within treatment groups.

**Methods** DNA samples obtained from patients in the PLATO trial were genotyped for *CYP2C19* loss-of-function alleles (*2, *3, *4, *5, *6, *7, and *8), the *CYP2C19* gain-of-function allele *17, and the *ABCB1* single nucleotide polymorphism 3435C→T. For the *CYP2C19* genotype, patients were stratified by the presence or absence of any loss-of-function allele, and for the *ABCB1* genotype, patients were stratified by predicted gene expression (high, intermediate, or low). The primary efficacy endpoint was the composite of cardiovascular death, myocardial infarction, or stroke after up to 12 months' treatment with ticagrelor or clopidogrel.

**Findings** 10 285 patients provided samples for genetic analysis. The primary outcome occurred less often with ticagrelor versus clopidogrel, irrespective of *CYP2C19* genotype: 8·6% versus 11·2% (hazard ratio 0·77, 95% CI 0·60–0·99, p=0·0380) in patients with any loss-of-function allele; and 8·8% versus 10·0% (0·86, 0·74–1·01, p=0·0608) in those without any loss-of-function allele (interaction p=0·46). For the *ABCB1* genotype, event rates for the primary outcome were also consistently lower in the ticagrelor than in the clopidogrel group for all genotype groups (interaction p=0·39; 8·8% *vs* 11·9%; 0·71, 0·55–0·92 for the high-expression genotype). In the clopidogrel group, the event rate at 30 days was higher in patients with than in those without any loss-of-function *CYP2C19* alleles (5·7% *vs* 3·8%, p=0·028), leading to earlier separation of event rates between treatment groups in patients with loss-of-function alleles. Patients on clopidogrel who had any gain-of-function *CYP2C19* allele had a higher frequency of major bleeding (11·9%) than did those without any gain-of-function or loss-of-function alleles (9·5%; p=0·022), but interaction between treatment and genotype groups was not significant for any type of major bleeding.

**Interpretation** Ticagrelor is a more efficacious treatment for acute coronary syndromes than is clopidogrel, irrespective of *CYP2C19* and *ABCB1* polymorphisms. Use of ticagrelor instead of clopidogrel eliminates the need for presently recommended genetic testing before dual antiplatelet treatment.

**Funding** AstraZeneca.

## Introduction

Dual antiplatelet treatment with aspirin and a thienopyridine is recommended treatment for acute coronary syndromes to reduce the rate of recurrent ischaemic events and stent thrombosis.[1–5] Thienopyridines (clopidogrel and prasugrel) are oral prodrugs that need to be converted to active metabolites to irreversibly bind to the $P2Y_{12}$ receptor. About 85% of clopidogrel is hydrolysed to an inactive metabolite, with the remainder converted to the active metabolite by two sequential steps dependent on cytochrome P450 (CYP), with contributions from the isoenzymes CYP2C19, CYP3A4 or CYP3A5, CYP2C9, CYP1A2, and CYP2B6.[6–8] The *CYP2C19* genotype affects both metabolic steps and is the most important determinant of the pharmacokinetic and pharmacodynamic response to clopidogrel, although it only explains about 12% of reported variability.[9–12] In patients treated with clopidogrel after an acute coronary syndrome event or stenting, or both, the presence of any loss-of-function *CYP2C19* allele (*2, *3, *4, *5, *6, *7, and *8) is associated with an increased risk of ischaemic events and stent thrombosis,[9,10,13,14] whereas the presence of any gain-of-function *CYP2C19* allele (*17) is associated with a raised risk of bleeding.[15] Variations in the genes regulating clopidogrel absorption and efflux, such as the gene encoding the P-glycoprotein multidrug resistant-1 efflux transporter, ABCB1,[16] might also affect the rate of clinical events during treatment.[17]

Ticagrelor is an oral, reversible platelet inhibitor that binds directly to the $P2Y_{12}$ receptor and does not need metabolic activation for pharmacodynamic activity.[18] Compared with clopidogrel, ticagrelor provides more pronounced and consistent platelet inhibition with a faster onset and offset of the effect of treatment.[18,19] At present, no genetic determinants of the ticagrelor response are known, although ticagrelor absorption might be affected by *ABCB1* polymorphisms.[20] In the PLATelet inhibition and patient Outcomes (PLATO) trial,[21] ticagrelor reduced events of the primary composite endpoint of cardiovascular death, myocardial infarction, or stroke by 16% (95% CI 8–21), without any difference in overall major bleeding, but increased events of major bleeding related to non-coronary artery bypass graft (CABG) by 19% (95% CI 2–38). In this first substudy from the PLATO genetics programme, we aimed to investigate the role of *CYP2C19* and *ABCB1* polymorphisms on efficacy and safety outcomes both between and within the ticagrelor and clopidogrel arms of the PLATO study.

## Methods

### Study design

The detailed design and outcomes of the PLATO study have previously been reported.[21,22] In brief, PLATO was a prospective, randomised, double-blind, double-dummy, parallel-group, international, multicentre phase 3 study of 18 624 patients with or without ST-elevation acute coronary syndrome. The study assessed the efficacy and safety of up to 12 months' treatment with either 90 mg ticagrelor twice daily (180 mg loading dose) or 75 mg clopidogrel once daily (300–600 mg loading dose) for the prevention of cardiovascular death, myocardial infarction, and stroke. The maximum duration of treatment was 12 months, which was shortened to 6 or 9 months at the end of the study, providing a median treatment duration of 277 days.

Participation in the genetic substudy of the PLATO trial was voluntary for sites and patients. Collection and genetic analysis of samples was subject to informed consent, separate to that of the PLATO study, from all patients and approval by local ethics committees. A blood sample was obtained from every participant as close to randomisation as possible. Genotyping was done at the AstraZeneca Research and Development and Genetics Laboratory (Alderley Park, UK) with TaqMan assays (Applied Biosystems, Life Technologies, Pleasanton, CA, USA). We classified every *CYP2C19* allele by established nomenclature and its reported effect on enzymatic function according to published reports and databases. The alleles genotyped in the total PLATO genetics population were: *CYP2C19* loss-of-function alleles *2, *3, *4, *5, *6, *7, and *8; *CYP2C19* gain-of-function allele *17; and *ABCB1* single nucleotide polymorphism 3435C→T (rs1045642). Genotyping success rates ranged from 98·8% to 99·5% of all samples genotyped, and all single nucleotide polymorphisms passed AstraZeneca's internal quality control criteria for Hardy-Weinberg equilibrium (p=1 for seven of nine single nucleotide polymorphisms, p=0·94 for the *CYP2C19*5* single nucleotide polymorphism, and p=0·32 for the *CYP2C19*2* single nucleotide polymorphism).

### Statistical analysis

The statistical analysis plan for the genetic substudy was prespecified before any genetic results were available. The genetic information was merged with the clinical database for the genetics subset of the intention-to-treat population. Genotype frequencies were assessed for the entire genetics cohort to show that the cohort was representative of a white population and for individual treatment groups to ensure balance between groups. For the *CYP2C19* genotype, patients were stratified into six groups to represent their predicted phenotypes: extensive (*1/*1), intermediate (*1/*2–*8), poor (*2–*8/*2–*8), poor or rapid heterozygote (*2–*8/*17), rapid heterozygote (*1/*17), and ultra rapid (*17/*17). As per the analysis plan, we used a data-driven statistical approach with a guided decision to choose the most appropriate *CYP2C19* genotype groupings for each composite endpoint within each treatment arm. The first step was an overall assessment of any effect of gain-of-function alleles, followed by an ordered assessment of different logical groupings of the six predicted *CYP2C19* phenotypes with calculation of hazard ratios (HRs) and 95% CIs. In the absence of significant effects with application of any

| | 90 mg ticagrelor twice daily (n=5137) | 75 mg clopidogrel once daily (n=5148) |
|---|---|---|
| Age (years) | 62·5 (10·90) | 62·5 (11·04) |
| ≥75 | 760 (15%) | 835 (16%) |
| Men | 3560 (69%) | 3571 (69%) |
| White | 5057 (98%) | 5058 (98%) |
| Weight (kg) | 81·9 (15·27) | 81·8 (15·47) |
| Body-mass index ≥30 kg/m² | 1560 (30%) | 1520 (30%) |
| Smoking status | | |
| Non-smoker | 1994 (39%) | 2049 (40%) |
| Ex-smoker | 1347 (26%) | 1270 (25%) |
| Habitual smoker | 1796 (35%) | 1829 (36%) |
| Diabetes mellitus | 1177 (23%) | 1189 (23%) |
| Drug use at randomisation | | |
| Proton-pump inhibitor | 2154 (42%) | 2083 (40%) |
| Statin | 4079 (79%) | 4059 (79%) |
| Aspirin | 4962 (97%) | 4946 (96%) |
| Open-label clopidogrel | 2467 (48%) | 2486 (48%) |
| Planned invasive treatment | 3403 (66%) | 3375 (66%) |
| Troponin positive | 4149 (81%) | 4199 (82%) |

Data are mean (SD) or number (%).

***Table 1:*** **Selected characteristics at baseline for the genetic substudy population**

For more on ***CYP2C19* alleles** see http://www.cypalleles.ki.se

appropriate *CYP2C19* genotype groups derived from the within-arm analysis, we did a between-arm analysis by use of phenotype groupings based on the presence or absence of loss-of-function alleles (ie, extensive, ultra rapid, and rapid heterozygote *vs* intermediate, poor, and poor or rapid heterozygote) to allow direct comparisons with previous reports.[9,23] For the *ABCB1* genotype, patients were stratified by predicted gene expression: high (C/C), intermediate (C/T), and low (T/T).

This substudy was not prospectively powered and had to be based on the maximum number of patients consenting to provide a blood sample for genetic analysis. As analyses were based on a data-driven approach, the number and size of the final groupings were unknown until the analyses were complete. For the *CYP2C19* genotype, 892 primary outcome events occurred in the two genotype groups: 264 in the group with and 628 in the group without any loss-of-function allele. These numbers of events, with a two-sided α level of 0·05, could detect hazard ratios of 0·786 and 0·855, respectively. The reliability of other results should be based on the final 95% CIs.

Cox regression was used to compare outcomes between treatment groups and between genotype groups in each treatment group, and to analyse interaction between treatment groups and genotype groups, with adjustment for covariates: ethnic group, sex, use of a proton-pump inhibitor, aspirin dose, smoking status, and diabetes. Primary analyses for comparisons between treatment groups yielded HRs stratified by genotype group (as established by analyses within each treatment group) for six outcomes: composite of cardiovascular death, myocardial infarction, or stroke (primary endpoint); composite of cardiovascular death or myocardial infarction; stent thrombosis; total major bleeding; total major bleeding related to non-CABG; total major bleeding related to CABG; and the net clinical benefit to cardiovascular death, myocardial infarction, stroke, major bleeding related to non-CABG, and major fatal or life threatening bleeding related to CABG. No adjustment for multiple comparisons was used. Kaplan-Meier estimates of the cumulative risk to the first occurrence of outcome events were calculated and plotted.

| | 90 mg ticagrelor twice daily (n=5137) | 75 mg clopidogrel once daily (n=5148) |
|---|---|---|
| ***CYP2C19* genotype** | | |
| *1/*1 | 1849 (36%) | 1862 (36%) |
| *1/*17 | 1437 (28%) | 1386 (27%) |
| *1/*2 | 855 (17%) | 898 (17%) |
| *1/*3 | 8 (<1%) | 6 (<1%) |
| *1/*4 | 10 (<1%) | 8 (<1%) |
| *1/*6 | 0 | 2 (<1%) |
| *1/*8 | 21 (<1%) | 21 (<1%) |
| *17/*17 | 268 (5%) | 268 (5%) |
| *2/*17 | 353 (7%) | 318 (6%) |
| *2/*2 | 114 (2%) | 115 (2%) |
| *2/*4 | 4 (<1%) | 3 (<1%) |
| *2/*5 | 0 | 1 (<1%) |
| *2/*8 | 3 (<1%) | 6 (<1%) |
| *3/*17 | 1 (<1%) | 1 (<1%) |
| *4/*17 | 0 | 1 (<1%) |
| *8/*17 | 15 (<1%) | 8 (<1%) |
| Missing | 199 (4%) | 244 (5%) |
| ***CYP2C19* predicted phenotype** | | |
| Extensive (*1/*1) | 1849 (36%) | 1862 (36%) |
| Intermediate (*1/*2–*8) | 894 (17%) | 935 (18%) |
| Poor (*2–*8/*2–*8) | 121 (2%) | 125 (2%) |
| Poor or rapid heterozygote (*2–*8/*17) | 369 (7%) | 328 (6%) |
| Rapid heterozygote (*1/*17) | 1437 (28%) | 1386 (27%) |
| Ultra rapid (*17/*17) | 268 (5%) | 268 (5%) |
| Missing | 199 (4%) | 244 (5%) |
| ***ABCB1* predicted phenotype** | | |
| High expression (C/C) | 1167 (23%) | 1195 (23%) |
| Intermediate expression (C/T) | 2570 (50%) | 2518 (49%) |
| Low expression (T/T) | 1349 (26%) | 1386 (27%) |
| Missing | 51 (1%) | 49 (1%) |

*Table 2:* **Genotype and predicted phenotypes, by treatment**

See Online for webappendix

### Role of the funding source

Academic members of the executive committee designed the trial in collaboration with representatives from AstraZeneca. AstraZeneca Research and Development coordinated data management. Statistical analysis was done by Worldwide Clinical Trials, a contract research organisation, in collaboration with investigators who had full access to the final study data. Results were interpreted by the authors, with representatives from the academic investigators and the sponsor. The corresponding author drafted the report and was responsible for the decision to submit for publication after all coauthors commented on the report.

## Results

10 285 patients consented to give a blood sample for genetic analysis. Demographic indicators and drug use were well balanced between the treatment groups at baseline (table 1 and webappendix). These characteristics and study outcomes did not differ from that of the total PLATO population, apart from ethnic group: 98% (n=10 115 patients) of the genetics cohort compared with 92% (n=17 077) of the total cohort were white. Predicted phenotypes and allele frequencies were representative of a white population and were balanced between treatment groups (table 2).

In outcomes within each treatment group in relation to the *CYP2C19* genotype and predicted phenotype groupings, we did not identify any model explaining the variation in clinical outcomes so genotype groupings in the final comparisons were based on the presence or absence of any loss-of-function allele. The primary composite outcome of cardiovascular death, myocardial infarction, or stroke up to 12 months was consistently reduced with ticagrelor versus

clopidogrel in patients in each genotype group (table 3). This difference was driven by consistent reductions in cardiovascular death and myocardial infarction. Rates of stent thrombosis were low in both treatment groups and were also consistently lower in the ticagrelor than in the clopidogrel group (table 3). For the primary composite endpoint, Kaplan-Meier curves showed an early separation of event rates at 30 days for patients with any loss-of-function allele between the ticagrelor (4·1%) and clopidogrel groups (5·7%; HR 0·73, 95% CI 0·52–1·03, p=0·078), but not for patients without any loss-of-function allele (3·8% *vs* 3·8%; 0·96, 0·76–1·22, p=0·76; interaction p=0·20; figure 1). In a landmark analysis of the primary composite endpoint from day 31 onwards, event rates at end of follow-up were similar between treatment groups for patients with any loss-of-function allele (0·82, 0·58–1·17, p=0·28), but were lower in the ticagrelor group than in the clopidogrel group for those without any loss-of-function allele (0·77, 0·63–0·96, p=0·017; interaction p=0·77; figure 2).

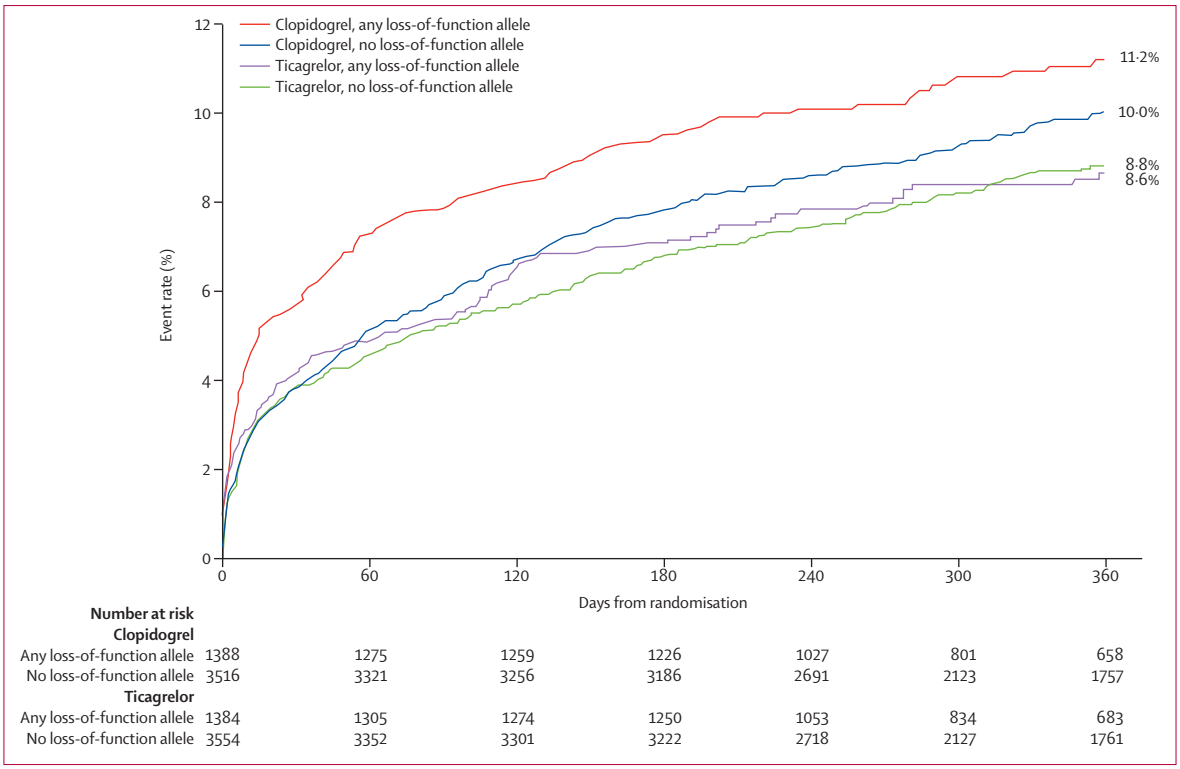
In analysis of outcome between the genotype groups in each treatment group, the event rate for the primary composite endpoint was numerically greater in the clopidogrel group for patients with versus those without any loss-of-function allele (p=0·25; table 3). This difference was caused by an early separation of event rates between the genotype groups at 30 days (1·37, 1·04–1·82, p=0·028). For all other efficacy events, no differences in genotype group were significant for comparisons within each treatment group (table 3).

For major bleeding events in relation to the *CYP2C19* genotype, patients in the clopidogrel group who had any gain-of-function allele had a higher rate of events than did those without any gain-of-function or loss-of-function alleles (p=0·022). Therefore, comparisons between treatment groups were separated for patients with gain-of-function alleles, those with loss-of-function but no gain-of-function alleles, and those without any loss-of-function or gain-of-function alleles (table 3). Irrespective of *CYP2C19* genotype group, the interaction between treatment groups and genotype groups was not significant for any type of major bleeding. Accordingly, the results for these genetic groups were consistent with the results for the entire PLATO patient population. For the outcome of net clinical benefit, the improvement with ticagrelor versus clopidogrel

| | 90 mg ticagrelor twice daily | | | 75 mg clopidogrel once daily | | | Hazard ratio (95% CI) | p value | p value (interaction)* |
|---|---|---|---|---|---|---|---|---|---|
| | Number of patients | Patients with events | Kaplan-Meier event rate | Number of patients | Patients with events | Kaplan-Meier event rate | | | |
| **Cardiovascular death, myocardial infarction, and stroke** | | | | | | | | | |
| Any loss-of-function allele | 1384 | 115 (8·3%) | 8·6% | 1388 | 149 (10·7%) | 11·2% | 0·77 (0·60–0·99) | 0·0380 | 0·46 |
| No loss-of-function allele | 3554 | 296 (8·3%) | 8·8% | 3516 | 332 (9·4%) | 10·0% | 0·86 (0·74–1·01) | 0·0608 | .. |
| **Cardiovascular death and myocardial infarction** | | | | | | | | | |
| Any loss-of-function allele | 1384 | 102 (7·4%) | 7·7% | 1388 | 138 (9·9%) | 10·4% | 0·73 (0·57–0·95) | 0·0184 | 0·30 |
| No loss-of-function allele | 3554 | 273 (7·7%) | 8·0% | 3516 | 306 (8·7%) | 9·2% | 0·86 (0·73–1·01) | 0·0734 | .. |
| **Definite stent thrombosis†** | | | | | | | | | |
| Any loss-of-function allele | 943 | 15 (1·6%) | 1·6% | 934 | 21 (2·2%) | 2·3% | 0·71 (0·36–1·37) | 0·30 | ‡ |
| No loss-of-function allele | 2341 | 22 (0·9%) | 1·0% | 2300 | 35 (1·5%) | 1·5% | 0·62 (0·36–1·05) | 0·0772 | .. |
| **Major bleeding (loss-of-function allele)** | | | | | | | | | |
| Any loss-of-function allele | 1380 | 149 (10·8%) | 11·8% | 1380 | 143 (10·4%) | 11·3% | 1·04 (0·82–1·30) | 0·77 | 0·60 |
| No loss-of-function allele | 3547 | 331 (9·3%) | 10·3% | 3506 | 340 (9·7%) | 10·6% | 0·96 (0·83–1·12) | 0·61 | .. |
| **Major bleeding (gain-of-function allele)** | | | | | | | | | |
| No loss-of-function or gain-of-function allele | 1846 | 176 (9·5%) | 10·5% | 1856 | 161 (8·7%) | 9·5% | 1·12 (0·90–1·38) | 0·31 | 0·19 |
| Any loss-of-function but no gain-of-function allele | 1011 | 108 (10·7%) | 11·6% | 1053 | 108 (10·3%) | 11·1% | 1·03 (0·79–1·34) | 0·84 | .. |
| Any gain-of-function allele | 2070 | 196 (9·5%) | 10·5% | 1977 | 214 (10·8%) | 11·9% | 0·86 (0·71–1·05) | 0·13 | .. |
| **Major bleeding related to non-CABG** | | | | | | | | | |
| Any loss-of-function allele | 1380 | 56 (4·1%) | 4·6% | 1380 | 41 (3·0%) | 3·2% | 1·39 (0·93–2·08) | 0·11 | 0·31 |
| No loss-of-function allele | 3547 | 121 (3·4%) | 3·9% | 3506 | 110 (3·1%) | 3·6% | 1·08 (0·84–1·40) | 0·55 | .. |
| **Major bleeding related to CABG** | | | | | | | | | |
| Any loss-of-function allele | 1380 | 96 (7·0%) | 7·6% | 1380 | 107 (7·8%) | 8·6% | 0·87 (0·66–1·14) | 0·31 | 0·93 |
| No loss-of-function allele | 3547 | 218 (6·1%) | 6·8% | 3506 | 246 (7·0%) | 7·7% | 0·88 (0·73–1·05) | 0·16 | .. |
| **Net clinical benefit** | | | | | | | | | |
| Any loss-of-function allele | 1384 | 204 (14·7%) | 15·2% | 1388 | 231 (16·6%) | 17·1% | 0·88 (0·72–1·06) | 0·17 | 0·88 |
| No loss-of-function allele | 3554 | 476 (13·4%) | 14·0% | 3516 | 533 (15·2%) | 15·8% | 0·86 (0·76–0·97) | 0·0172 | .. |

CABG=coronary artery bypass graft. *p value of interaction indicates significance of effects of genotype groups on the results of comparisons between treatment groups. †Stent thrombosis population includes patients who received at least one stent at any time during the study, which was about 64% of patients participating in the genetic substudy. ‡Interaction p value not calculated because of low number of events.

***Table 3:*** **Outcomes in relation to the *CYP2C19* genotype**




| Number at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Clopidogrel** | | | | | | | |
| Any loss-of-function allele | 1388 | 1275 | 1259 | 1226 | 1027 | 801 | 658 |
| No loss-of-function allele | 3516 | 3321 | 3256 | 3186 | 2691 | 2123 | 1757 |
| **Ticagrelor** | | | | | | | |
| Any loss-of-function allele | 1384 | 1305 | 1274 | 1250 | 1053 | 834 | 683 |
| No loss-of-function allele | 3554 | 3352 | 3301 | 3222 | 2718 | 2127 | 1761 |

***Figure 1:*** **Kaplan-Meier estimates of events of the primary efficacy outcome in relation to the *CYP2C19* genotype**

was not affected by the genotype group (table 3). Differences in Kaplan-Meier event rates between genotype groups were similar for ticagrelor (1·2%) and clopidogrel (1·3%), and event rates in the ticagrelor group were lower than in the clopidogrel group, irrespective of genotype group (table 3).

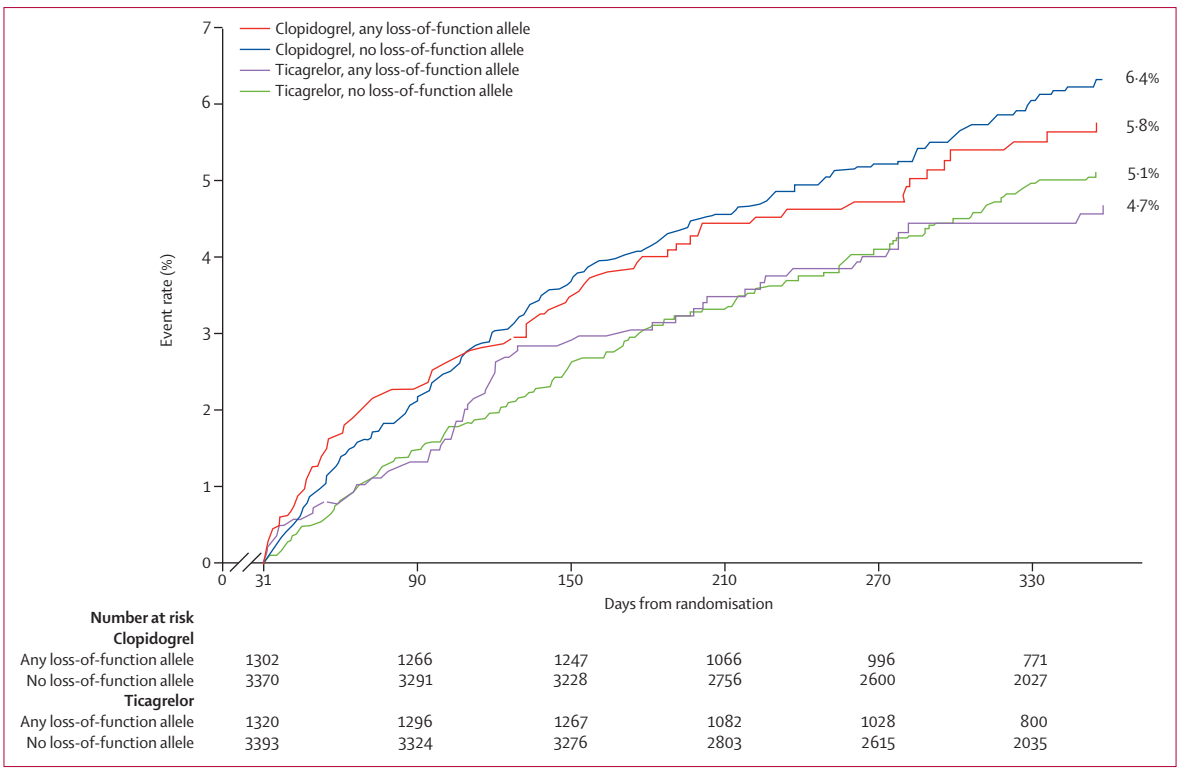
In relation to the *ABCB1* genotype, rates of cardiovascular death, myocardial infarction, and stent thrombosis were consistently lower in the ticagrelor group than in the clopidogrel group, irrespective of *ABCB1* polymorphism. Differences in rates of cardiovascular death, myocardial infarction, and stent thrombosis were significant in the group with the putative predicted high-expression genotype, although the interaction between genotype and treatment group was not significant (table 4). *ABCB1* genotype group had no effect on major bleeding overall or that related to non-CABG or CABG for comparisons between or within treatment groups, and, accordingly, interactions between genotype and treatment group were not significant (table 4).

To quantify the maximum effect of genetic polymorphisms on the composite efficacy outcome, we did a post-hoc analysis with combination of data for *CYP2C19* and *ABCB1* polymorphisms. In patients with either any loss-of-function *CYP2C19* allele or the predicted high-expression *ABCB1* phenotype, Kaplan-Meier event rates were 8·6% in the ticagrelor group (n=2253) versus 11·2% in the clopidogrel group (n=2248; 0·75, 0·62–0·91, p=0·004). In patients without these alleles, event rates were 8·9% in the ticagrelor group (n=2710) versus 9·5% in the clopidogrel group (n=2698; 0·92, 0·77–1·11, p=0·39). However, this genetic grouping did not have a significant interaction with the overall effects of ticagrelor versus clopidogrel (p=0·13).

## Discussion

Treatment with ticagrelor versus clopidogrel in a large population with acute coronary syndromes was associated with lower rates of cardiovascular death and myocardial infarction, similar rates of total major bleeding, and higher rates of major bleeding related to non-CABG, irrespective of *CYP2C19* and *ABCB1* polymorphisms. These findings are from the large, double-blind randomised PLATO trial, so they should provide reliable information about pharmacogenomic interactions of these genetic polymorphisms with outcomes, for comparisons between and within drug groups, during long-term treatment of patients managed invasively and non-invasively. Furthermore, 98% of our study population was white and comparison of genotype data with other reports indicated that our study sample was representative of other white populations: *CYP2C19* allele frequencies were consistent with those of white populations,[24,25] and the percentages of the predicted phenotypes of *ABCB1* of high, intermediate, and low expression were similar to those in another white population.[26]

The results of our study clearly show the absence of interaction between the occurrence of any *CYP2C19*




| Number at risk | | | | | | |
|---|---|---|---|---|---|---|
| **Clopidogrel** | | | | | | |
| Any loss-of-function allele | 1302 | 1266 | 1247 | 1066 | 996 | 771 |
| No loss-of-function allele | 3370 | 3291 | 3228 | 2756 | 2600 | 2027 |
| **Ticagrelor** | | | | | | |
| Any loss-of-function allele | 1320 | 1296 | 1267 | 1082 | 1028 | 800 |
| No loss-of-function allele | 3393 | 3324 | 3276 | 2803 | 2615 | 2035 |

***Figure 2:*** **Kaplan-Meier estimates of events of the primary efficacy outcome in relation to the *CYP2C19* genotype, as a landmark analysis from day 31 to end of follow-up**

loss-of-function allele and the superiority of ticagrelor over clopidogrel for all efficacy events tested. So far, no direct comparison of outcomes with prasugrel versus clopidogrel in relation to the presence of any *CYP2C19* loss-of-function allele have been published from the genetic substudy of the TRITON-TIMI 38 trial.[9,27] Thus, ticagrelor is the only $P2Y_{12}$ inhibitor with evidence for superiority over clopidogrel for treatment of acute coronary syndromes, irrespective of the effects of *CYP2C19* genetic polymorphisms.

We did not record any evidence of interaction of the *CYP2C19* genotype group in patients on ticagrelor, with almost identical ischaemic event rates between patients with and without any loss-of-function allele. By contrast, during the first 30 days of treatment with clopidogrel, a higher rate of ischaemic events was recorded in patients with than in those without any loss-of-function allele, which is consistent with previous reports.[9,14,23] However, when the full follow-up period was considered, the difference in outcomes between patients with and without any loss-of-function allele was not significant and was less prominent than that seen in some, although not all, of previous observational trials.[23] In most reports of stronger interactions than we recorded, ischaemic events and stent thrombosis occurred early after start of clopidogrel treatment in association with percutaneous coronary intervention and stent procedures.[9,10,14,28,29] Fewer or milder interactions than we recorded have been reported in mixed populations of patients managed invasively and non-invasively during long-term treatment with clopidogrel.[9,17,30]

Patients with acute coronary syndromes were recruited to the PLATO trial irrespective of previous treatment with clopidogrel or whether invasive or medical management was planned, and only 64% of the genetic cohort had a percutaneous coronary intervention stent procedure at any time during the trial. The low rate of percutaneous coronary intervention procedures in association with the acute event and the aversion to undertaking of percutaneous coronary intervention procedures very early after start of clopidogrel might have contributed to the lower rate of stent thrombosis and reduced interaction with *CYP2C19* polymorphisms in this trial than in previous reports. During long-term clopidogrel treatment, *CYP2C19* polymorphisms seem to have moderate effect on concentration of the active metabolite[11] and platelet aggregation,[12,30] which also might explain the restricted effect of these polymorphisms on clinical events in our study.

Potential interactions between polymorphisms and the effects of clopidogrel on clinical events seemed to be time dependent in our study, with significantly higher event rates in patients with versus those without any *CYP2C19* loss-of-function allele at 30 days, but no significant difference between the genotype groups thereafter. This finding corresponds with the genetic substudy of the

| | 90 mg ticagrelor twice daily | | | 75 mg clopidogrel once daily | | | Hazard ratio (95% CI) | p value | p value (interaction)* |
|---|---|---|---|---|---|---|---|---|---|
| | Number of patients | Patients with events | Kaplan-Meier event rate | Number of patients | Patients with events | Kaplan-Meier event rate | | | |
| **Cardiovascular death, myocardial infarction, and stroke** | | | | | | | | | |
| Low expression | 1349 | 122 (9·0%) | 9·5% | 1386 | 137 (9·9%) | 10·5% | 0·90 (0·70–1·15) | 0·40 | 0·39 |
| Intermediate expression | 2570 | 208 (8·1%) | 8·5% | 2518 | 233 (9·3%) | 9·8% | 0·86 (0·71–1·03) | 0·11 | .. |
| High expression | 1167 | 98 (8·4%) | 8·8% | 1195 | 138 (11·5%) | 11·9% | 0·71 (0·55–0·92) | 0·0104 | .. |
| **Cardiovascular death and myocardial infarction** | | | | | | | | | |
| Low expression | 1349 | 110 (8·2%) | 8·5% | 1386 | 124 (8·9%) | 9·5% | 0·89 (0·69–1·16) | 0·40 | 0·46 |
| Intermediate expression | 2570 | 188 (7·3%) | 7·7% | 2518 | 218 (8·7%) | 9·2% | 0·83 (0·68–1·01) | 0·0571 | .. |
| High expression | 1167 | 91 (7·8%) | 8·2% | 1195 | 128 (10·7%) | 11·1% | 0·71 (0·54–0·93) | 0·0128 | .. |
| **Definite stent thrombosis†** | | | | | | | | | |
| Low expression | 905 | 9 (1·0%) | 1·1% | 917 | 14 (1·5%) | 1·5% | 0·65 (0·28–1·50) | 0·31 | ‡ |
| Intermediate expression | 1711 | 23 (1·3%) | 1·4% | 1653 | 28 (1·7%) | 1·6% | 0·80 (0·46–1·38) | 0·42 | .. |
| High expression | 756 | 6 (0·8%) | 0·8% | 793 | 17 (2·1%) | 2·2% | 0·37 (0·14–0·93) | 0·0351 | .. |
| **Major bleeding** | | | | | | | | | |
| Low expression | 1345 | 132 (9·8%) | 10·9% | 1382 | 137 (9·9%) | 10·9% | 0·97 (0·76–1·23) | 0·77 | 0·80 |
| Intermediate expression | 2567 | 240 (9·3%) | 10·3% | 2508 | 245 (9·8%) | 10·6% | 0·96 (0·80–1·15) | 0·66 | .. |
| High expression | 1164 | 121 (10·4%) | 11·5% | 1188 | 116 (9·8%) | 10·8% | 1·06 (0·83–1·37) | 0·63 | .. |
| **Major bleeding related to non-CABG** | | | | | | | | | |
| Low expression | 1345 | 47 (3·5%) | 4·0% | 1382 | 35 (2·5%) | 3·0% | 1·39 (0·90–2·15) | 0·14 | 0·64 |
| Intermediate expression | 2567 | 91 (3·5%) | 4·0% | 2508 | 80 (3·2%) | 3·5% | 1·10 (0·81–1·49) | 0·53 | .. |
| High expression | 1164 | 39 (3·4%) | 3·7% | 1188 | 37 (3·1%) | 3·5% | 1·07 (0·68–1·68) | 0·77 | |
| **Major bleeding related to CABG** | | | | | | | | | |
| Low expression | 1345 | 88 (6·5%) | 7·2% | 1382 | 105 (7·6%) | 8·2% | 0·83 (0·63–1·10) | 0·20 | 0·56 |
| Intermediate expression | 2567 | 155 (6·0%) | 6·6% | 2508 | 178 (7·1%) | 7·8% | 0·85 (0·69–1·06) | 0·15 | .. |
| High expression | 1164 | 83 (7·1%) | 7·9% | 1188 | 83 (7·0%) | 7·8% | 1·02 (0·75–1·38) | 0·89 | .. |
| **Net clinical benefit** | | | | | | | | | |
| Low expression | 1349 | 192 (14·2%) | 14·8% | 1386 | 219 (15·8%) | 16·6% | 0·87 (0·72–1·06) | 0·16 | 0·19 |
| Intermediate expression | 2570 | 357 (13·9%) | 14·4% | 2518 | 370 (14·7%) | 15·3% | 0·93 (0·81–1·08) | 0·35 | .. |
| High expression | 1167 | 157 (13·5%) | 14·0% | 1195 | 210 (17·6%) | 18·1% | 0·74 (0·60–0·91) | 0·0041 | .. |

CABG=coronary artery bypass graft. *p value of interaction indicates significance of effects of genotype groups on the results of comparisons between treatment groups. †Stent thrombosis population includes patients who received at least one stent at any time during the study, which was about 64% of patients participating in the genetic substudy. ‡Interaction p value not calculated because of low number of events.

***Table 4:*** **Outcomes in relation to the *ABCB1* genotype**

TRITON-TIMI 38 trial,[9] in which event rates differed between patients with and without any *CYP2C19* loss-of-function allele in the first week after start of clopidogrel treatment, in association with the stent procedure, and this difference persisted thereafter during long-term treatment. Our results also showed that the lower event rate in the ticagrelor versus the clopidogrel group from 31 days until end of follow-up was not affected by *CYP2C19* genotype group.

Findings of the PLATO trial showed no significant difference in rates of total major bleeding events between the treatment groups. In accordance with previous research,[15] we showed that patients on clopidogrel who had any *CYP2C19* gain-of-function allele had a higher rate of major bleeding events than did those without any gain-of-function or loss-of-function alleles, but presence of any loss-of-function allele was not significantly related to event rate. By contrast, we recorded no interactions between genetic polymorphisms and bleeding event rates in the ticagrelor group or between bleeding event rates in the two treatment groups. In the main PLATO trial, ticagrelor treatment was associated with a 19% increase in bleeding events related to non-CABG, but we recorded no significant interactions of these events with any *CYP2C19* gain-of-function or loss-of-function alleles within or between the treatment groups. Accordingly, events of bleeding related to non-CABG consistently increased with ticagrelor, irrespective of *CYP2C19* polymorphisms.

This study also investigated effects of the *ABCB1* polymorphism. The *ABCB1* 3435C→T genotype putatively affects expression of the P-glycoprotein efflux transporter, although this data is ambiguous.[31,32] High expression of *ABCB1* might therefore increase expression of this transporter, and thereby affect the systemic exposure to either ticagrelor or clopidogrel and its active metabolite and the clinical effects of these drugs.[16] Even though

ticagrelor is a putative P-glycoprotein substrate, the *ABCB1* polymorphism had no interaction with ischaemic or bleeding events in the ticagrelor group. In the clopidogrel group, patients with the high-expression *ABCB1* polymorphism had a higher rate of ischaemic events than did those with polymorphisms of intermediate or low expression. Despite biological plausibility, the direction of this effect contrasts with previous findings.[17] Although no significant interactions were recorded within each treatment group, event rates of cardiovascular death, myocardial infarction, and stent thrombosis were significantly lower with ticagrelor than with clopidogrel in patients with the high-expression *ABCB1* polymorphism. These findings led to a post-hoc analysis, indicating that combination of information from several genes could be useful to identify patients who would benefit more from ticagrelor than from clopidogrel. Although we did not record any significant interactions between genotype and treatment group, future studies might explore such combined approaches for tailoring of treatments to individual patients.

This study has several limitations. First, we did not include all genetic polymorphisms that could affect the pharmacokinetic, pharmacodynamic, and clinical effects of ticagrelor, such as *CYP3A4* or *CYP3A5* or other genetic variants possibly participating in the response to $P2Y_{12}$ inhibitors.[33] However, such investigations could be done in a pharmacokinetic and pharmacodynamic study and by expansion of analyses of available data into a genome-wide association study. Second, our study might underestimate the influence of genetic polymorphisms on the effects of clopidogrel in certain settings—eg, in clopidogrel-naive patients at start of clopidogrel treatment, and in patients with high risk of ischaemic events because treatment is accompanied by percutaneous coronary intervention and stent procedures. Because the data have not been adjusted for multiple statistical testing, significant results that do not follow a general pattern or have not been verified by other findings should be interpreted with caution. Last, 98% of the substudy cohort were white, so these results might only be relevant to white populations.

#### Contributors

SJ, RFS, MA, BJB, JH, SH, HK, PGS, and RCB designed the study under the leadership of LW. LW, MA, BJB, and JH planned the genetic and statistical analyses, which were done at AstraZeneca Research and Development and Genetics Laboratory (Alderley Park, UK; genetic analyses) and Worldwide Clinical Trials (Nottingham, UK; statistical analyses) under the leadership of MA and BJB. LW was the principal investigator, and SJ, RFS, JH, SH, HK, PGS, and RCB were members of the executive committee of the PLATO trial and accrued clinical data. All authors interpreted the results. LW drafted the report in collaboration with the coauthors who vouch for the accuracy and completeness of the reported data.

#### Conflicts of interest

LW has received research grants from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, and Schering-Plough; honoraria from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Schering-Plough, and Eli Lilly; consultancy fees from Regado Biotechnologies, Athera Biotechnologies, Boehringer Ingelheim, AstraZeneca, GlaxoSmithKline, and Eli Lilly; and lecture fees from AstraZeneca, Boehringer Ingelheim, and Eli Lilly. SJ has received research grants from AstraZeneca and Eli Lilly; advisory board member fees, travel support, and lecture fees from AstraZeneca; and honoraria from AstraZeneca, Bristol-Myers Squibb, Merck, Sanofi-Aventis, and Eli-Lilly. RFS has received research grants from AstraZeneca, Dynabyte, Eli Lilly/Daiichi Sankyo alliance, and Schering-Plough; advisory board fees from Eli Lilly/Daiichi Sankyo alliance and Schering-Plough; honoraria from AstraZeneca, Eli Lilly/Daiichi Sankyo alliance, Novartis, Medscape, GlaxoSmithKline, and Schering-Plough; consultancy fees from AstraZeneca, Eli Lilly/Daiichi Sankyo alliance, Schering-Plough, Teva, Novartis, GlaxoSmithKline, Sanofi-Aventis/Bristol-Myers Squibb, and the Medicines Company; travel support from AstraZeneca, Eli Lilly/Daiichi Sankyo alliance, and Schering-Plough. MA, BJB, and JH are employees of AstraZeneca and have equity ownership in AstraZeneca. SH has received advisory board membership fees from AstraZeneca, Bristol-Myers Squibb, Pfizer, Sanofi-Aventis, and Bayer; research grants from AstraZeneca, Bristol-Myers Squibb, Pfizer, Sanofi-Aventis, Bayer, and Boehringer Ingelheim; honoraria from AstraZeneca, Bristol-Myers Squibb, Bayer, Sanofi-Aventis, and Pfizer; lecture fees from AstraZeneca; travel support from AstraZeneca, Boehringer Ingelheim, Pfizer, and Eli Lilly; and consultancy fees from AstraZeneca and Leo Pharmaceuticals. HK has received honoraria from Eli-Lilly, GlaxoSmithKline, Roche, and Bayer; and holds a patent jointly with Roche and receives royalties for this patent. PGS has received research grants from Servier; has received fees for consultancy or participation in advisory board meetings from Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo/Eli Lilly alliance, GlaxoSmithKline, Medtronic, Merck, Otsuka Pharmaceutical, Roche, Sanofi-Aventis, Servier, and the Medicines Company; has received payment for development of educational presentations from Boehringer Ingelheim, AstraZeneca, and Merck; and has equity ownership in Aterovax. SHS has no conflicts of interest. RCB has received research grants from AstraZeneca, Bristol-Myers Squibb/Sanofi-Aventis, Johnson and Johnson, Regado Biosciences, Schering-Plough, and the Medicines Company; consultancy fees from Portola Pharmaceuticals, Regado Biosciences, and the Medicines Company; travel or accommodation expenses from AstraZeneca, Regado Biosciences, and Merck; and honoraria from AstraZeneca and Daiichi Sankyo/Eli Lilly alliance.

#### Acknowledgments

We thank the patients, investigators, and members of all committees who participated in the PLATO trial. This study was funded by AstraZeneca, which provided research grants for the PLATO clinical trial and biomarker analyses, consulting fees or honorarium, support for travel to executive committee meetings, and fees for participation in review activities.

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