Impact of genetic variants on major bleeding after percutaneous coronary intervention based on a prospective multicenter registry

Jung-Joon Cha¹,¹², Hyung Joon Joo¹,¹², Jae Hyoung Park⁴, Soon Jun Hong¹, Tae Hoon Ahn¹, Byeong-Keuk Kim³, WonYong Shin³, Sung Gyun Ahn⁵, JungHan Yoon⁶, Yong Hoon Kim⁵, Yun-Hyeong Cho⁶, Woong Chol Kang⁷, Weon Kim⁸, Young-Hyo Lim⁹, HyeonCheol Gwon¹⁰, WoongGil Choi¹¹ & Do-Sun Lim¹

Although dual antiplatelet therapy (DAPT) is essential for patients who undergo percutaneous coronary interventions, the risk of bleeding remains an unsolved problem, and there is limited information on the potential relationship between genetic variants and major bleeding. We analyzed the correlations between four major single nucleotide polymorphisms (CYP2C19, ABCB1, PON1, and P2Y12 G52T polymorphisms) and clinical outcomes in 4489 patients from a prospective multicenter registry. The primary endpoint was major bleeding, defined as a Bleeding Academic Research Consortium ≥ 3 bleeding event. The allelic frequencies of ABCB1, PON1, and both individual and combined CYP2C19 variants did not differ significantly between patient groups with and without major bleeding. However, the allelic frequency of the P2Y12 variant differed significantly between the two groups. Focusing on the P2Y12 G52T variant, patients in the TT group had a significantly higher rate of major bleeding (6.4%; adjusted hazard ratio [HR] 2.51; 95% confidence interval [CI] 1.08–5.84; p = 0.033) than patients in the other groups (GG [2.9%] or GT [1.9%]). Therefore, the TT variant of the P2Y12 G52T polymorphism may be an independent predictor of major bleeding.

Trial registration: NCT02707445 (https://clinicaltrials.gov/ct2/show/NCT02707445?term=02707445&draw=2&rank=1).

Dual antiplatelet therapy (DAPT) is essential for reducing the occurrence of ischemic events in patients undergoing percutaneous coronary intervention (PCI)¹. However, the risk of bleeding associated with DAPT remains an unsolved problem, especially in patients with a high bleeding risk (HBR)². The current guidelines recommend short-term DAPT for patients at HBR, although the current evidence is insufficient³⁴. A recently reported...
consensus statement has established that customized DAPT should be considered for patients at HBR. However, there is a lack of studies on genetic factors that affect bleeding risk.

To address this issue, we evaluated the associations of the single nucleotide polymorphisms of four genes (CYP2C19, ABCB1, PON1, and P2Y12 G52T) with major bleeding; these four genes are known to be involved in the modulation of clopidogrel absorption, metabolic activation, and biologic activity. We evaluated these associations in patients who underwent PCI and DAPT over a 1-year follow-up period.

Results

Characteristics of the enrolled patients. A total of 4489 patients were enrolled in the current study. The mean loading dose of clopidogrel was 600 mg before the index PCI, and 93.3% of patients continued to receive DAPT for at least 6 months. A total of 122 (2.7%) patients showed major bleeding during the follow-up period. Among the patients showing major bleeding events, 99 patients (81.1%) had non-procedure-related bleeding and 23 patients (18.9%) had periprocedural bleeding. The rates of the individual secondary endpoints of all-cause mortality, cardiac death, non-fatal myocardial infarction, stent thrombosis, target lesion revascularization, and stroke were 1.4%, 0.9%, 0.8%, 0.5%, 5.0%, and 0.6%, respectively. Patients who had major bleeding were more likely to be female; to be older; and to have a medical history of hypertension, diabetes mellitus, hypercholesterolemia, anemia, or chronic kidney disease than patients who did not have major bleeding. The usage of aspirin, clopidogrel, cilostazol, proton-pump inhibitors, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and beta-blockers was similar between patients with and without major bleeding. However, patients who had major bleeding were less likely to receive statins and short-term DAPT than those who did not (Table 1).

Allelic frequencies according to major bleeding. The allelic frequencies of ABCB1, PON1, and both the individual and combined CYP2C19 variants did not differ significantly between patients with and without major bleeding (Table 2). However, the allelic frequency of the P2Y12 variant differed significantly between patients with and without major bleeding (Table 2).

P2Y12 G52T polymorphisms. The patients were divided into three groups according to the P2Y12 G52T variant observed (GG, GT, and TT). The baseline characteristics of patients in all three groups showed similar trends, including HBR factors such as chronic kidney disease and anemia. The prevalence of the other genetic polymorphisms (CYP2C19, PON1, and ABCB1) did not differ among the three groups (Table 3). The number of treated vessels, the total number of stents, minimal stent size, length of the stent, P2Y12 reaction units, DAPT duration, and discharge medication were also not significantly different among the three groups (Supplementary Table 1).

Regarding the primary endpoint, the TT group showed the highest incidence of major bleeding compared to the other groups (GG vs. GT vs. TT: 2.9% vs. 1.9% vs. 6.4%, log-rank p = 0.026) (Fig. 1). However, there were no significant differences in the secondary endpoints (any cause mortality, cardiac death, myocardial infarction, stent thrombosis, target lesion revascularization, and stroke) among the groups.

Multivariate analysis for poor prognostic factors of major bleeding. In the multivariate Cox regression analysis for major bleeding, age (per 1-year increase; adjusted hazard ratio [HR] 1.03; 95% confidence interval [CI] 1.01–1.05; p = 0.004), diabetes mellitus (adjusted HR 1.45; 95% CI 1.00–2.09; p = 0.049), chronic kidney disease (adjusted HR 2.10; 95% CI 1.24–3.55; p = 0.006), anemia (adjusted HR 4.20; 95% CI 2.79–6.34; p < 0.001), and the TT variant (adjusted HR 2.51; 95% CI 1.08–5.84; p = 0.033) were found to be poor prognostic predictors after adjusting for various factors.

Discussion

We investigated the clinical impact of genetic variants on major bleeding in patients after PCI. The two key findings are as follows: (1) The P2Y12 G52T polymorphism was a predictor of HBR in patients who underwent PCI and received DAPT; and (2) patients with the TT variant had a higher incidence of major bleeding than those with other variants. Furthermore, the TT variant was found to increase the bleeding risk after PCI as per multivariate analysis.

In a recent consensus statement from the Academic Research Consortium, several factors, such as renal failure, liver failure, and anemia, have been suggested as potential contributors to HBR. In patients with HBR, short-term DAPT is recommended; however, the current guidelines provide insufficient information regarding the adjustment of the DAPT duration based on genetic information. In a recent report, the genotype-guided DAPT group showed a significant decrease in the incidence of bleeding events without differences in the total combined clinical outcomes compared to the standard-treatment DAPT group. These findings suggest that genotype-guided therapy and precision medicine may improve clinical outcomes in this patient group. In this study, the TT variant of the P2Y12 G52T polymorphism was an independent predictor of major bleeding. Multivariate analysis showed the same tendency as that reported by the current consensus on HBR in terms of renal disease and anemia, suggesting that a novel factor (the TT variant) should be considered to achieve better clinical outcomes in HBR patients.

Previous studies that evaluated the association between genetic variations and clinical outcomes have mainly focused on ischemic outcomes such as cardiac death, myocardial infarction, stent thrombosis, and target lesion revascularization. CYP2C19 is the most commonly studied gene, and several studies on this gene have shown that the gain-of-function group had a higher occurrence of bleeding events than the loss-of-function group. However, the prevalence of gain-of-function in Asians with the CYP2C19 variant is very low compared to that...
Table 1. Patients’ baseline and lesion characteristics and characteristics of in-hospital care. Data are presented as number (%) or mean (standard deviation). ACS acute coronary syndrome, MI myocardial infarction, PCI percutaneous coronary intervention, CABG coronary artery bypass graft, CVA cerebrovascular accident, CAD coronary artery disease, PRU P2Y12 reaction unit, DAPT dual antiplatelet therapy.

| Characteristics                        | Total (N = 4489) | Patients without major bleeding (N = 4367) | Patients with major bleeding (N = 122) | p     |
|----------------------------------------|------------------|-------------------------------------------|---------------------------------------|-------|
| **Baseline characteristics**           |                  |                                           |                                       |       |
| Male sex                               | 3172 (70.7%)     | 3096 (70.9%)                              | 76 (62.3%)                            | 0.050 |
| Age (years)                            | 64.5 ± 10.7      | 64.3 ± 10.7                               | 70.0 ± 10.0                           | <0.001|
| Current smoker                         | 1149 (25.6%)     | 1121 (25.7%)                              | 28 (23.0%)                            | 0.566 |
| Hypertension                           | 2824 (62.9%)     | 2728 (62.5%)                              | 96 (78.7%)                            | <0.001|
| Diabetes mellitus                      | 1468 (32.7%)     | 1406 (32.2%)                              | 62 (50.8%)                            | <0.001|
| Hypercholesterolemia                   | 1670 (37.2%)     | 1640 (37.6%)                              | 30 (24.6%)                            | 0.005 |
| Previous MI                            | 318 (7.1%)       | 306 (7.0%)                                | 12 (9.8%)                             | 0.307 |
| Previous CABG                          | 630 (14.0%)      | 608 (13.9%)                               | 22 (18.0%)                            | 0.247 |
| Previous PCI                           | 74 (1.6%)        | 70 (1.6%)                                 | 4 (3.3%)                              | 0.283 |
| Previous CVA                           | 330 (7.4%)       | 321 (7.4%)                                | 9 (7.4%)                              | 1.000 |
| Congestive heart failure               | 151 (3.4%)       | 145 (3.3%)                                | 6 (4.9%)                              | 0.477 |
| Chronic kidney disease                 | 158 (3.5%)       | 159 (3.2%)                                | 19 (15.6%)                            | <0.001|
| Anemia                                 | 1071 (23.9%)     | 987 (22.7%)                               | 84 (68.6%)                            | <0.001|
| Familial history of CAD                | 404 (9.0%)       | 387 (8.9%)                                | 17 (13.9%)                            | 0.077 |
| **Lesion characteristics**             |                  |                                           |                                       |       |
| Multivessel disease                    | 819 (18.2%)      | 796 (18.2%)                               | 23 (18.9%)                            | 0.954 |
| Presentation with ACS                  | 2381 (53.0%)     | 2311 (52.9%)                              | 70 (57.4%)                            | 0.378 |
| Left anterior descending artery         | 2689 (59.9%)     | 2626 (60.1%)                              | 63 (51.6%)                            | 0.073 |
| Left circumflex artery                 | 1097 (24.4%)     | 1064 (24.4%)                              | 33 (27.0%)                            | 0.566 |
| Right coronary artery                  | 1488 (33.1%)     | 1443 (33.0%)                              | 45 (36.9%)                            | 0.429 |
| Left main                              | 184 (4.1%)       | 178 (4.1%)                                | 6 (4.9%)                              | 0.817 |
| Presence of thrombus                   | 213 (4.7%)       | 207 (4.7%)                                | 6 (4.9%)                              | 1.000 |
| Thrombosis                             | 221 (4.9%)       | 217 (5.0%)                                | 4 (3.3%)                              | 0.523 |
| **Number of stents**                   |                  |                                           |                                       |       |
| 1                                      | 3267 (72.8%)     | 3183 (72.9%)                              | 84 (68.9%)                            | 0.187 |
| 2                                      | 970 (21.6%)      | 941 (21.5%)                               | 29 (23.8%)                            |       |
| 3 or over                              | 252 (5.6%)       | 243 (5.6%)                                | 9 (7.3%)                              |       |
| Number of lesions                      | 1.4 ± 1.0        | 1.4 ± 1.0                                 | 1.4 ± 1.0                             | 0.847 |
| Minimal stent size                     | 3.0 ± 0.5        | 3.0 ± 0.5                                 | 2.9 ± 0.4                             | 0.080 |
| Total length of stent                  | 32.1 ± 17.7      | 32.0 ± 17.6                               | 33.2 ± 20.0                           | 0.509 |
| **In-hospital care**                   |                  |                                           |                                       |       |
| **Platelet function test**             |                  |                                           |                                       |       |
| VerifyNow PRU                          | 214.1 ± 76.0     | 213.7 ± 75.8                              | 229.3 ± 81.8                          | 0.025 |
| **Discharge medication**               |                  |                                           |                                       |       |
| Aspirin                                | 4467 (99.5%)     | 4347 (99.5%)                              | 120 (98.4%)                           | 0.236 |
| Clopidogrel                            | 4407 (98.2%)     | 4287 (98.2%)                              | 120 (98.4%)                           | 1.000 |
| Cilostazol                             | 316 (7.0%)       | 303 (6.9%)                                | 13 (10.7%)                            | 0.160 |
| Proton pump inhibitor                  | 716 (16.0%)      | 692 (15.8%)                               | 24 (19.7%)                            | 0.311 |
| CCB                                    | 1247 (27.8%)     | 1219 (27.9%)                              | 28 (23.0%)                            | 0.269 |
| Statin                                 | 4198 (93.5%)     | 4091 (93.7%)                              | 107 (87.7%)                           | 0.014 |
| ARB                                    | 1533 (34.2%)     | 1493 (34.2%)                              | 40 (32.8%)                            | 0.822 |
| ACEi                                   | 1206 (26.9%)     | 1166 (26.7%)                              | 40 (32.8%)                            | 0.164 |
| BB                                     | 2756 (61.4%)     | 2688 (61.6%)                              | 68 (55.7%)                            | 0.227 |
| **Duration of DAPT**                   |                  |                                           |                                       |       |
| Total duration (days)                  | 322.4 ± 87.4     | 323.4 ± 86.3                              | 285.8 ± 114.3                         | <0.001|
| > 6 months                             | 4187 (93.3%)     | 4087 (93.6%)                              | 100 (82.0%)                           | <0.001|
| > 12 months                            | 3645 (81.2%)     | 3561 (81.5%)                              | 84 (68.9%)                            | 0.001 |
in Caucasians with the CYP2C19 variant. Another study on the Asian population found no association between the gain-of-function allele and bleeding. In addition, ABCB1, PON1, and P2Y12 showed a trend for poor clinical outcomes in terms of ischemic event. However, similar to that for CYP2C19, there was a lack of evidence regarding the association with poor clinical outcomes in terms of major bleeding for these genes.

Our results are similar to those of previous studies that showed CYP2C19, ABCB1, and PON1 variants were not associated with significant differences in major bleeding. However, our study revealed that the P2Y12 G52T variant had a significant relationship with major bleeding; this is important since studies on the association between P2Y12 and major bleeding have rarely been reported.

Fontana et al. reported that the P2Y12 G52T polymorphism is one of P2Y12 gene polymorphisms. To investigate the correlation between P2Y12 gene polymorphisms and clinical outcomes, i-T744C (rs2046934), C34T (rs6785930), and G52T (rs6809699) were evaluated. Studies on P2Y12 gene polymorphisms have not been widely conducted as compared to studies on CYP2C19 polymorphisms; this may be because the clinical impact of the P2Y12 gene polymorphism is relatively weaker than that of the CYP2C19 polymorphism.

A recent meta-analysis reported clinical outcomes according to P2Y12 gene polymorphisms. Briefly, the study found that P2Y12 gene polymorphisms may be associated with poor clinical outcomes (specifically, ischemic events, such as stent thrombosis and non-fatal myocardial infarction) and have no significant effect on bleeding. However, the meta-analysis evaluated these associations based on studies with relatively small patient populations. In addition, the bleeding analysis only included two polymorphisms (i-T744C and C34T) among the various P2Y12 receptor gene polymorphisms. One study reported that the P2Y12 G52T variant was associated with a higher incidence of major bleeding in patients with ST-elevation myocardial infarction.

A plausible explanation for the lack of association between P2Y12 G52T polymorphisms and major bleeding in previous studies is the low prevalence of the TT variant. In this study, the prevalence of the TT variant of P2Y12 G52T was 2.1%; previous genetic studies have shown a similar prevalence (2–3%). Furthermore, the prevalence of the TT variant of P2Y12 G52T was similar across different ethnic populations, unlike that of the gain-of-function allele of CYP2C19.

In G52T, the prevalence of the TT variant was relatively lower than that of the other allelic variants (i-T744C and C34T). In context, our findings suggest that previous studies may have underestimated the association between the TT variant and the risk of major bleeding owing to the low prevalence of the P2Y12 G52T variant. Plausible explanations of the mechanism include the following: (1) Inherited defects of the P2Y12 receptor, which has a potential role in platelet function, are related to platelet dysfunction and bleeding diathesis; and (2) there may be differences in ADP-induced maximal aggregation according to the P2Y12 G52T variant. Furthermore, the TT variant was related to higher ADP-induced maximal aggregation than other variants (GG or GT), which may have affected bleeding during the DAPT period. Thus, further studies are needed to address the mechanisms of major bleeding associated with the G52T variant and to confirm our results.

This study has some limitations. First, although a significantly higher occurrence of major bleeding was associated with the TT variant, there may be concerns about applying this result in real-world practice owing

| Genetic variants of four major single-nucleotide polymorphisms according to the major bleeding. |
|---------------------------------------------------------------|
| Total | Patients without major bleeding | Patients with major bleeding |
|-------|---------------------------------|------------------------------|
| (N = 4489) | (N = 4367) | (N = 122) | p |
| CYP2C19 |
| Normal metabolizer (*1/*1) | 1682 (37.5%) | 1633 (37.4%) | 49 (40.2%) | 0.817 |
| Intermediate metabolizer | 2171 (48.4%) | 2115 (48.4%) | 56 (45.9%) |
| *1/*2 | 1610 (35.9%) | 1570 (36.0%) | 40 (32.8%) |
| *1/*3 | 561 (12.5%) | 545 (12.5%) | 16 (13.1%) |
| Poor metabolizer | 636 (14.2%) | 619 (14.2%) | 17 (13.9%) |
| *2/*2 | 342 (7.6%) | 333 (7.6%) | 9 (7.4%) |
| *2/*3 | 245 (5.5%) | 238 (5.4%) | 7 (5.7%) |
| *3/*3 | 49 (1.1%) | 48 (1.1%) | 1 (0.8%) |
| PON1 |
| RR | 539 (12.0%) | 522 (12.0%) | 17 (13.9%) | 0.800 |
| QR | 2131 (47.5%) | 2074 (47.5%) | 57 (46.7%) |
| QQ | 1819 (40.5%) | 1771 (40.6%) | 48 (39.3%) |
| ABCB1 |
| CC | 1824 (40.6%) | 1769 (40.5%) | 55 (45.1%) | 0.597 |
| CT | 2060 (45.9%) | 2008 (46.0%) | 52 (42.6%) |
| TT | 605 (13.5%) | 590 (13.5%) | 15 (12.3%) |
| P2Y12 G52T (rs6809699) |
| GG | 3407 (75.9%) | 3310 (75.8%) | 97 (79.5%) | 0.025 |
| GT | 988 (22.0%) | 969 (22.2%) | 19 (15.6%) |
| TT | 94 (2.1%) | 88 (2.0%) | 6 (4.9%) |
to the low prevalence of the TT variant. However, this study is the largest population study to elucidate the correlation between the P2Y12 G52T polymorphism and major bleeding. Second, this study aimed to determine the impact of genetic variants on major bleeding after PCI. Although evaluation of the clinical impact of tailored DAPT was beyond the scope of this study, in the subgroup analysis of patients who received DAPT for 3 months, there was no significant difference in the incidence of major bleeding according to the P2Y12 G52T variant. However, since the suggested duration of DAPT was 1 year in this study, the number of patients who used DAPT for 3 months was relatively small. Thus, we cannot rule out the possibility that the number of patients included in this subgroup analysis was insufficient to achieve adequate statistical power. Third, we evaluated clinical outcomes after a 1-year follow-up after PCI. Although a long-term investigation may provide insights into the clinical impact of P2Y12 G52T polymorphisms, major bleeding is expected to be less frequent after the discontinuation of DAPT after 1 year of PCI.

In conclusion, the TT variant of the P2Y12 G52T polymorphism might be an independent predictor of major bleeding. Therefore, short-term DAPT should be considered for patients with the TT variant to prevent major bleeding.

Methods

**Study population.** From 2012 to 2014, the GENIUS study included 5000 patients who underwent PCI for coronary artery disease in 20 tertiary hospitals and investigated the influence of various genotypes on coronary artery stenting outcomes. Among the 5000 patients, 413 patients did not meet inclusion/exclusion criteria, withdrew consent, had missing genotyping results, or had missing platelet function test results. In addition, 98 patients with rapid metabolizers (*17) in CYP2C19 were excluded from the analysis owing to the confounding effects of these substances. Ultimately, 4489 total patients were evaluated in the current study.

| P2Y12 G52T (rs6809699) | GG (N = 3407) | GT (N = 988) | TT (N = 94) | p |
|------------------------|--------------|-------------|-------------|---|
| **Baseline characteristics** | | | | |
| Male sex | 2410 (70.7%) | 702 (71.1%) | 60 (63.8%) | 0.333 |
| Age (years) | 64.4 ± 10.7 | 64.7 ± 10.8 | 65.6 ± 11.8 | 0.379 |
| Body mass index (kg/m²) | 24.6 ± 3.1 | 24.6 ± 3.0 | 24.4 ± 2.9 | 0.703 |
| Current smoker | 878 (25.8%) | 254 (25.7%) | 17 (18.1%) | 0.241 |
| Hypertension | 2126 (62.4%) | 640 (64.8%) | 58 (61.7%) | 0.384 |
| Diabetes mellitus | 1115 (32.7%) | 325 (32.9%) | 28 (29.8%) | 0.827 |
| Hypercholesterolemia | 1252 (36.7%) | 388 (39.3%) | 30 (31.9%) | 0.198 |
| Previous MI | 236 (6.9%) | 73 (7.4%) | 9 (9.6%) | 0.562 |
| Previous PCI | 476 (14.0%) | 142 (14.4%) | 12 (12.8%) | 0.891 |
| Previous CABG | 55 (1.6%) | 17 (1.7%) | 2 (2.1%) | 0.910 |
| Previous CVA | 246 (7.2%) | 75 (7.6%) | 9 (9.6%) | 0.653 |
| Congestive heart failure | 106 (3.1%) | 43 (4.4%) | 2 (2.1%) | 0.130 |
| Chronic kidney disease | 127 (3.7%) | 25 (2.5%) | 6 (6.4%) | 0.062 |
| Anemia | 812 (23.8%) | 238 (24.1%) | 21 (22.3%) | 0.928 |
| Familial history of CAD | 296 (8.7%) | 99 (10.0%) | 9 (9.6%) | 0.428 |
| Presentation with ACS | 1823 (53.5%) | 509 (51.5%) | 49 (52.1%) | 0.536 |

| Genetic variants | | | | |
| CYP2C19 | | | | |
| Normal metabolizer | 1288 (37.8%) | 363 (36.7%) | 31 (33.0%) | 0.141 |
| Intermediate metabolizer | 1658 (48.7%) | 462 (46.8%) | 51 (54.3%) | |
| Poor metabolizer | 461 (13.5%) | 163 (16.5%) | 12 (12.8%) | |
| PON1 | | | | |
| RR | 401 (11.8%) | 126 (12.8%) | 12 (12.8%) | 0.705 |
| QR | 1612 (47.3%) | 478 (48.4%) | 41 (43.6%) | |
| QQ | 1394 (40.9%) | 384 (38.9%) | 41 (43.6%) | |
| ABCB1 | | | | |
| CC | 1378 (40.4%) | 410 (41.5%) | 36 (38.3%) | 0.930 |
| CT | 1564 (45.9%) | 450 (45.5%) | 46 (48.9%) | |
| TT | 465 (13.6%) | 128 (13.0%) | 12 (12.8%) | |

Table 3. Baseline characteristics and genetic variants according to P2Y12 G52T gene polymorphism. Data are presented as number (%) or mean (standard deviation). ACS acute coronary syndrome, MI myocardial infarction, PCI percutaneous coronary intervention, CABG coronary artery bypass graft, CVA cerebrovascular accident, CAD coronary artery disease.
DAPT was recommended for 1 year (3 months minimum) after the index PCI (Fig. 2). DAPT included aspirin (100 mg daily) and clopidogrel (75 mg daily). No other P2Y12 inhibitors, such as ticagrelor and prasugrel, or anticoagulants, were prescribed after PCI. The study protocol was approved by the Institutional Review Board at each participating center including the Korea University Anam Hospital, Seoul, South Korea. Written informed consent was obtained from all patients at enrollment. This study complied with the Declaration of Helsinki and was registered with ClinicalTrials.gov (number NCT02707445).

**Genotype and platelet reactivity.** Measured single nucleotide polymorphisms (SNPs) included CYP2C19*2 (rs4244285), CYP2C19*3 (rs4986893), CYP2C19*17 (rs12248560), ABCB1 (rs1045642), PON1 (rs662), and P2Y12 (rs6809699). The genotype of each SNP was determined by pyrosequencing using a PSQ 96MA Pyrosequencer (Pyrosequencing AB, Uppsala, Sweden), as previously reported. To measure the inhibitory effect of clopidogrel on platelet reactivity, the VerifyNow P2Y12 assay (Accumetrics, San Diego, California, USA) was used. Physicians and patients were blinded to residual platelet reactivity and genotype results.

**Endpoint.** The primary endpoints were major bleeding, defined as Bleeding Academic Research Consortium (BARC) 3, 4, and 5. The secondary endpoints were any cause mortality, cardiac death, myocardial infarction, stent thrombosis, target lesion revascularization, and stroke.

**Statistical analysis.** Comparisons between groups were performed using independent Student's t-test or analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables. Post hoc subgroup analysis was performed based on the baseline characteristics. To estimate the effect of the clinical outcomes, including major bleeding, any cause mortality, cardiac death, myocardial infarction, stent thrombosis, target lesion revascularization, and stroke according to genetic variation, the hazard ratio (HR) was calculated using the Cox proportional hazard model. In the multivariate Cox regression analysis, the HR was adjusted for sex, age, hypertension, diabetes mellitus, previous history of myocardial infarction, previous history of PCIs, congestive heart failure, chronic kidney disease, current smoking status, anemia, clinical presentation to acute coronary syndrome (unstable angina, non-ST elevation myocardial infarction, and ST-elevation myocardial infarction), genetic variants (P2Y12 G52T, CYP2C19, PON1, and ABCB1), duration of DAPT, multivessel involvement, minimal stent size, and total stent length. Two-tailed p-values were used, and p-values of < 0.05 were considered statistically significant. All statistical analyses were performed using the SPSS version 25.0 software (SPSS Inc., Chicago, IL, USA).
5,000 patients were assessed for eligibility

Exclusion due to
- Inclusion/exclusion criteria violation (n=81)
- Follow-up loss (n=107)
- Consent withdrawal (n=8)
- Not performing genotyping (n=26)
- Not performing VerifyNow tests (n=378)
- The gain-of-function allele CYP2C19*17 (n=98)

4,489 patients of P2Y12 G52T
  - GG (n=3407)
  - GT (n=988)
  - TT (n=94)

1 year follow-up after PCI

Primary endpoint
- Major bleeding (BARC ≥ 3)

Secondary endpoint
- Any mortality
- Cardiac death
- Myocardial infarction
- Stent thrombosis
- Target lesion revascularization
- Stroke

Figure 2. Flow chart.

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Author contributions
D.-S.L. designed the study. J.-J.C. and H.J.J. wrote the first draft. J.-J.C. and H.J.J. planned and performed statistical analyses. J.H.P., S.J.H., T.H.A., B.-K.K., W.S., S.G.A., J.Y., Y.H.K., Y.-H.C., W.C.K., W.K., Y.-H.L., H.G., W.C., and D.-S.L. contributed to the collection of data, discussions, and interpretation of the data. The decision to submit this manuscript for publication was made by all the authors and study principal investigators.

Competing interests
The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to D.-S.L.

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