**Appendix Table D11. Clinical outcome information – bleeding**

| **Author,year**  **UID**  **Country**  **Study name** | **Treatment** | **Genetic Test Used [index test]** | **Clinical Outcome** | **Outcome Definition** | **Timing of measurement** | **Genotype groups** | | **No. with outcome status within phenotype group** | **Comparative metric** | | **95% CI** | **P (between which groups?)**  **[statistical test]** | **Statistical Adjustment**  **[If YES, for what factors?]** | **Procedures for multiple comparisons** | **Comments** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Mega, 2009{Mega, 2009 141 /id}  19106084  Multinational  Genetics substudy of TRITON-TIMI 38 [Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction] | Clopidogrel 300 mg loading dose, 75 mg maintenance | CYP2C19 | Minor or major bleeding | TIMI major or minor bleeding not related to CABG; all outcomes were adjudicated by a committee unaware of group assignments | Up to 15 mo (maximum duration of treatment on trial) | IM or PM (1/\*2A, \*1A/\*3, \*1A/\*4, \*1A/\*8, \*2A/\*2A, \*2A/\*3, \*2A/\*4, \*2A/\*5A, \*2A/\*8) | | N = 11  Rate = 12.1% (Kaplan-Meier) | HR = 1.01 | | 0.51, 2.01 | 0.98 [Kaplan-Meier] | YES  [ACS subtype (STE or NSTE was used as a stratification factor)] | NO | Secondary outcome |
|  |  |  |  |  |  | EM (\*1A/\*1A)  N = 1061  (patients who received clopidogrel treatment) | | N = 30  Rate = 8.0% (Kaplan-Meier rate) |  | |  |  |  |  |  |
| Gladding, 2009{Gladding, 2009 248 /id}  19926050  New Zealand  NR | Clopidogrel 150 mg daily | Autogenomics 2C19+ assay | Bleeding | NR | 7 d | CYP2C19\*2 (and CYP2C9\*3) carriers  N=NR | | 0 | NR | | NR | NR | NR | NR | NR |
|  |  |  |  |  |  | CYP2C19\*2/\*17  N=NR | | 0 |  | |  |  |  |  |  |
| Sibbing, 2010{Sibbing, 2010 95 /id}  20083681  Germany  Part of a prospective study of the Multiplate analyzer | Clopidogrel 600 mg loading dose; clopidogrel 75 mg (1/d) and aspirin 100 mg (2/d) maintenance. | CYP2C19 \*17 | TIMI major and minor bleeding | Combined major or minor bleeding according to TIMI criteria | 30 d | \*17/\*17  N = 76 | | 6 (7.9%) | OR = 3.27 | | 1.33, 8.10 | (\*17/\*17 vs. \*1/\*1) [logistic regression]  P = 0.1 (across 3 groups) [chi-square test for trend] | NO | NO | Primary safety endpoint |
|  |  |  |  |  |  | \*17/\*1  N = 546 | | 22 (4%) |  | |  |  |  |  |  |
|  |  |  |  |  |  | \*1/\*1  N = 902 | | 23 (2.5%) |  | |  |  |  |  |  |
|  |  |  | TIMI major and minor bleeding | Combined major or minor bleeding according to TIMI criteria | 30 d | \*17/\*17 or \*17/\*1  N = 622 | | 28 (4.5%) | OR = 1.80 | | 1.03, 3.14 | NR | NO | NO | Primary safety endpoint |
|  |  |  |  |  |  | \*1/\*1  N = 902 | | 23 (2.5%) |  | |  |  |  |  |  |
|  |  |  | TIMI major and minor bleeding | Combined major or minor bleeding according to TIMI criteria | 30 d | \*17/\*17 or \*17/\*1  N = 622 | | 28 (4.5%) | OR = 1.85  OR = 3.41 | | 1.19, 2.86  1.42, 8.17 | P = 0.006  (carriers vs. non-carriers) [multivariable logistic regression]  P = NR  (\*17/\*17 vs. \*1/\*1) [multivariable logistic regression] | YES (age, sex, BMI, serum Creatinine, PPIs, abciximab, clopidogrel loading interval) | NO | Primary safety endpoint |
|  |  |  |  |  |  | \*1/\*1  N = 902 | | 23 (2.5%) |  | |  |  |  |  |  |
|  |  |  | TIMI major bleeding | Major bleeding according to TIMI criteria | 30 d | \*17/\*17  N = 76 | | 1 (1.3%) | OR = 2.04  OR = 2.39 | | 0.68, 6.12  0.95, 2.10 | (carriers vs. non-cariers)[logistic regression]  (\*17/\*17 vs. \*1/\*1) [logistic regression]  P = 0.22 (across 3 groups) [chi-square test for trend] | NO | NO | Secondary safety endpoint |
|  |  |  |  |  |  | \*17/\*1  N = 546 | | 6 (1.1%) |  | |  |  |  |  |  |
|  |  |  |  |  |  | \*1/\*1  N = 902 | | 5 (0.6%) |  | |  |  |  |  |  |
|  |  |  | TIMI minor bleeding | Minor bleeding according to TIMI criteria | 30 d | \*17/\*17  N = 76 | | 5 (6.6%) | OR = 1.72  OR = 3.46 | | 0.92, 3.22  1.30, 9.27 | (carriers vs. non-cariers)[logistic regression]  (\*17/\*17 vs. \*1/\*1) [logistic regression]  P = 0.025 (across 3 groups) [chi-square test for trend] | NO | NO | Secondary safety endpoint |
|  |  |  |  |  |  | \*17/\*1  N = 546 | | 16 (2.9%) |  | |  |  |  |  |  |
|  |  |  |  |  |  | \*1/\*1  N = 902 | | 18 (2%) |  | |  |  |  |  |  |
|  |  |  | Fatal intracranial bleeding | Fatal intracranial bleeding | 30 d | \*17/\*17  N = 76 | | 1 (1.3%) | NR | | NR | NR | NO | NO | Not mentioned as an explicit predefined endpoint |
|  |  |  |  |  |  | \*17/\*1  N = 546 | | 1 (0.2%) |  | |  |  |  |  |  |
|  |  |  |  |  |  | \*1/\*1  N = 902 | | 0 (0%) |  | |  |  |  |  |  |
| Wallentin, 2010{Wallentin, 2010 56 /id}  20801498  Multiple countries (43 countries in North America, South America, Europe, Asia, Australia)  PLATO | 75 mg  clopidogrel once daily (300–600 mg loading dose) | CYP2C19 genotyping | Major bleeding | Major bleeding | Median treatment duration = 277 d | Any LOF allele (\*2-\*8)  N = 1380 | | 143 (10%) | NR | | NR | NR | NO | NO | None |
|  |  |  |  |  |  | No LOF allele  N = 3506 | | 340 (10%) |  | |  |  |  |  |  |
|  |  |  | Major bleeding | Major bleeding | Median treatment duration = 277 d | No LOF or GOF allele  N = 1856 | | 161 (9%) | NR | | NR | 0.022 GOF allele vs. all others  [Cox regression] | NO | NO | None |
|  |  |  |  |  |  | Any LOF but no GOF allele  N = 1053 | | 108 (10%) |  | |  |  |  |  |  |
|  |  |  |  |  |  | Any GOF allele  N = 1977 | | 214 (11%) |  | |  |  |  |  |  |
|  |  |  | Major bleeding related to non-CABG | Major bleeding related to non-CABG | Median treatment duration = 277 d | Any LOF allele (\*2-\*8)  N = 1380 | | 41 (3%) | NR | | NR | NR | NO | NO | None |
|  |  |  |  |  |  | No LOF allele  N = 3506 | | 110 (3%) |  | |  |  |  |  |  |
|  |  |  | Major bleeding related to CABG | Major bleeding related to CABG | Median treatment duration = 277 d | Any LOF allele (\*2-\*8)  N = 1380 | | 107 (8%) | NR | | NR | NR | NO | NO | None |
|  |  |  |  |  |  | No LOF allele  N = 3506 | | 246 (7%) |  | |  |  |  |  |  |
| Bonello{Bonello, 2010 45 /id}  2010  20708365  France  NR | Oral LDs of 250 mg aspirin and 600 mg clopidogrel | CYP2C19\*2 | TIMI major bleeding | TIMI major bleeding | In hospital | Wild-type  N = 277 | | 0 (%) | NR | | NR | NS | NR | NR | None |
|  |  |  |  |  |  | Heterozygotes 2C19\*2  N = 123 | | 0 (0%) |  | |  |  |  |  |  |
|  |  |  |  |  |  | Homozygotes 2C19\*2  N = 11 | | 0 (0%) |  | |  |  |  |  |  |
|  |  |  | TIMI minor bleeding | TIMI minor bleeding | In hospital | Wild-type  N = 277 | | 4 (1%) | NR | | NR | NS | NR | NR | None |
|  |  |  |  |  |  | Heterozygotes 2C19\*2  N = 123 | | 0 (0%) |  | |  |  |  |  |  |
|  |  |  |  |  |  | Homozygotes 2C19\*2  N = 11 | | 0 (0%) |  | |  |  |  |  |  |
|  |  |  | TIMI major or minorbleeding | TIMI minor bleeding | In hospital | Wild-type  N = 277 | | 4 (1%) | NR | | NR | NS | NR | NR | None |
|  |  |  |  |  |  | Heterozygotes 2C19\*2  N = 123 | | 0 (0%) |  | |  |  |  |  |  |
|  |  |  |  |  |  | Homozygotes 2C19\*2  N = 11 | | 0 (0%) |  | |  |  |  |  |  |
| Sorich, 2010{Sorich, 2010 49 /id}  20492467  707 sites in 30 countries  Substudy of TRITON-TIMI 38 | clopidogrel (300-mg loading dose and 75-mg daily maintenance dose) for 6–15 months. | CYP2C19 | Major or minor bleeding | Major or minor bleeding | 15 months | extensive metabolizers | | NR | 3.4% | | 2.6-4.2 | NR | NR | No |  |
|  |  |  | Major or minor bleeding | Major or minor bleeding | 15 months | RM | | NR | 3.5% | | 2.0-5.5 | NR | NR | No |  |
| Pare{Pare, 2010 46 /id}  2010  20979470  Multinational  CURE | clopidogrel (at a dose  of 75 mg per day) in combination  with aspirin | CYP2C19 | Major Bleeding - CURE trial | Major bleeding | 12 months | Poor metabolizers  N = 61 | | 0 (0%) | NR | | NR | NR | NR | NR | None |
|  |  |  |  |  |  | Intermediate metabolizers  N = 437 | | 19 (4%) |  | |  |  |  |  |  |
|  |  |  |  |  |  | Extensive metabolizers  N = 1033 | | 42 (4%) |  | |  |  |  |  |  |
|  |  |  |  |  |  | Ultra metabolizers  N = 847 | | 39 (5%) |  | |  |  |  |  |  |
|  |  |  |  |  |  | Unknown status  N = 152 | | 2 (1%) |  | |  |  |  |  |  |
| Pare{Pare, 2010 46 /id}  2010  20979470  Multinational  ACTIVE-A | clopidogrel (at a dose  of 75 mg per day) in combination  with aspirin | CYP2C19 | Major Bleeding – ACTIVE trial | Major bleeding | Median 3.6 y | Poor  N = 9 | | 0 (0%) | NR | | NR | NR | NR | NR | None |
|  |  |  |  |  |  | Intermediate metabolizers  N = 93 | | 10 (11%) |  | |  |  |  |  |  |
|  |  |  |  |  |  | Extensive metabolizers  N = 199 | | 10 (5%) |  | |  |  |  |  |  |
|  |  |  |  |  |  | Ultra metabolizers  N = 222 | | 8 (4%) |  | |  |  |  |  |  |
|  |  |  |  |  |  | Unknown status  N = 37 | | 4 (11%) |  | |  |  |  |  |  |
| Campo  2011{Campo, 2011 13 /id}  21679849  Italy  NR | Clopidogrel + aspirin | TaqMan | Bleeding event | Major + minor (TIMI classification) | 1 mo to 1 yr after PCI | | \*2 noncarriers  N = 219 | 219 | | 16 (7.3%) | NR | 0.4 vs, next row [Fisher exact test] | NO | NO | no |
|  |  |  |  |  |  | | \*2 carriers  N = 81 | 81 | | 3 (3.7%) |  |  |  |  |  |
|  |  |  |  |  |  | | \*17 noncarriers  N = 198 | 198 | | 6 (3%) | NR | 0.01 vs, next row [Fisher exact test] |  | NO | NO |
|  |  |  |  |  |  | | \*17 carriers  N = 102 | 102 | | 13 (1.7%) |  |  |  |  |  |
|  |  |  |  | Superficial  (BleedScore classification) | 1 mo to 1 yr after PCI | | \*2 noncarriers  N = 219 | 219 | | 22 (10.1%) | NR | NR | NO | NO | NO |
|  |  |  |  |  |  | | \*2 carriers  N = 81 | 81 | | 8 (9.8%) |  |  |  |  |  |
|  |  |  |  |  |  | | \*17 noncarriers  N = 198 | 198 | | 4 (2.0%) | NR | NR | NO | NO | NO |
|  |  |  |  |  |  | | \*17 carriers  N = 102 | 102 | | 18 (9.1%) |  |  |  |  |  |
|  |  |  |  | Internal (melena, hematuria, hematemesis, epistaxis)+ alarming (intracranial or needing transfusion) | 1 mo to 1 yr after PCI | | \*2 noncarriers  N = 219 | 219 | | 20 (9.1%) | NR | 0.4 vs, next row [Fisher exact test] | NO | NO | NO |
|  |  |  |  |  |  | | \*2 carriers  N = 81 | 81 | | 6 (7.4%) |  |  |  |  |  |
|  |  |  |  |  |  | | \*17 noncarriers  N = 198 | 198 | | 10 (5%) | NR | 0.01 vs, next row [Fisher exact test] | NO | NO | NO |
|  |  |  |  |  |  | | \*17 carriers  N = 102 | 102 | | 16 (16%) |  |  |  |  |  |
|  |  |  |  | “Composite bleeding endpoints” | 1 mo to 1 yr after PCI | | \*17 carriers  N = 102 | NR | | HR = 2.3 | 1.03-5.3 | 0.03  [Cox proportional hazards model] | YES  [age, on-clopidogrel platelet reactivity at 30 d, additional clinical, angiographic, and genetic characteristics] | NO | NO |
|  |  |  |  |  |  | | \*17 noncarriers  N = 198 | NR | |  |  |  |  |  |  |
| Harmsze, 2012{Harmsze, 2012 18224 /id}  22228204  Netherlands  NR | Clopidogrel | Real-time PCR | TIMI major bleeding | NR | 1 yr after PCI | | Ultrarapid metabolizer (\*1 or \*17/\*17) [n=240] | 5.0% | | HR 2.7 vs. extensive metabolizer | 1.1-7.0 | For HR, 0.039  Also 0.048 among this and next 2 rows  [Cox proportional hazards] | YES (sex, age, BMI, current smoking, eGFR <60ml/min, clopidogrel loading dose, coumarin use) | NR | NONE |
|  |  |  |  |  |  | |  |  | | HR adj. for LTA, 2.8  HR adj. for VerifyNow, 2.4 | 1.1-7.7  1.0-6.3 | 0.038  0.046  [Cox proportional hazards] | YES (same as above + ptatelet function data) |  |  |
|  |  |  |  |  |  | | Extensive metabolizer (\*1/\*1)  [n=351] | 2.0% | | NR | NR | NR |  |  |  |
|  |  |  |  |  |  | | Intermediate/poor metabolizer (\*2/\*1, \*2, or \*17) [n=229] | 2.3% | | HR 1.3 vs. extensive metabolizer | 0.45-4.0 | 0.60  [Cox proportional hazards] | YES (sex, age, BMI, current smoking, eGFR <60ml/min, clopidogrel loading dose, coumarin use) |  |  |
| Luo, 2011{Luo, 2011 18198 /id}  22118006  China  NR | LD clopidogrel 300mg and MD 75mg/d and aspirin 300mg LD and MD 100mg/d | CYP2C19  \*1/\*1 | bleeding | bleeding | 6 months | | CYP2C19  \*1/\*1 | 33/936 | | HR 0.72 | 0.38-2.58 | >0.05  comparing with the next row  chi-square test | NR | NR |  |
|  |  | CYP2C19  \*1/\*2 or \*2/\*2 |  |  |  | | CYP2C19  \*1/\*2 or \*2/\*2 | 30/802 | |  |  |  |  |  |  |
| Dai, 2012{Dai, 2012 18226 /id}  22704413  China  NR | Clopidogrel and aspirin | PCR-FRLP | TIMI total bleeding | Major or minor, including GI bleed, purpura, hematuria, retinal bleeding, and intracranial hemorrhage | 1 month | | \*17/\*17 (n=6) | 1 | | NR | NR | NS vs. wild type/wild type  [chi-square test for trend] | NR | NR | NONE |
|  |  |  |  |  |  | | \*17/wild type (n=71) | 10 | |  |  | <0.01 vs. wild type/wild type  [chi-square test for trend] | NR |  |  |
|  |  |  |  |  |  | | Wild type/wild type (n=443) | 20 | |  |  |  | NR |  |  |
|  |  |  |  |  |  | | \*17 carriers (n=77) | 11 | | OR 1.95 | 1.31-3.16 | <0.01 vs. noncarriers [mutilple logistic regression model] | YES age, sex, BMI, serum creatinine |  |  |
|  |  |  |  |  |  | | \*17 noncarriers (n=443) | 20 | |  |  |  | NR |  |  |
|  |  |  | TIMI major bleeding |  |  | | \*17/\*17 (n=6) | 1 | |  |  | NS vs. wild type/wild type  [chi-square test for trend] | NR |  |  |
|  |  |  |  |  |  | | \*17/wild type (n=71) | 5 | |  |  | <0.05 vs. wild type/wild type  [chi-square test for trend] | NR |  |  |
|  |  |  |  |  |  | | Wild type/wild type (n=443) | 9 | |  |  |  | NR |  |  |
|  |  |  | TIMI minor bleeding |  |  | | \*17/\*17 (n=6) | 0 | |  |  | <0.01 vs. wild type/wild type  [chi-square test for trend] | NR |  |  |
|  |  |  |  |  |  | | \*17/wild type (n=71) | 5 | |  |  | <0.01 vs. wild type/wild type  [chi-square test for trend] | NR |  |  |
|  |  |  |  |  |  | | Wild type/wild type (n=443) | 11 | |  |  |  | NR |  |  |
| Bhatt, 2012{Bhatt, 2012 18205 /id}  22450429  USA  CHARISMA | clopidogrel | CYP2C19\*2or\*3  (carrier of loss of function allele) | major bleeding | major bleeding | 800 days | | CYP2C19\*2 or \*3 | carriers 28/665 | | NR | NR | 0.59  comparing with non-carriers  log-rank test | NR | NR | NR |
|  |  |  |  |  |  | |  | non-carriers  60/1601 | |  |  |  |  |  |  |
| Bhatt, 2012{Bhatt, 2012 18205 /id}  22450429  USA  CHARISMA | clopidogrel | CYP2C19\*2or\*3  (carrier of loss of function allele) | all bleedings | all bleedings | 800 days | | CYP2C19\*2 or \*3 | carriers 240/665 | | NR | NR | 0.005  comparing with non-carriers  log-rank test | NR | NR | NR |
|  |  |  |  |  |  | |  | non-carriers  681/1601 | |  |  |  |  |  |  |
|  |  |  |  |  |  | |  |  | |  |  |  |  |  |  |
| Bhatt, 2012{Bhatt, 2012 18205 /id}  22450429  USA  CHARISMA | clopidogrel | CYP2C19\*2or\*3  (carrier of gain of function allele) | major bleeding | major bleeding | 800 days | | CYP2C19\*17 | carriers 32/872 | | NR | NR | 0.677  comparing with non-carriers  log-rank test | NR | NR | NR |
|  |  |  |  |  |  | |  | non-carriers  56/1394 | |  |  |  |  |  |  |
| Bhatt, 2012{Bhatt, 2012 18205 /id}  22450429  USA  CHARISMA | clopidogrel | CYP2C19\*2or\*3  (carrier of gain of function allele) | all bleedings | all bleedings | 800 days | | CYP2C19\*17 | carriers 367/872 | | NR | NR | 0.203  comparing with non-carriers  log-rank test | NR | NR | NR |
|  |  |  |  |  |  | |  | non-carriers  554/1394 | |  |  |  |  |  |  |
|  |  |  |  |  |  | |  |  | |  |  |  |  |  |  |
| Bhatt, 2012{Bhatt, 2012 18205 /id}  22450429  USA  CHARISMA | clopidogrel | CYP2C19\*2/\*2 or \*2/\*3 | major bleeding | major bleeding | 800 days | | CYP2C19\*2/\*2 | n=0 (0) | | NR | NR | NR | NR | NR | NR |
| Bhatt, 2012{Bhatt, 2012 18205 /id}  22450429  USA  CHARISMA | clopidogrel | CYP2C19 wt/\*2 or wt/\*3 | major bleeding | major bleeding | 800 days | | CYP2C19 wt/\*2 or wt/\*3 | n=22(4.8%) | | NR | NR | NR | NR | NR | NR |
| Bhatt, 2012{Bhatt, 2012 18205 /id}  22450429  USA  CHARISMA | clopidogrel | CYP2C19 wt/wt | major bleeding | major bleeding | 800 days | | CYP2C19 wt/wt | n=34 (3.8%) | | NR | NR | NR | NR | NR | NR |
| Bhatt, 2012{Bhatt, 2012 18205 /id}  22450429  USA  CHARISMA | clopidogrel | CYP2C19 Wt/\*17 or \*17/\*17 | major bleeding | major bleeding | 800 days | | CYP2C19 Wt/\*17 or \*17/\*17 | 26 (3.6%) | | NR | NR | NR | NR | NR | NR |
| Bhatt, 2012{Bhatt, 2012 18205 /id}  22450429  USA  CHARISMA | clopidogrel | CYP2C19 \*2/\*17 or \*3/\*17 | major bleeding | major bleeding | 800 days | | CYP2C19 \*2/\*17 or \*3/\*17 | n=6 (3.8%) | | NR | NR | NR | NR | NR | NR |
| Bhatt, 2012{Bhatt, 2012 18205 /id}  22450429  USA  CHARISMA | clopidogrel | total | major bleeding | major bleeding | 800 days | | total | n=88 (3.9%) | | NR | NR | NR | NR | NR | NR |
|  |  |  |  |  |  | |  |  | |  |  |  |  |  |  |
|  |  |  |  |  |  | |  |  | |  |  |  |  |  |  |
| Bhatt, 2012{Bhatt, 2012 18205 /id}  22450429  USA  CHARISMA | clopidogrel | CYP2C19\*2/\*2 or \*2/\*3 | all bleeding | all bleeding | 800 days | | CYP2C19\*2/\*2 | n=11 (21.2%) | | NR | NR | NR | NR | NR | NR |
| Bhatt, 2012{Bhatt, 2012 18205 /id}  22450429  USA  CHARISMA | clopidogrel | CYP2C19 wt/\*2 or wt/\*3 | all bleeding | all bleeding | 800 days | | CYP2C19 wt/\*2 or wt/\*3 | n=174(38.1%) | | NR | NR | NR | NR | NR | NR |
| Bhatt, 2012{Bhatt, 2012 18205 /id}  22450429  USA  CHARISMA | clopidogrel | CYP2C19 wt/wt | all bleeding | all bleeding | 800 days | | CYP2C19 wt/wt | n=369 (41.7%) | | NR | NR | NR | NR | NR | NR |
| Bhatt, 2012{Bhatt, 2012 18205 /id}  22450429  USA  CHARISMA | clopidogrel | CYP2C19 Wt/\*17 or \*17/\*17 | all bleeding | all bleeding | 800 days | | CYP2C19 Wt/\*17 or \*17/\*17 | 312(43.6%) | | NR | NR | NR | NR | NR | NR |
| Bhatt, 2012{Bhatt, 2012 18205 /id}  22450429  USA  CHARISMA | clopidogrel | CYP2C19 \*2/\*17 or \*3/\*17 | all bleeding | all bleeding | 800 days | | CYP2C19 \*2/\*17 or \*3/\*17 | n=55 (35.3%) | | NR | NR | NR | NR | NR | NR |
| Bhatt, 2012{Bhatt, 2012 18205 /id}  22450429  USA  CHARISMA | clopidogrel | total | all bleeding | all bleeding | 800 days | | total | n=921 (40.6%) | | NR | NR | NR | NR | NR | NR |
| Kim, 2012 {Kim, 2012 18236 /id}  22007612  Korea  ACCEL-TRIPLE | cilostazol 100 mg twice a day  clopidogrel 75 mg once a day  aspirin 200mg once a day | CYP2C19 | bleeding | bleeding | 30 days | | EM | 48 | | 0/48=0 | NR | NR | NR | NR | none |
|  |  |  |  |  |  | | IM | 54 | | 0/54=0 |  |  |  |  |  |
|  |  |  |  |  |  | | PM | 25 | | 0/25=0 |  |  |  |  |  |
| Goodman, 2012{Goodman, 2012 18213 /id}  22261200  Multi-country  PLATO | Clopidogrel 300-mg loading dose, 75-mg daily maintenance  dose | CYP2C19 \*2 | major bleeding | TIMI major bleeding | 12 months | | CYP2C19 loss-of-function carriers (\*2 through \*8) on a PPI  n=434 | 35 (8%) | | HR= 1.46 | 1.08–1.96 | NR | no | NR |  |
|  |  |  |  |  |  | | non carriers of CYP2C19 loss-of-function allele or not taking a PPI  n=2418 | 126 (5.2%) | |  |  |  |  |  |  |
| Siller-matula, 2012{Siller-Matula, 2012 1 /id}22260716  Austria  PEGASUS-PCI | clopidogrel LD 600mg, MD 75mg | CYP2C19 \*2 | Major bleeding | TIMI major bleeding | 12 months | | regular metabolizers (CYP2C19\*1/\*1)  n=167 | 4 (2.2%) | |  |  | 0.487  (carrier vs noncarrier)  [log rank test] | No | NR |  |
|  |  |  |  |  |  | | ultra-metabolizers  (CYP2C19\*1/\*17 or \*17/\*17)  N=141 | 6 (4.1%) | |  |  |  |  |  |  |
|  |  | CYP2C19 \*2 | Major bleeding | TIMI major bleeding | 12 months | | regular metabolizers (CYP2C19\*1/\*1)  n=167 | 5 (2.9%) | | NR | NR | P = 0.053  (ANOVA)  (between regular and heterozygote and homozygote poor metabolizers) |  |  |  |
|  |  |  |  |  |  | | heterozygote ultra-metabolizers  (CYP2C19\*1/\*17  N=nr | 2% | |  |  |  |  |  |  |
|  |  |  |  |  |  | | homozygote ultra-metabolizers (CYP2C19\*17/\*17  n=NR | 9.5% | |  |  |  |  |  |  |
| Jeong, 2011{Jeong, 2011 18207 /id}  22045970  Korea  NR | LD: 600 mg clopidogrel & 300 mg aspirin  MD: 75 mg/d clopidogrel & aspirin 200 mg/d for 1 month and 100-200 mg/day for 1 year | CYP2C19 \*1, \*2, and \*3 | Bleeding | All bleeding | 1 year | | 1/\*1  N=104 | 3 (2.9) | | NR | NR | P=0.810  (0,1 and 2 CYP2C19 LOF allele)  [Cox regression]  P=0.057  (across all groups)  [Cox regression] |  |  |  |
|  |  |  |  |  |  | | \*1/\*2  N=98 | 1 (1.0) | |  |  |  |  |  |  |
|  |  |  |  |  |  | | \*1/\*3  N=30 | 4 (13.3) | |  |  |  |  |  |  |
|  |  |  |  |  |  | | \*2/\*2  N=20 | 0 | |  |  |  |  |  |  |
|  |  |  |  |  |  | | \*2/\*3  N=14 | 0 | |  |  |  |  |  |  |
| Jeong, 2012{Jeong, 2012 18322 /id}  22837373  Korea  ACCEL-DM | elective patients LD clopidogrel 300mg.  Acute MI clopidogrel LD 600 mg. after randomization, triple group receive cilostazol 100mg bid, clopidogrel 75mg MD, aspirin 200 mg/d, double group receive clopidogrel 150mg/d MD, and aspirin 200 mg/d. | CYP2C19 | bleeding events | bleeding events | 30-day | | CYP2C19\*1 | 46 | | 0/46 | NR | NR | NR | NR | comparing with the lower row 0.097  t-test |
|  |  |  |  |  |  | | CYP2C19\*2 | 26 | | 0/26 |  |  |  |  |  |
|  |  |  |  |  |  | | CYP2C19\*3 | 8 | | 0/8 |  |  |  |  |  |

NR = not reported; NS = non-significant.