**Appendix Table E36. Results from studies assessing the ability of VerifyNow to predict major adverse cardiovascular events in patients with ischemic heart disease**

| **Author, year**  **UID**  **Country**  **Study name** | **Treatment** | **Pheno-typic Test Used [index test]** | **Clinical Outcome** | **Outcome Definition** | **Timing of measurement** | **Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP** | **Outcome status (e.g., bleeding or no bleeding)** | **No. with outcome status within phenotype group** | **Comparative metric (OR, RR, HR)** | **95% CI** | **P (between which groups?)**  **[statistical test]** | **Adjusted? [YES, NO, NR]**  **If YES, for what factors?** | **Procedures for multiple comparisons [YES, NO, NR]** | **Comments (e.g., additional data in figures)** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Cotton, 2010  20406238  UK  NR | 300 mg or 600 mg LD Clopidogrel and maintaining 75 mg + Aspirin | Verify Now | MACE | MI + revasculari-zation + cardio-vascular admissions | 1 year | PRU<240  (n=19) | MACE | 0 | NR | NR | P<0.02  (high PRU vs low PRU)  [Fisher’s exact] | NR | NR |  |
|  |  |  |  |  |  | PRU>240  (n=29) |  | 5 |  |  |  |  |  |  |
| Breet, 2010  20179285  Netherlands  POPULAR | maintaining Clopidogrel 75 mg daily + aspirin 80-100mg daily | Verify Now P2Y12 | Death combined | All-cause death, nonfatal MI, stent thrombosis and stroke | 1-year | High OTPR  >236 PRU  (n=406) | Death combined | 54 (13.3) | OR=2.53 | 1.63-3.91 | <0.001  (high OTPR vs low OTPR)  [Fisher’s exact] | No | NR |  |
|  |  |  |  |  |  | Normal  OTPR  ≤236 PRU  (n=646) |  | 37 (5.7) |  |  |  |  |  |  |
|  | maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily | Verify Now P2Y12 | Death combined | All-cause death, nonfatal MI, stent thrombosis and stroke | 1-year | High OTPR  >236 PRU  (n=406) | Death combined | 54(406)  (13.3) | AUC: 0.62  Sens: 0.604  Spec: 0.631 | 0.57-0.67  0.502-0.699  0.6-0.661 | NR | No | NR |  |
| Kim, 2010  20449634  Korea  NR | 300-600mg LD and 75 mg maintain dose clopidogrel | Verify Now P2Y12 (PRU) | composite | composite | 6 months | <240  (n=512) | composite | 1.7% | OR=2.82 | 1.23-6.48 | 0.011 | NR | NR |  |
|  |  |  |  |  |  | ≥240  (n=546) |  | 4.6% |  |  |  |  |  |  |
| Ko, 2011  21315223  Korea  NR | 75 mg/d clopidogrel & 100 mg/d aspirin | Verify Now P2Y12 Assay | Major adverse cardio-vascular events (MACE) | Death, MI, stroke, and target vessel revasculari-zation | 30 days | Hyporespon-siveness (PRU>274)  (n=121) | MACE+ | NR | OR=5.95 | 1.26-28.1) | P=0.024 between hyporesponsive vs normal responsive | YES; All Only variables with p <0.15 were entered into final model; final list is NR; only reported variables include: total stent length, hyporesponsive-ness to clopidogrel, and no previous use of statin | NR |  |
|  | 75 mg/d clopidogrel & 100 mg/d aspirin | Verify Now P2Y12 Assay | Major adverse cardio-vascular events (MACE) | Death, MI, stroke, and target vessel revasculari-zation | From PCI to 30 days | Hyporespon-siveness (PRU>274)  (n=101) | MACE + | NR | Sens=0.833  Spec=0.481 | NR | NR | NR | NR | NR |
|  | 75 mg/d clopidogrel & 100 mg/d aspirin | Verify Now P2Y12 Assay | Major adverse cardio-vascular events (MACE) | Death, MI, stroke, and target vessel revasculari-zation | From PCI to 30 days | NR | MACE + | NR | NR | NR | NR | NR | NR | AUC = 0.649; P=0.032  (Fig2b) |
| Campo, 2010  20951320  10 sites in Italy, Belgium, France, Spain  3T/2R trial | Clopidogrel LD 300 or 600 mg or maintaining 75mg daily | Verify Now P2Y12 | Composite primary end point | death, MI, and stroke | 1-year | Full responder  (n=289) | Composite primary end point | 17 (5.9) | HR=1.20 | 1.1-1.3 | <0.01 | NR | NR |  |
|  |  |  |  |  |  | Poor responder  (n=179) |  | 31 (17.3) |  |  |  |  |  |  |
|  | Clopidogrel LD 300 or 600 mg or maintaining 75mg daily | Verify Now P2Y12 | Composite primary end point | death, MI, and stroke | 1-year | Full responder  (n=289) | death, MI, and stroke | 17 (5.9) | HR=1.3 | 1.07-1.56 | 0.01 | Yes, variables with p-value>0.2 | NR |  |
|  |  |  |  |  |  | Poor responder  (n=179) |  | 31 (17.3) |  |  |  |  |  |  |
|  | Clopidogrel LD 300 or 600 mg or maintaining 75mg daily | Verify Now P2Y12 | Composite primary end point | death, MI, and stroke | 0-3 days | Full responder  (n=289) | death, MI, and stroke | 8 (2.8) | NR | NR | 0.004 | NR | NR |  |
|  |  |  |  |  |  | Poor responder  (n=179) |  | 20 (11.1) |  |  |  |  |  |  |
|  | Clopidogrel LD 300 or 600 mg or maintaining 75mg daily | Verify Now P2Y12 | Composite primary end point | death, MI, and stroke | 3-365 days | Full responder  (n=289) | death, MI, and stroke | 11 (3.8) | HR=1.15 | 1.05-1.29 | 0.01 | NR | NR |  |
|  |  |  |  |  |  | Poor responder  (n=179) |  | 17 (9.5) |  |  |  |  |  |  |
|  | Clopidogrel LD 300 or 600 mg or maintaining 75mg daily | Verify Now P2Y12 | Composite primary end point | death, MI, and stroke | 3-365 days | Full responder  (n=289) | death, MI, and stroke |  | HR=1.12 | 1.06-1.25 | 0.03 | Yes, variables with p-value>0.2 | NR |  |
|  |  |  |  |  |  | Poor responder  (n=179) |  |  |  |  |  |  |  |  |
| Campo, 2011  21679849  Italy  NR | Clopidogrel + aspirin | Verify Now | Death, MI, or stroke |  |  | Poor response at baseline (N=107) |  | 14 | HR 3.1 | 1.3-7.3 | Table 3 gives <0.01 but text gives 0.02 vs. next row (t-test) |  |  | Maybe HR not for composite end point but rather any AE? Text unclear |
|  |  |  |  |  |  | Full response at baseline (n=193) |  | 7 |  |  |  |  |  |  |
|  | Clopidogrel + aspirin | Verify Now | Death, MI, or stroke |  |  | Poor response at 1 mo (n=40) |  | 17 | HR 28.5 | 8-104 | <0.01 vs. next row (t-test) |  |  |  |
|  |  |  |  |  |  | Full response at 1 mo (n=260) |  | 4 |  |  |  |  |  |  |
|  | Clopidogrel + aspirin | Verify Now | Death, MI, or stroke |  |  | Full response at baseline but poor response at 1 mo (n=8) |  |  |  |  | <0.01vs. next row (1-way ANOVA) |  |  | Kaplan-Meier curves given in Fig 3 |
|  |  |  |  |  |  | Poor response at baseline and at 1 mo (n=32) |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  | Poor response at baseline but full response at 1 mo (n=75) |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  | Full response at baseline but poor response at 1 mo (n=185) |  |  |  |  |  |  |  |  |
|  | Clopidogrel + aspirin | Verify Now | Death, MI, or stroke |  |  | Enhanced response (PRU ≤85) at 1 mo (n=75) |  | 1 |  |  |  |  |  | This and rest of data in table from Fig 5 |
|  |  |  |  |  |  | Normal response (PRU 86-238) at 1 mo (N=185) |  | 3 |  |  |  |  |  |  |
|  |  |  |  |  |  | Poor response (PRU ≥239) at 1 mo (n=40) |  | 17 |  |  |  |  |  |  |
|  | Clopidogrel + aspirin | Verify Now | Ischemic endpoints (details NR) |  |  |  |  |  | Difference in AUC for 1 mo vs baseline, 0.21 | 0.05-0.33 | <0.01 |  |  |  |
|  |  |  |  |  | Baseline | >/=214 PRU cutoff |  |  | AUC 0.69 | 0.63-0.74 |  |  |  |  |
|  |  |  |  |  |  |  |  |  | Sensitivity 78%, specificity 63%, PPV 14%, NPV 97% |  |  |  |  |  |
|  |  |  |  |  | 1 mo | >/=239 PRU cutoff |  |  | AUC 0.87 | 0.63-0.74 |  |  |  |  |
|  |  |  |  |  |  |  |  |  | Sensitivity 81%, specificity 92%, PPV 43%, NPV 98% |  |  |  |  |  |
| De Miguel Castro, 2009  19232185  Spain  NR | clopidogrel 300 mg LD + 75 mg/d MD w/ aspirin250 mg LD + 100 mg MD | Verify Now | MACE | Death from any cause, nonfatal acute myocardial infarction, new revasculari-zation (CABG or PCI) after readmission for NSTEACS, and ischemic stroke | 1 year | PRU>175 | MACE | 13 (20%) | Sensitivity 0.75  Specificity 0.64 | NR | NR | NR | NR |  |
|  |  |  |  |  |  | PRU≤175 |  | 5 (5%) |  |  |  |  |  |  |
|  | clopidogrel 300 mg LD + 75 mg/d MD w/ aspirin 250 mg LD + 100 mg MD | Verify Now | MACE | Death from any cause, nonfatal acute myocardial infarction, new revasculari-zation (CABG or PCI) after readmission for NSTEACS, and ischemic stroke | 1 year | PRU>175 | MACE | 13 (20%) |  |  | P=0.0013  (Between PRU>175 and PRU ≤175)  [Event free survival by kaplan meir method and Log rank test] | NR | NR |  |
|  |  |  |  |  |  | PRU≤175 |  | 5 (5%) |  |  |  |  |  |  |
|  | clopidogrel 300 mg LD + 75 mg/d MD w/ aspirin 250 mg LD + 100 mg MD | Verify Now | MACE | Death from any cause, nonfatal acute myocardial infarction, new revasculari-zation (CABG or PCI) after readmission for NSTEACS, and ischemic stroke | 1 year | PRU>175 | MACE | 13 (20%) | OR=3.9 | 1.2-15.4 | P=0.024  (Between PRU>175 and PRU ≤175)  [logistic regression] | Yes;  not listed - All variables (demographic, clinical, and angiographic) that had shown an association with PPR, percentage of IPA, or MACE with a probability value of P≤.20 in the univariate models | NR |  |
|  | clopidogrel 300 mg LD + 75 mg/d MD w/ aspirin 250 mg LD + 100 mg MD | Verify Now | MACE | Death from any cause, nonfatal acute myocardial infarction, new revasculari-zation (CABG or PCI) after readmission for NSTEACS, and ischemic stroke | 1 year | Quartile 1 (<115 PRU) | MACE | 1 (2.7%) |  |  | P=0.009  (Between quartiles)  [Chi square or Fishers exact test] | NO | NR |  |
|  |  |  |  |  |  | Quartile 2 (115 -164 PRU) |  | 3 (7.9%) |  |  |  |  |  |  |
|  |  |  |  |  |  | Quartile 3 (165 -206 PRU) |  | 4 (10.5%) |  |  |  |  |  |  |
|  |  |  |  |  |  | Quartile 4 ( >206 PRU) |  | 9 (21.6%) |  |  |  |  |  |  |
| Huczek, 2011  21443410  Poland  NR | Clopidogrel 600mg LD and 75mg MD  Aspirin: 300 mg LD & 75 mg MD | Verify Now P2Y12 assay | Composite ischemic end point | CV death (defined as death from cardiac causes or stroke) and non-fatal myocardial infarction (defined as rise in CK-MB of at least twice the upper limit of normal with either ischemic symptoms or typical ECG changes); | 30 days | Low PR | Ischemic events | 7  (Non-fatal MI:4  Cardio-vascular death: 3  Early stent thrombosis\*: 2) | Ref group vs high | Ref group vs high | Ref group vs high |  |  |  |
|  |  |  |  |  |  | Medium PR | Ischemic events | 2  (Non-fatal MI:1  Cardiovascular death:1 Early stent thrombosis: 0) | Ref group vs high | Ref group vs high | Ref group vs high |  |  |  |
|  |  |  |  |  |  | High PR | Ischemic events | 17  (Non-fatal MI:8  Cardio-vascular death: 9 Early stent thrombosis: 5) | 7.26  1.51 | 1.67‑31.6  0.96‑2.36 | 0.008 (High vs medium)  0.074 (High vs Low) | YES  female sex, BMI, diabetes, ejection fraction | NR | Kaplan–Meier time-to-event curves in Fig 4 |
|  | Clopidogrel 600mg LD and 75mg MD  Aspirin: 300 mg LD & 75 mg MD | Verify Now P2Y12 assay | Composite ischemic end point | CV death (defined as death from cardiac causes or stroke) and non-fatal myocardial infarction (defined as rise in CK-MB of at least twice the upper limit of normal with either ischemic symptoms or typical ECG changes); | 30 days | PRU ≥225 | Ischemic events | NR | Sensitivity: 61.5%  specificity: 77%  Area under the curve (AUC): 0.64 | Sensitiv-ity of (40.6-79.8)  specifi-city (72.3-81.3)  0.59–0.69 | P=0.038 | NR | NR | ROC curve Fig 5 |
|  | Clopidogrel 600mg LD and 75mg MD  Aspirin: 300 mg LD & 75 mg MD | Verify Now P2Y12 assay | Combined end point of ischemic events and bleeding | CV death (defined as death from cardiac causes or stroke) and non-fatal myocardial infarction (defined as rise in CK-MB of at least twice the upper limit of normal with either ischemic symptoms or typical ECG changes) | 30 days | Low PR | Ischemic events + bleeding | 20 | Ref group vs medium | Ref group vs medium | Ref group vs medium |  |  |  |
|  |  |  |  |  |  | Medium PR | Ischemic events | 6 | 0.3  0.31 | 0.12-0.75  0.12-0.77 | 0.01 (Medium vs low)  0.012 (Medium vs High) | YES  female sex, BMI, diabetes,  ejection fraction | NR | Kaplan–Meier time-to-event curves in Fig 6 |
|  |  |  |  |  |  | High PR | Ischemic events | 19 | Ref group vs medium | Ref group vs medium | Ref group vs medium |  |  |  |
|  | Clopidogrel 600mg LD and 75mg MD  Aspirin: 300 mg LD & 75 mg MD | Verify Now P2Y12 assay | Composite ischemic end point | CV death (defined as death from cardiac causes or stroke) and non-fatal myocardial infarction (defined as rise in CK-MB of at least twice the upper limit of normal with either ischemic symptoms or typical ECG changes) | 30 days | Medium PR defined with a different range than before (≥161 to <225 PRU) | Ischemic events + bleeding | NR | 0.14  0.42 | 0.05-0.4  0.24-0.73 | 0.0003 (Medium vs low)  0.002 (Medium vs High) | YES  female sex, BMI, diabetes, ejection fraction | NR | Kaplan–Meier time-to-event curves in Fig 6 |
| Kim, 2011  21786434  South Korea  CiLostazol administration before pErcutaneous coronAry intervention for Reduction of periprocedural myonecrosis trial (CLEAR trial) | Clopidogrel + aspirin | Verify Now | Cardiac death, MI, target-lesion revascu-larization, or cerebro-vascular accident |  | 6 mo | Clopidogrel resistance |  | 4/37 (11%) |  |  | NS vs. next row (chi-square statistics or Fisher ‘s exact test) |  |  |  |
|  |  |  |  |  |  | Normal response |  | 2/73 (3%) |  |  |  |  |  |  |
| Lee, 2009  20049136  South Korea  NR | 600 mg clopidogrel + 300 mg aspirinLD & in pts with DES, 100 mg aspirin +75 mg clopidogrel | Verify Now | Any stent thrombosis or cardiac death |  | 6 months | Normal response |  | 1 (0.7%) |  |  | 0.012 vs. next row (chi-square or Fisher’s exact) |  |  |  |
|  |  |  |  |  |  | Low response |  | 6 (6.3%) | vs previous row:  OR (also stated as relative risk), 12.074 (multi-variate logistic regression)  Relative risk, 9.646 (univariate logistic regression) | 1.205-120.992 for multi-variate OR  1.139-81.679 for uni-variate RR | 0.034 for multivariate OR  0.038 for univariate RR | YES age and sex for OR/RR |  |  |
| Marcucci, 2009  19118249  Italy  NR | clopidogrel 600 mg LD + 75 mg MD & ASA 500 mg IV LD + 100-325 mg MD | Verify Now | MACE | Cardiovascular death and nonfatal MI | 12 months | high residual platelet reactivity (PRU≥240) | MACE | 27 (12.3) | HR=2.52 | 1.30–5.13 | P=0.011  (RPR vs no RPR) | NO | NR |  |
|  |  |  |  |  |  | No residual platelet reactivity (PRU<240) |  | 17 (3.6) |  |  |  |  |  |  |
|  | clopidogrel 600 mg LD + 75 mg MD & ASA 500 mg IV LD + 100-325 mg MD | Verify Now | MACE | Cardio-vascular death and nonfatal MI | 12 months | high residual platelet reactivity (PRU≥240) | MACE | 27 (12.3) | Sens: 0.61  Spec: 0.7  AUC 0.66 | 0.47-0.758  0.664-0.735  0.57-0.78 | P<0.001 | NO | NR |  |
|  |  |  |  |  |  | No residual platelet reactivity (PRU<240) |  | 17 (3.6) |  |  |  |  |  |  |
|  | clopidogrel 600 mg LD + 75 mg MD & ASA 500 mg IV LD + 100-325 mg MD | Verify Now | MACE | Cardio-vascular death and nonfatal MI | 12 months | Quartile 1 ≤129 | MACE | NR | HR=1.1  HR=1.6  HR=3.6 | 0.4-3.4  0.6-4.5  1.5-9.1 | P>0.05  (Quartile II vs 1)  P>0.05  (Quartile III vs 1)  P<0.05  (Quartile IV vs 1) | NO | NR |  |
|  |  |  |  |  |  | Quartile 2 130-195 |  | NR |  |  |  |  |  |  |
|  |  |  |  |  |  | Quartile 3 196-257 |  | NR |  |  |  |  |  |  |
|  |  |  |  |  |  | Quartile 4 ≥258 |  | NR |  |  |  |  |  |  |
| Patti, 2008  18804738  Italy  ARMYDA-PRO (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Platelet Reactivity Predicts Outcome) | Clopidogrel 75 mg/day | Verify Now P2Y12 | major adverse cardiac events  (MACE) | Cardiac death, myocardial infarction (MI)†, target vessel revasculari-zation§ | 30 days | 1st quartile | MACE+ | 1 (3 %) | Ref group | Ref Group | Ref group | NO | NR |  |
|  |  |  |  |  |  | 2nd quartile | MACE+ | 2 (5%) | NR | NR | NR | NR | NR |  |
|  |  |  |  |  |  | 3rd quartile | MACE+ | 4 (10%) | NR | NR | NR | NR | NR |  |
|  |  |  |  |  |  | 4th quartile | MACE+ | 8 (20%) | OR=12.67 (4th vs. 1st)\*\* | 1.49-107.7 | P=0.034 (between 4th and 1st quartile); Fisher’s exact/ Chi square | NO | NR |  |
|  |  |  |  |  | 6 months | 1st quartile | MACE+ | 4 (10%) | Ref group | Ref Group | Ref group | NO | NR |  |
|  |  |  |  |  |  | 2nd quartile | MACE+ | 5 (13%) | NR | NR | NR | NR | NR |  |
|  |  |  |  |  |  | 3rd quartile | MACE+ | 7 (17%) | NR | NR | NR | NR | NR |  |
|  |  |  |  |  |  | 4th quartile | MACE+ | 12 (30%) | OR=6 (4th vs. 1st)02\*\* | 1.67-21.6 | P=0.05 (between 4th and 1st quartile); Fisher’s exact/Chi square | NO | NR |  |
|  |  |  |  |  | 30 days | 1st quartile | MACE+ | 1 (3 %) | Ref group | Ref Group | Ref group | YES | NR |  |
|  |  |  |  |  |  | 2nd quartile | MACE+ | 2 (5%) |  |  | P=0.71 (between 1st and 2nd quartile); Logistic regression | YES |  |  |
|  |  |  |  |  |  | 3rd quartile | MACE+ | 4 (10%) |  |  | P=0.68 (between 1st and 3rd quartile); Logistic regression | YES |  |  |
|  |  |  |  |  |  | 4th quartile | MACE+ | 8 (20%) | OR=6.1 (4th vs. 1st) | 1.1-18.3 | P=0.033 (between 4th and 1st quartile); Logistic regression | YES; All Only variables with p <0.15  were entered into final model; final list is NR; only reported variables include: Age >70  years, left ventricular dysfunction, and use of glycoprotein IIb/IIIa inhibitors, statin therapy |  |  |
|  | Clopidogrel 75 mg/day | Verify Now P2Y12 | major adverse cardiac events  (MACE) | Cardiac death, myocardial infarction (MI)†, target vessel revasculari-zation§ | 30 days | PRU≥ 240 units | MACE+ | NR | Sens=0.81; spec=0.53 | NR | NR | NR | NR | AUC= 0.69 (95% CI: 0.56 to 0.81; p= 0.016) |
| Price, 2011  21406646  USA  Gauging Responsive-ness with A VerifyNow assay—Impact on Thrombosis And Safety (GRAVITAS) | Clopidogrel 75 mg/d MD+ Aspirin 75-162 mg/d MD | Verify Now | MACE | Death from cardio-vascular causes, nonfatal myocardial infarction, or stent thrombosis‡ | 6 months | High on-treatment reactivity was  defined (PRU≥230)  n=586 | MACE | 25 (2.3%) | HR=1.68 | 0.76-3.72 | P=0.20  (high vs not high)  [log-rank test stratified by acute coronary syndromes status] | NO | NR | Secondary analysis |
|  |  |  |  |  |  | Not High On-Treatment Reactivity (PRU<230)  n=1109 |  | 8 (1.4%) |  |  |  |  |  |  |
|  | Clopidogrel 75 mg/d MD+ Aspirin 75-162 mg/d MD | Verify Now | MACE | Death from cardio-vascular causes, nonfatal myocardial infarction, or stent thrombosis‡ | 30 days | High on-treatment reactivity was defined (PRU≥230)  n=586 | MACE | 17 (1.6%) | HR=2.27 | 0.76-6.74 | P=0.13  (high vs not high)  [log-rank test stratified by acute coronary syndromes status] | NO | NR | Landmark analysis |
|  |  |  |  |  |  | Not High On-Treatment Reactivity (PRU<230)  n=1109 |  | 4 (0.7%) |  |  |  |  |  |  |
| Price, 2008  18263931  USA  NR | Clopidogrel LD 600 mg and maintaining 75mg daily | Verify Now P2Y12 assay | CV death, non-fatal MI, Stent thrombosis | CV death, non-fatal MI, Stent thrombosis | 6-months | Lower reactivity | CV death, non-fatal MI, Stent thrombosis | 2/209  (1) | NR | NR | 0.008 comparing with the following row | NR | NR |  |
|  |  |  |  |  |  | High reactivity |  | 7/108 (6.5) |  |  |  |  |  |  |
|  |  |  |  |  |  | Total |  | 9/317 (2.8) |  |  |  |  |  |  |
|  | Clopidogrel LD 600 mg and maintaining 75mg daily | Verify Now P2Y12 assay | CV death, non-fatal MI, Stent thrombosis | CV death, non-fatal MI, Stent thrombosis | 6-months follow-up with a minimal of 3 months post-procedure | Lower reactivity | CV death, non-fatal MI, Stent thrombosis | 2/252  (2) | NR | NR | 0.008 comparing with the following row | NR | NR |  |
|  |  |  |  |  |  | High reactivity |  | 7/121 (5.8) |  |  |  |  |  |  |
|  |  |  |  |  |  | Total |  | 9/373  (2.4) |  |  |  |  |  |  |
| Saw, 2008  19463380  Canada  BRIEF-PCI | Clopidogrel LD 600 mg and maintaining 75mg daily | Verify Now P2Y12 | 30-day death, MI, urgent TVR | 30-day death, MI, urgent TVR | 30 day | Low-responder  (n=51) | 30-day death, MI, urgent TVR | 1 (2%) | NR | NR | 0.766  (low vs normal responder)  [Fisher’s exact] | NR | NR |  |
|  |  |  |  |  |  | Responder  (n=147) |  | 4 (2.7%) | NR |  |  |  |  |  |
| Vavuranakis, 2011  21712606  Greece  NR | 300-600 mg LD + 75 mg MD; Aspirin 325 mg X 7 days then 100 mg MD | Verify Now P2Y12 | MACE | death; myocardial infarction; stroke | Mean followup: 203±152 | NR | MACE | 4 (death: 2; myocardial infarction: 2;  stroke: 0) | NR | NR | NR  [Cox regression (stepwise backward conditional method)] | NR | NR | “Multi-variate analysis did not revealed any significant relation-ship between PRU and MACE.” |
| Breet, 2011  21478385  The Netherlands  POPular | Clopidogrel LD 300 or 600mg or maintaining 75 mg daily | Verify Now | Death, MI, ST, stroke | Death, MI, ST, stroke | 1 year | HCPR (high on-clopidogrel platelet reactivity or dual HPR)  N=168 | Death, MI, ST, stroke | 21 | OR (calculate)= 3.16 | 1.5-6.7 | P=0.003  (HCPR or Dual HPR vs NPR)  [Fisher’s exact] | NR | NR |  |
|  |  |  |  |  |  | NPR (normal on-clopidogrel platelet reactivity or only high aspirin PR)  N=254 |  | 11 |  |  |  |  |  |  |
| Suh, 2011  21232664  Korea  CILON-T | Aspirin (100 mg daily) and clopidogrel (75 mg daily | VerifyNow | primary end point | composite of cardiac death, non fatal MI, ischemic stroke and TLR | 6 months | PRU 0-184 | primary end point | NR | NR | NR | 0.077 | NR | NR | figure 4 A showed bar graphs |
|  |  |  |  |  |  | PRU 185-264 |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  | PRU 265-438 |  |  |  |  |  |  |  |  |
|  | Aspirin (100 mg daily) and clopidogrel (75 mg daily | Verify Now | Athero-thrombotic complica-tions | composite of cardiac death, non fatal MI, ischemic stroke | 6 months | PRU 0-184 | Athero-thrombotic compli-cations | 0% | NR | NR | 0.037 | NR | NR | figure 4 A showed bar graphs |
|  |  |  |  |  |  | PRU 185-264 |  | 2% |  |  |  |  |  |  |
|  |  |  |  |  |  | PRU 265-438 |  | 2.9% |  |  |  |  |  |  |
|  | Aspirin (100 mg daily) and clopidogrel (75 mg daily | Verify Now | target lesion revasculari-zation | composite of cardiac death, non fatal MI, ischemic stroke | 6 months | PRU 0-184 | target lesion revasculari-zation | NR | NR | NR | 0.486 | NR | NR | figure 4 A showed bar graphs |
|  |  |  |  |  |  | PRU 185-264 |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  | PRU 265-438 |  |  |  |  |  |  |  |  |
|  | Aspirin (100 mg daily) and clopidogrel (75 mg daily | Verify Now | composite clinical outcomes | composite of cardiac death, non fatal MI, ischemic stroke | 6 months | high PRU level (every increase of tertile) | composite clinical outcomes | NR | HR=1.42 | 1.04-1.93 | NR | NR | NR |  |
|  | Aspirin (100 mg daily) and clopidogrel (75 mg daily | VerifyNow | composite clinical outcomes | composite of cardiac death, non fatal MI, ischemic stroke | 6 months | high PRU level (every increase of tertile) | composite clinical outcomes | NR | HR=1.61 | 1.16-2.25 | NR | yes (age, sex, Diabetes, HTN, hypercholesterol-emia, previous MI, cnilical diagnosis, lesion length, reference vessel diameter, multivessel intervention, type of DES, the use of cilostazol, PRU level at discharge) | NR |  |
| Price, 2011  21875913  USA  Gauging Responsive-ness with A VerifyNow assay—Impact on Thrombosis And Safety (GRAVITAS) | Highdose  clopidogrel : 600 mg LD + 150 mg daily MD  Standard-dose  Clopidogrel: 75 mg/day MD  Aspirin: 75 to  162 mg daily | VerifyNow | MACE | Cardiovas-cular death, nonfatal myocardial infarction, and stent thrombosis | 60 days | Platelet reactivity <208  (n=1156) | MACE | 12 | HR=0.18 | 0.04-0.79 | P=0.02 (PRU<208 vs PRU ≥208)  [Cox regression] | No | NR |  |
|  |  |  |  |  |  | Platelet reactivity ≥208  (n=1397) | MACE | 46 |  |  |  |  |  |  |
|  |  |  |  |  | 60 days | Platelet reactivity <208  (n=1156) | MACE | 12 | HR=0.23 | 0.05-0.98 | P=0.047 (PRU<208 vs PRU ≥208)  [Cox regression] | Yes; ACS presentation, Diabetes mellitus, Prior myocardial infarction, Prior CABG, Prior PCI, creatinine clearance, beta-Blocker at discharg, Total stented length in mm | NR |  |
|  |  |  |  |  |  | Platelet reactivity ≥208  (n=1397) | MACE | 46 |  |  |  |  |  |  |
|  |  |  |  |  | 60 days | Platelet reactivity <230  (n=1448) | MACE | NR | HR=0.62 | 0.25-1.51 | P=0.3 (PRU<230 vs PRU ≥230)  [Cox regression] | No | NR |  |
|  |  |  |  |  |  | Platelet reactivity ≥230  (n=1105) | MACE | NR |  |  |  |  |  |  |
|  |  |  |  |  | 6 months | Platelet reactivity <208  (n=1156) | MACE | 12 | HR=0.43 | 0.23-0.82 | P=0.047(PRU<208 vs PRU ≥208)  [Cox regression] | No | NR |  |
|  |  |  |  |  |  | Platelet reactivity ≥208  (n=1397) | MACE | 46 |  |  |  |  |  |  |
|  |  |  |  |  | 6 months | Platelet reactivity <208  (n=1156) | MACE | 12 | HR=0.54 | 0.28-1.04 | P=0.065 (PRU<208 vs PRU ≥208)  [Cox regression] | Yes; ACS presentation, Diabetes mellitus, Prior myocardial infarction, Prior CABG, Prior PCI, creatinine clearance, beta-Blocker at discharge, Total stented length in mm | NR |  |
|  |  |  |  |  |  | Platelet reactivity ≥208  (n=1397) | MACE | 46 |  |  |  |  |  |  |
|  |  |  |  |  | 6 months | Platelet reactivity <230  (n=1448) | MACE | NR | HR=0.71 | 0.41-1.23 | P=0.22 (PRU<230 vs PRU ≥230)  [Cox regression] | No | NR |  |
|  |  |  |  |  |  | Platelet reactivity ≥230  (n=1105) | MACE | NR |  |  |  |  |  |  |
| Park, 2011  22152948  Korea  NR | clopidogrel LD 300 or 600 mg>=12h before PCI, MD 75mg/day  aspirin LD 200mg, MD 100-200 mg/day | Verify Now | composite | death, MI, stent thrombosis, or stroke | 2-year | HTPR (PRU >235 and/or a % inhibition <15%)  N=1660 | composite | 58 (2.8%) | HR=1.33 | 0.88-2.01 | 0.18  (HTPR vs normal PR)  [cox regression] | NR | NR |  |
|  |  |  |  |  |  | Normal PR N=1189 |  | 38 (2.4%) |  |  |  |  |  |  |
| Park, 2011  21880289  Korea  CROSS-VERIFY | clopidogrel LD 300 or 600 mg, MD 75mg/day; aspirin MD 100 mg/day | Verify Now | MACE | Cardiac death and nonfatal spontaneous MI | 1 year | high OPR (HOPR) ≥235 PRU  n=407 | MACE | 10 (2.5%) | NR | NR | P=0.022  (HOPR vs no HOPR)  Log rank test | NR | NR |  |
|  |  |  |  |  |  | No HOPR <235 PRU  n=402 |  | 2 (0.5%) |  |  |  |  |  |  |
|  |  |  |  |  |  | high OPR (HOPR) ≥235 PRU  n=407 | MACE | 10 (2.5%) | OR=6.64 | 1.27-34.84 | P=0.025  (HOPR vs no HOPR)  Logistic regression | YES; age, gender, clinical diagnosis, smoking status, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, body mass index, left ventricular ejection fraction, extent of involved vessels, target vessel location, use of a drug-eluting stent, implanted stent number, stent diameter, stent length | NR |  |
|  |  |  |  |  |  | No HOPR <235 PRU  n=402 |  | 2 (0.5%) |  |  |  |  |  |  |
|  |  |  |  |  |  | HTN+ & high OPR (HOPR) ≥235 PRU | MACE | 1.7% | NR | NR | P=0.374  (HOPR vs no HOPR)  Log rank test  **NS (HTN+ vs HTN -)** | NR | NR |  |
|  |  |  |  |  |  | HTN+ & No HOPR <235 PRU |  | 0.8% |  |  |  |  |  |  |
|  |  |  |  |  |  | HTN- & high OPR (HOPR) ≥235 PRU | MACE | 4.4% | NR | NR | P=0.007  (HOPR vs no HOPR)  Log rank test | NR | NR |  |
|  |  |  |  |  |  | HTN- & No HOPR <235 PRU |  | 0% |  |  |  |  |  |  |
|  |  |  |  |  |  | DYSLIPIDE-MIA+ & high OPR (HOPR) ≥235 PRU | MACE | 2.6% | NR | NR | P=0.288  (HOPR vs no HOPR)  Log rank test  **NS (DYSLIPIDEMIA+ vs DYSLIPIDEMIA-)** | NR | NR |  |
|  |  |  |  |  |  | DYSLIPIDE-MIA+ & No HOPR <235 PRU |  | 1.1% |  |  |  |  |  |  |
|  |  |  |  |  |  | DYSLIPIDE-MIA- & high OPR (HOPR) ≥235 PRU | MACE | 2.3% | NR | NR | P=0.023  (HOPR vs no HOPR)  Log rank test | NR | NR |  |
|  |  |  |  |  |  | DYSLIPIDE-MIA- & No HOPR <235 PRU |  | 0% |  |  |  |  |  |  |
|  |  |  |  |  |  | DM+ & high OPR (HOPR) ≥235 PRU | MACE | 0.7% | NR | NR | P=0.374  (HOPR vs no HOPR)  Log rank test  **NS (DM+ vs DM-)** | NR | NR |  |
|  |  |  |  |  |  | DM+ & No HOPR <235 PRU |  | 0% |  |  |  |  |  |  |
|  |  |  |  |  |  | DM- & high OPR (HOPR) ≥235 PRU | MACE | 3.3% | NR | NR | P=0.023  (HOPR vs no HOPR)  Log rank test | NR | NR |  |
|  |  |  |  |  |  | DM- & No HOPR <235 PRU |  | 0.7% |  |  |  |  |  |  |
|  |  |  |  |  |  | high OPR (HOPR) ≥275 PRU  n=247 | MACE | 7(2.8%) | NR | NR | P=0.035  (HOPR vs no HOPR)  Log rank test | NR | NR |  |
|  |  |  |  |  |  | No HOPR <275 PRU  n=562 |  | 5 (0.9%) |  |  |  |  |  |  |
|  |  |  |  |  |  | Hyporespon-ders <5% inhibition of platelet aggregation  n=195 | MACE | 6(3.1%) | NR | NR | P=0.035  (hypo- vs normal responders)  Log rank test | NR | NR | Supp fig 5 has incorrect info on N at risk |
|  |  |  |  |  |  | responders ≥5% inhibition of platelet aggregation  n=614 |  | 6 (1%) |  |  |  |  |  |  |
|  |  |  |  |  |  | ≥ 275 PRU & Hyporespon-ders <5% inhibition of platelet aggregation  n=126 | MACE | 5 (4%) | NR | NR | P=0.035  (hypo- vs normal responders)  Log rank test | NR | NR |  |
|  |  |  |  |  |  | ≥ 275 PRU & normal responders ≥5% inhibition of platelet aggregation  n=121 |  | 2 (1.7%) |  |  |  |  |  |  |
|  |  |  |  |  |  | < 275 PRU & Hyporespon-ders <5% inhibition of platelet aggregation  n=69 |  | 1 (1.4%) |  |  |  |  |  |  |
|  |  |  |  |  |  | < 275 PRU & normal responders ≥5% inhibition of platelet aggregation  n=493 |  | 4 (0.8%) |  |  |  |  |  |  |
| Mangiacapra, 2012  22440493  Italy & Belgium  ARMYDA-PROVE | Clopidogrel LD: 600 mg loading dose ≥6 h before PCI or 75 mg/d x 5 days  Clopidogrel MD: 75 mg/d from 4 weeks to 12 months  Aspirin 80-100 mg/day | Verify Now | MACE | Death, MI, target vessel revasculari-zation, bleeding events, hematoma | 30 days | Normal PR (PRU between ≥179 and ≤238)  n = 244 | MACE | 35 (14.1%) | OR=0.49 | 0.29-0.83 | P=0.008 (NPR vs HPR+LPR)  [logistic regression] | No | NR |  |
|  |  |  |  |  |  | Low PR (PRU ≤178) or High PR (PRU ≥239)  n = 488 |  | 72 (14.8%) |  |  |  |  |  |  |
|  |  |  | MACE | Death, MI, target vessel revasculari-zation, bleeding events, hematoma | 30 days | Normal PR (PRU between ≥179 and ≤238)  n = 244 | MACE | 35 (14.1%) | OR=0.47 | 0.27-0.81 | P<0.001 (NPR vs HPR+LPR)  [logistic regression] | Yes; Diabetes mellitus, multivessel disease, chronic renal failure, total stent length, glycoprotein IIb/IIIa inhibitors | NR |  |
|  |  |  |  |  |  | Low PR (PRU ≤178) or High PR (PRU ≥239)  n = 488 |  | 72 (14.8%) |  |  |  |  |  |  |
|  |  |  | MACE | Death, MI, target vessel revasculari-zation, bleeding events, hematoma | 30 days | Low PR (PRU ≤178)  n = 248 | MACE | 35 (14.1%) | NR | NR | P=0.034  [log rank test]  P=0.007 (NPR vs HPR+LPR)  P=0.025 (NPR vs LPR)  P=0.005 (NPR vs HPR)  [chi square test] | No | NR |  |
|  |  |  |  |  |  | Normal PR (PRU between ≥179 and ≤238)  n = 244 |  | 19 (7.8%) |  |  |  |  |  |  |
|  |  |  |  |  |  | High PR (PRU ≥239)  n = 240 |  | 37 (15.4%) |  |  |  |  |  |  |
|  |  |  | MACE-free survival | MACE-free survival | 30 days | Low PR (PRU ≤178)  n = 248 | MACE-free survival | 213 (85.9%) | NR | NR | P=0.034  [log rank test] | No | NR |  |
|  |  |  |  |  |  | Normal PR (PRU between ≥179 and ≤238)  n = 244 |  | 225 (92.2%) |  |  |  |  |  |  |
|  |  |  |  |  |  | High PR (PRU ≥239)  n = 240 |  | 203 (84.6%) |  |  |  |  |  |  |
|  |  |  | Ischemic events | Death, MI, target vessel revasculari-zation | 30 days | Low PR (PRU ≤178)  n = 248 | MACE | 10 (4%) | NR | NR | P for trend <0.001  [chi square test] | No | NR |  |
|  |  |  |  |  |  | Normal PR (PRU between ≥179 and ≤238)  n = 244 |  | 12 (4.9%) |  |  |  |  |  |  |
|  |  |  |  |  |  | High PR (PRU ≥239)  n = 240 |  | 36 (15%) |  |  |  |  |  |  |
| Jin, 2012  Korea  NR | 600mg clopidogrel and 300 mg aspirin LD, 75 mg clopidogrel and 100 mg aspirin as MD | VerifyNow P2Y12 | MACE | cardiovas-cular death, nonfatal MI and ischemic stroke | 12 months | no HPR | MACE | 5/127=3.9% | HR=6.24 | 2.05-18.99 | 0.001comparing with HPR  cox-model | **yes** | **No** |  |
|  |  |  |  |  |  | HPR | MACE | 11/54=20.4% |  |  |  |  |  |  |
| Saraf, 2010  20447533  UK  NR | Clopidogrel LD 300 mg, MD 75 mg; Aspirin LD 300 mg, MD 75 mg | VerifyNow P2Y12 | MACE | CV death, nonfatal MI, stroke | 12 months | PRU≥ 240 | MACE | NR | NR | NR | NR | NR | NR | “no relationship between VerifyNow results and MACE in our population**”** |
|  |  |  |  |  |  | PRU<240 |  | NR |  |  |  |  |  |  |
| Ari, 2011  21239075  Turkey  EFFICIENT | clopidogrel 75 mg/day | VerifyNow P2Y12 | MACCE | major adverse cardiac and cerebral events | 1 month | group 1  platelet inhibition >40% | MACCE | 3/98=3.1% | absolute risk difference 3.3% | -14.5 to 14.2 | 0.34 group 1 comparing with group 2 | NR | NR | **no** |
|  | clopidogrel 75 mg/day | VerifyNow P2Y12 | MACCE | major adverse cardiac and cerebral events | 1 month | group 2  platelet inhibition <40% | MACCE | 3/47=6.4% | absolute risk difference 1.2% | -5.1 to 11.3 | 0.71 group 1 comparing with group 3 | NR | NR | **no** |
|  | clopidogrel 150 mg/day | Verify Now P2Y12 | MACCE | major adverse cardiac and cerebral events | 1 month | group 3  platelet inhibition <40% | MACCE | 2/47=4.3% | absolute risk difference 2.1% | -8.7 to 3.3 | 0.64 group 2 comparing with group 3 | NR | NR | **no** |
|  | clopidogrel 75 mg/day | Verify Now P2Y12 | MACCE | major adverse cardiac and cerebral events | 2-6 month | group 1  platelet inhibition >40% | MACCE | 2/98=2% | absolute risk difference 8.6% | 1.7-20.8 | 0.02 group 1 comparing with group 2 | NR | NR | **no** |
|  | clopidogrel 75 mg/day | Verify Now P2Y12 | MACCE | major adverse cardiac and cerebral events | 2-6 month | group 2  platelet inhibition <40% | MACCE | 5/47=10.6% | absolute risk difference 2.0% | -19 to 7.1 | 0.32 group 1 comparing with group 3 | NR | NR | **no** |
|  | clopidogrel 150 mg/day | Verify Now P2Y12 | MACCE | major adverse cardiac and cerebral events | 2-6 month | group 3  platelet inhibition <40% | MACCE | 47 | absolute risk difference 10.6% | 0.8 to 30 | 0.02 group 2 comparing with group 3 | NR | NR | **no** |
|  | clopidogrel 75 mg/day | Verify Now P2Y12 | total MACCE | major adverse cardiac and cerebral events | 6 month | group 1  platelet inhibition >40% | total MACCE | 5/98=5.1% | absolute risk difference 11.9% | -1.4 to 22.2 | 0.019 group 1 comparing with group 2 | NR | NR | **no** |
|  | clopidogrel 75 mg/day | Verify Now P2Y12 | total MACCE | major adverse cardiac and cerebral events | 6 month | group 2  platelet inhibition <40% | total MACCE | 8/47=17% | absolute risk difference 0.8% | -9.5 to 7.7 | 0.82 group 1 comparing with group 3 | NR | NR | **no** |
|  | clopidogrel 150 mg/day | Verify Now P2Y12 | total MACCE | major adverse cardiac and cerebral events | 6 month | group 3  platelet inhibition <40% | total MACCE | 2/47=4.3% | absolute risk difference 12.7% | 7.5 to 39.7 | 0.045 group 2 comparing with group 3 | NR | NR | **no** |
|  | clopidogrel 75 mg/day | Verify Now P2Y12 | NACE | TIMI major or minor bleeding, or total MACCE | 6 month | group 1  platelet inhibition >40% | NACE | 9/98=9.2% | absolute risk difference 9.9% | -4.1 to 21.2 | 0.08 group 1 comparing with group 2 | NR | NR | **no** |
|  | clopidogrel 75 mg/day | Verify Now P2Y12 | NACE | TIMI major or minor bleeding, or total MACCE | 6 month | group 2  platelet inhibition <40% | NACE | 9/47=19.1% | absolute risk difference 3.6% | -9.4 to 13.5 | 0.50 group 1 comparing with group 3 | NR | NR | **no** |
|  | clopidogrel 150 mg/day | Verify Now P2Y12 | NACE | TIMI major or minor bleeding, or total MACCE | 6 month | group 3  platelet inhibition <40% | NACE | 6/47=12.8% | absolute risk difference 6.3% | -8.7 to 21.3 | 0.39 group 2 comparing with group 3 | NR | NR | **no** |

\*Each case of stent thrombosis resulted in MI.  
†Myocardial infarction was defined as post-procedural increase of cardiac biomarkers (Tn or CK-MB) >3 × 99th percentile of the upper reference limit.  
§Target vessel revascularization included by-pass surgery or repeat PCI of the target vessel(s).  
\*\*Calculated; P value only reported for 1st vs 4th.  
‡All deaths were considered cardiovascular unless an unequivocal noncardiovascular cause could be established; hemorrhagic deaths were also considered to be cardiovascular. Myocardial infarction followed the American College of Cardiology definition. Stent thrombosis was defined as definite or probable according to the Academic Research Consortium definitions.