Appendix Table E31. Phenotypic test details in studies assessing the predictive ability of VerifyNow in patients with ischemic heart disease

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| --- | --- | --- | --- | --- | --- | --- |
| **Author, year [ref]**  **UID**  **Country**  **Study Name** | **Test/Device name**  **Device category Device name & manufacturer\*** | **Agonist used** | **Sample Collection and Procurement**  **Anticoagulant used**  **Interval between clopidogrel doses and blood sampling (in days)**  **Interval between sampling and testing (in days):** | **Grouping of Phenotypes\*\* [Definition]** | **Rational for the grouping of phenotypes reported (Yes/No)**  **[short description]** | **Frequency of phenotypes** |
| Cotton, 2010{Cotton, 2010 75 /id}  20406238  UK  NR | VerifyNow  VerifyNow  Accumetrics, San Diego, CA, USA) | ADP | After discarding 5 mL, arterial sheath blood was drawn into vacutainer R tubes and analyzed using the Verify-Now system  containing sodium citrate  0.109 M  NR  NR | PRU≤240  PRU >240 | Based on previous literature | PRU≤240  PRU >240 |
| Angiolillo, 2007{Angiolillo, 2008 180 /id}  18312754  USA  OPTIMUS | VerifyNow P2Y12  VerifyNow P2Y12 | ADP | 2 to 4 hours after antiplatelet therapy intake  NR  2 to 4 hours after antiplatelet therapy intake  NR | P2Y12 inhibition ≥50%  P2Y12 inhibition <50% | Not explicitly reported. | P2Y12 inhibition ≥50%: n=17 (50%)  P2Y12 inhibition <50%: n=17 (50%) |
| Breet, 2010{Breet, 2010 86 /id}  20179285  Netherlands  POPULAR | VerifyNowP2Y12assay  Accumetrics,  SanDiego,California | ADP | NR  Greiner tubes  NR  Within 2 hours after blood collection. | Verify now P2Y12 <236  Verify now P2Y12 ≥ 236 | Based on ROC curves | Verify now P2Y12 <236: n=646  Verify now P2Y12 ≥236: n=406 |
| Kim, 2010{Kim, 2010 241 /id}  20449634  Korea  NR | turbidimetry-based optical detection device  VerifyNowP2Y12assay  NR | 20 μmol/L ADP | Blood was drawn into a Greiner Bio-One 3.2% citrate Vacuette tube  sodium citrate 3.2%  clopidogrel- naı¨ve patients received a 300-mg loading-dose (LD) of clopidogrel at least 12 h before procedure, and blood sampling was performed after insertion of the arterial sheath. In the case of patients who were already on chronic clopidogrel therapy, blood sampling was performed at the catheterization lab without clopidogrel LD  60 minutes | PRU<240  PRU≥240 | Based on literature | PRU<240 n=512  PRU≥240 n=546 |
| Ko, 2011{Ko, 2011 26 /id}  21315223  Korea  NR | turbidimetric-based optical detection system  VerifyNow P2Y12 Assay  Accumetrics | ADP | Before PCI; 8 and 24 hrs after PCI  lepirudin (25 μg/mL)  5 days (clopidogrel came first)  0.125 days (Within 3 hrs) | Hyporesponsiveness to clopidogrel (PRU≥ 274)  Normal responsiveness to clopidogrel (PRU<274) | For identification of PRU cutoff, ROC curve analysis that presented the highest sum of sensitivity and specificity was used | Hyporesponsiveness to clopidogrel (PRU≥ 274): 121 (54.5)  Normal responsiveness to clopidogrel (PRU<274): 101 (45.5) |
| Campo, 2010{Campo, 2010 58 /id}  20951320  10 sites in Italy, Belgium, France, Sprain  3T/2R trial | VerifyNowP2Y12assay  NR  Accumetrics,  SanDiego,California | NR | NR  NR  NR  NR | Full responder (%PI≥40% full responder)  Poor responder (%PI<40 poor responder ) | Based on literature | Full responder (%PI≥40% full responder ): N=289  Poor responder (%PI<40 poor responder ): N=179 |
| Campo, 2011{Campo, 2011 13 /id}  21679849  Italy  NR | VerifyNowP2Y12assay  NR  Accumetrics,  SanDiego,California | NR | NR  NR  All samples obrtained after clopidogrel started; Blood samples were drawn at baseline (just before PCI and administration of interventional therapy) and at 1 and 6 months after PCI.  NR | Clopidogrel poor response (PRU value ≥235) at baseline  Clopidogrel full response (PRU <235) at baseline  Enhanced response (PRU ≤85) at 1 mo  Normal response (PRU 86-238) at 1 mo  Poor response (≥239) at 1 month | For PRU≥235 vs <235: Based on literature  For enhanced, normal, poor: best cutoffs from ROC curves done in current study | Clopidogrel poor response (PRU value ≥235) at baseline, 107 (36%)  Clopidogrel full response (PRU <235) at baseline, 193 (64%)  Enhanced response (PRU ≤85) at 1 mo, 75 (25%)  Normal response (PRU 86-238) at 1 mo, 185 (62%)  Poor response (≥239) at 1 mo, 40 (13%) |
| Cuisset, 2008{Cuisset, 2008 168 /id}  18549843  Belgium  NR | VerifyNow P2Y12  VerifyNow P2Y12  NR | PGE1+ADP | Before PCI  NR  0.5 days (≥12 hrs)  Clopidogrel came first  NR | Quartile 1 (nonresponders) percent inhibition P2Y12 <15%  Quartile 2-4 (responders) percent inhibition P2Y12 ≥15% | Not explicitly reported. | Quartile 1 (nonresponders) percent inhibition P2Y12 <15%: 32 (25%)  Quartile 2-4 (responders) percent inhibition P2Y12 ≥15%: 90 (75%) |
| de\_Miguel\_Castro, 2009{de Miguel, 2009 136 /id}  19232185  Spain  NR | VerifyNow  VerifyNow® analyzer  Accumetrics Inc., San Diego, California | NR | Before angiography  3.2% sodium citrate  NR [clopidogrel came first]  0.04 (1 hr) | Post treatment platelet reactivity ≤ 175  Post treatment platelet reactivity >175  Quartile 1 (<115 PRU)  Quartile 2 (115 -164 PRU) Quartile 3 (165 -206 PRU) Quartile 4 ( >206 PRU) | Not explicitly reported. | Post treatment platelet reactivity ≤ 175: 97 (60.2%)  Post treatment platelet reactivity >175: 64 (39.8%)    Quartile 1 (<115 PRU): 40 (25%)  Quartile 2 (115 -164 PRU): 40 (25%)  Quartile 3 (165 -206 PRU): 40 (25%)  Quartile 4 ( >206 PRU):41 (25%) |
| Gladding, 2008{Gladding, 2008 149 /id}  19463375  New Zealand  Secondary (but not subgroup) analysis of PRINC (Plavix Response in Coronary Intervention) Trial | Agglutination plus light transmittance  VerifyNow point-of-care rapid platelet function analyzer (RPFA) and its P2Y12 cartridge  Accumetrics Ltd., San Diego, California | ADP, 20 mmol/l  [published as mmol but must be umol?] | Arterial blood was sampled through a 6-F femoral sheath and transferred immediately; collection tubes were inverted 4 times to mix the anticoagulant and left at ambient temperature (24°C)  3.2% citrate  Platelet function was tested at baseline, 2, 4, and 7 h from  10 mins | 600 mg Clopidogrel:  Nonresponse (inhibition <10%) at 7 hr  Response (inhibition >=10%) at 7 hr  1200 mg Clopidogrel  Nonresponse (inhibition <10%) at 7 hr  Response (inhibition >=10%) at 7 hr | Not explicitly reported. | 600 mg Clopidogrel  Nonresponse (inhibition <10%) at 7 hr: 6/26 (26%)  Response (inhibition >=10%) at 7 hr: 20/26 (77%)  1200 mg Clopidogrel  Nonresponse (inhibition <10%) at 7 hr:2/37 (5%)  Response (inhibition >=10%) at 7 hr:35/37 (95%) |
| Huczek, 2011{Huczek, 2011 239 /id}  21443410  Poland  NR | VerifyNow/ turbidoaggregometry  VerifyNow P2Y12 assay  Accumetrics Inc., San Diego, CA | ADP (with prostaglandin  E1 to reduce the nonspecific binding for ADP to  P2Y1 receptor) | Venous blood sample after clopidogrel  3.2% sodium citrate  0.5 ± 0.1 days (12± 2 hours); Clopidogrel came first  NR | low platelet reactivity (PRU≤150) - first  Medium platelet reactivity (PRU = 151-209  High platelet reactivity (PRU ≥210) – Third tertile | Not explicitly reported. | low platelet reactivity (PRU≤150) - first tertile - 124 (33.2%)  Medium platelet reactivity (PRU = 151-209) - Second tertile - 124 (33.2%)  High platelet reactivity (PRU ≥210) – Third tertile-124 (33.2%) |
| Kim, 2011{Kim, 2011 5 /id}  21786434  South Korea  CiLostazol administration before pErcutaneous coronAry intervention for Reduction of periprocedural myonecrosis trial (CLEAR trial) | VerifyNow P2Y12  NR  Accumetrics Inc., San Diego, CA | NR | Samples were obtained by antecubital venipunture using a 23-gauge syringe, and the initial 3 to 4 mm of blood was discarded. The second samples were collected in 4.5-mL plastic tubes for rapid platelet-function assay  3.2% citrate  Venous blood samples were drawn immediately after randomization (baseline, before clopidogrel), before PCI (7 days later after pre-treatment with clopidogrel), and 6 and 24 hours after PCI.  NR | clopidogrel resistance (% inhibition <20%)  normal response to clopidogrel (% inhibition ≥20%) | Based on literature | clopidogrel resistance (% inhibition <20%): 37/110 (34%)  normal response to clopidogrel (% inhibition ≥20%): 73/110 (66%) |
| Lee, 2009{Lee, 2009 230 /id}  20049136  South Korea  NR | VerifyNow P2Y12 assay  NR  NR | NR | samples were collected from the vein following PCI. Sampling was done in the hospital for patients who were continually hospitalized during this period or during the first follow-up for patients who had been discharged.  3.2% citrate  samples were collected after PCI and 5 days after initiating regular administration of clopidogrel (75 mg)  Within 8 hours | Clopidogrel low response (<20% inhibition)  Clopidogrel normal response (≥20% inhibition) | Based on literature | Clopidogrel low response (<20% inhibition): 95 (40%)  Clopidogrel normal response (≥20% inhibition):142 (60%) |
| Mangiacapra, 2010{Mangiacapra, 2010 83 /id}  20298992  Italy  NR | VerifyNow/optical turbidimetry  VerifyNow P2Y12 assay  Accumetrics, San Diego, California | 20-µmol adenosine diphosphate, | Before PCI  3.2% sodium citrate  NR [Clopidogrel came first]  NR | high platelet reactivity PRU value ≥240  not high platelet reactivity | Based on literature | high platelet reactivity PRU  value ≥240: 78 (31.2%)  Not high platelet reactivity: 172 (68.8%) |
| Mangiacapra, 2010{Mangiacapra, 2010 94 /id}  20129566  Belgium  NR | VerifyNow/optical turbidimetry  VerifyNow P2Y12 assay  Accumetrics, San Diego, California | 20-µmol adenosine diphosphate, | Before PCI  3.2% sodium citrate  NR [Clopidogrel came first]  NR | High platelet reactivity (HPR) - PRU value ≥240 units  Normal platelet reactivity - PRU value <240 units | Not explicitly reported. | High platelet reactivity (HPR) - PRU value ≥240 units: 101 (30%)  Normal platelet reactivity - PRU value <240 units: 237 (70%) |
| Mangiacapra, 2010{Mangiacapra, 2010 65 /id}  20723634  Italy  NR | VerifyNow/optical turbidimetry  VerifyNow P2Y12 assay  Accumetrics, San Diego, California | 20-µmol adenosine diphosphate, | Before PCI  3.2% sodium citrate  NR [Clopidogrel came first]  NR | high platelet reactivity PRU  value ≥240  not high platelet reactivity | Based on literature | high platelet reactivity PRU  value ≥240: 77 (27%)  not high platelet reactivity: 208 (73%) |
| Marcucci, 2009{Marcucci, 2009 144 /id}  19118249  Italy  NR | VerifyNow/optical turbidimetry  VerifyNow P2Y12 assay  Accumetrics, San Diego, California | ADP | 24 hours after  600-mg clopidogrel loading  sodium citrate 0.109 mol/L  1 day [clopidogrel came first]  NR | high residual platelet reactivity (PRU ≥ 240)  No residual platelet reactivity (PRU < 240)    high residual platelet reactivity (PRU ≥ 235)  No residual platelet reactivity (PRU < 235)  PRU quartiles  Quartile 1 ≤129  Quartile 2 130-195  Quartile 3 196-257  Quartile 4 ≥258 | ROC analysis; posttreatment PRU that provided the greatest sum of sensitivity and specificity. | high residual platelet reactivity (PRU ≥ 240): 219 (32.1%)  No residual platelet reactivity (PRU < 240): 464 (67.9%)    high residual platelet reactivity (PRU ≥ 235): 231 (33.8%)  No residual platelet reactivity (PRU < 235): 452 (66.2%)    PRU quartiles  Quartile 1 ≤129: 171 (25%)  Quartile 2 130-195: 171 (25%)  Quartile 3 196-257: 171 (25%)  Quartile 4 ≥258: 170 (25%) |
| Patti, 2008{Patti, 2011 22 /id}  18804738  Italy  ARMYDA-PRO (Antiplatelet  therapy for Reduction of MYocardial Damage during  Angioplasty-Platelet Reactivity Predicts Outcome) | VerifyNow/optical turbidimetry  VerifyNow P2Y12 assay  Accumetrics, San Diego, California | NR (ADP and PGE1 as per Ref 8) | Before PCI & 8 and 24 hrs after intervention  NR  0.25 days between clopidogrel dose & sampling in 120 pts; the other 40 were on chronic clopidogrel therapy  NR | First Quartile  Second Quartile  Third Quartile  Fourth Quartile | Not explicitly reported for quartile classification;  For identification of PRU cutoff, ROC curve analysis that presented the highest sum of sensitivity and specificity was used. | First Quartile: 40 (25)  Second Quartile:40 (25)  Third Quartile: 40 (25)  Fourth Quartile: 40 (25) |
| Patti, 2011{Patti, 2011 22 /id}  21256470  Italy  Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (ARMYDA)–Bleeding Study (ARMYDA-BLEEDS) | VerifyNow P2Y12 assay  NR  Accumetrics, Inc., San Diego, California | NR | NR  NR  Dose came first; reactivity tested immediately before PCI and at 8 and 24 hours after intervention  NR | PRU quartiles at baseline (before PCI):  1 (lowest PRU, which = highest inhibtion)  2  3  4  Also ROC-curve-based threshold  PRU>189 (low inhibition) PRU< or = 189 (high inhibition) | Not explicitly reported for quartiles; for cutoff at 187, authors did an ROC analysis in this study | PRU quartiles at baseline (before PCI):  1 (lowest PRU, which = highest inhibtion): 77 (25%)  2: 77 (25%)  3: 77 (25%)  4: 79 (25%)  Also ROC-curve-based threshold  PRU>189 (low inhibition): NR  PRU< or = 189 (high inhibition): NR |
| Price, 2011{Price, 2011 23 /id}  21406646  USA  Gauging Responsiveness with A VerifyNow assay—Impact on Thrombosis And Safety (GRAVITAS) | VerifyNow P2Y12 test/turbidoaggregometry  VerifyNow P2Y12 test  Accumetrics, San Diego, California | NR | 12 to 24 hours  after PCI; outcomes and repeat measurements at 30 days and 6 months NR  0.5-1 day (12-24 hrs)  Clopidogrel came first NR | High on-treatment reactivity (PRU≥230)  Not High On-Treatment Reactivity (PRU<230) | Based on literature | High on-treatment reactivity  (PRU≥230): 1105 (65.3%)  Not High On-Treatment Reactivity (PRU<230): 586 (34.7%) |
| Price, 2008{Price, 2008 174 /id}  18263931  USA  NR | VerifyNow P2Y12 assay  NR  Accumetrics Inc | 20-µmol adenosine diphosphate, | Whole blood was obtained at the time of catheterization prior to anticoagulant therapy in patients on previous clopidogrel therapy and by phlebotomy 12 h after PCI  3.2% sodium  Whole blood was obtained by phlebotomy 12 h after PCI and a 600 mg clopidogrel loading dose in patients who were clopidogrel naive  NR | Low reactivity (PRU<235)  High reactivity (PRU≥235) | ROC analysis | Low reactivity (PRU<235): 258  High reactivity (PRU≥235): 122 |
| Saw, 2008{Saw, 2008 242 /id}  19463380  Canada  BRIEF-PCI | VerifyNow P2Y12 assay  NR  Accumetrics Inc | ADP | Whole blood samples  3.2% sodium citrate  NR  NR | Low-responder (Clopidogrel low-responders were defined as those belonging to the lowest quartile of platelet inhibition)- <19%  Responder ≥19% | Not explicitly reported. | Low-responder (Clopidogrel low-responders were defined as those belonging to the lowest quartile of platelet inhibition): 51 (24.4)  responder: 147 (70.3) |
| Valgimigli, 2009{Valgimigli, 2009 244 /id}  19528337  10 sites in Europe (Italy, Belgium, France, Spain)  Tailoring Treatment With Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel (3T/2R) study | VerifyNow P2Y12 assay  NR  Accumetrics Inc | NR | NR  NR  Clopidogrel loading dose (300 or 600 mg) 2-6 hr before PCI except in those who’d been on clopidogrel for at least 7 days previously at a dose of 75 mg/day  NR | Clopidogrel nonresponders (<40% inhibition)  Dual (clopidogrel and aspirin) nonresponders  Aspirin nonresponder | Not explicitly reported | Clopidogrel nonresponders (<40% inhibition): 147  Dual (clopidogrel and aspirin) nonresponders: 26  Aspirin nonresponder: 136  For groups above, denominator unclear no % not given. The Ns sum to 309 patients but 54 were withdrawn—group affiliation not given. Total of 263 enrolled in the end. |
| Vavuranakis, 2011{Vavuranakis, 2011 245 /id}  21712606  Greece  NR | VerifyNow system/turbidoaggregometry  VerifyNow P2Y12 system  Accumetrics, SanDiego, CA, USA | NR | Whole blood ; prior to catheterization  0.2 ml buffered 3.2% sodium citrate solution  NR[clopidogrel came first]  0.01 ± 0.007 (15±1 min after collection) | NR | ROC analysis to predicts the presence of Large Thrombus  Burden | NR |
| Breet, 2011{Breet, 2011 15 /id}  21478385  The Netherlands  POPular | VerifyNow  NR  NR | ADP | NR  K3-EDTA  NR  2h | No HCPR (VerifyNow)  With HCPR and Dual HCPR (VerifyNow)  Cutoff: 236 P2Y12 reaction units | Based on literature | No HCPR (VerifyNow): 280  With HCPR and dual HPR (VerifyNow): 168 |
| Suh, 2011{Suh, 2011 33 /id}  21232664  Korea  CILON-T | VerifyNow/ turbidometric aggregation  NR  NR | 20uM ADP and 22nM PGE1 | NR  NR  NR  2h | low PRU 0-164 Middle PRU 165-264 High PRU ≥ 265 | ROC analysis | low PRU 0-164:<16%  Middle PRU 165-264:16-36%  High PRU ≥ 265:>36% |
| Price, 2011{Price, 2011 18182 /id}  21875913  USA  Gauging Responsiveness with A VerifyNow assay—Impact on Thrombosis And Safety (GRAVITAS) | VerifyNow P2Y12 test/turbidoaggregometry  VerifyNow P2Y12 test  Accumetrics, San Diego, California | NR | 12 to 24 hours  after PCI; outcomes and repeat measurements at 30 days and 6 months NR  0.5-1 day (12-24 hrs)  Clopidogrel came first  NR | High on-treatment reactivity at 30 days (PRU≥208)  Not high on-treatment reactivity at 30 days (PRU<208)  High on-treatment reactivity at 30 days (PRU≥230)  Not high on-treatment reactivity at 30 days (PRU<230) | Based on literature | Not high on-treatment reactivity (PRU<208): 1156(45.3%)  High On-Treatment Reactivity (PRU≥208): 1397 (54.7%)  Not high on-treatment reactivity (PRU<230): 1105 (56.7%)  High On-Treatment Reactivity (PRU≥230): 586 (43.3%) |
| Park, 2011 {Park, 2011 1 /id} 22152948  Korea  NR | VerifyNow P2Y12  NR  NR | ADP | NR  NR  NR  24 to 48 h post-PCI | HTPR was defined by a PRU value>235 and/or a % inhibition <15%. | Based on literature | High n=1660  normal n=1189 |
| Park, 2011{Park, 2011 18181 /id}  21880289  Korea  CROSS-VERIFY | VerifyNow P2Y12  NR  NR | NR | NR  NR  NR  NR | high OPR (HOPR) : ≥235 PRU | Based on literature | HOPR: n=407  No HOPR: n=402 |
| Mangiacapra, 2012{Mangiacapra, 2012 18179 /id}  22440493  Italy & Belgium  ARMYDA-PROVE | VerifyNow system/turbidoaggregometry  VerifyNow P2Y12 system  Accumetrics, SanDiego, CA, USA | NR | Whole blood; prior to catheterization  3.2% sodium citrate  NR[clopidogrel came first]  NR | Low platelet reactivity (LPR) (PRU ≤178) to predict bleeding events  Normal platelet reactivity NPR (PRU between ≥179 and ≤238)  High platelet reactivity (HPR) (PRU ≥239) to predict ischemic events | ROC analysis | LPR (PRU ≤178) : n = 248 [33.9%]  NPR (PRU between ≥179 and ≤238): n = 244 [33.3%]  HPR (PRU ≥239: n = 240 [32.8%] |
| Yu, 2012 {Yu, 2012 18231 /id}  22787468  Korea  NR | VerifyNow  NR  (Accumetrics Inc., San Diego, CA, USA | ADP | 12 to 24 hours post- PCI  3.2% sodium citrate  clopidogrel received at least 6 hours before PCI  NR | responder (PRU>235-240)  low responder | Ref 11, 21, 22 | responder n=186  low responder n=77 |
| Jin, 2012 {Jin, 2012 18230 /id} Korea  NR | VerifyNow P2Y12 point-of care assay  NR  (Accumetrics Inc., San Diego, CA, USA | 20 μmol of ADP | NR  NR  blood sample obtained at the time of discharge and run with 60 minutes while patients was taking MD clopidogrel | no HPR  HPR | Not explicitly reported. | no HPR N=127  HPR N=54 |
| Saraf, 2010{Saraf, 2010 18234 /id}  20447533  UK  NR | VerifyNow P2Y12 point-of care assay  NR  (Accumetrics Inc., San Diego, CA, USA | ADP | NR  sodium citrate 0.109 mol/L  NR  NR | PRU≥240  PRU<240 | Based on literature | PRU≥240 = NR  PRU<240 = NR |
| Ari, 2011  {Ari, 2012 18246 /id}  21239075  Turkey  EFFICIENT | VerifyNow P2Y12 | 20mM ADP | blood samples were drawn before PCI  3.2% sodium citrate  3 days  30 min to 4 hours | clopidogrel resistance inhibition <40% | NR | platelet inhibition <40%=94  platelet inhibition ≥40%=98 |
| Gaglia, 2012{Gaglia, 2011 18244 /id}  21919956  USA  NR | VerifyNow P2Y12 | 20 µM ADP | 6 hours following a loading  dose of clopidogrel  3.2% sodium citrate  6 hours  6 and 24 hours following PCI | PRU>235  PRI≤235 | Based on literature | PRU>235: 54  PRI≤235: 146 |
| Codner, 2012{Codner, 2012 18241 /id}  22534051  Israel  NR | VerifyNow P2Y12 | 20 µM ADP & prostaglandin E1 22 nmol | NR  3.2% citrate  NR  1 hr | PRU>235  PRI≤235 | Based on literature | PRU>235: 22  PRI≤235: 35 |

\*If more than one test, use separate rows

\*\*E.g., nonresponsive vs. responsive to clopidogrel, high vs. low platelet reactivity,