**Appendix Table E37. Results from studies assessing the ability of VerifyNow to predict bleeding events in patients with ischemic heart disease**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author,year**  **UID**  **Country**  **Study name** | **Treatment** | **Phenotypic 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)** |
| Kim, 2010{Kim, 2010 241 /id}20449634 Korea NR | 300-600mg LD and 75 mg maintain dose clopidogrel | PRU≥240 | TIMI bleeding | TIMI bleeding (major, minor) | 6 months | HPPR- PRU≥240 (n=546) | TIMI bleeding | 5.6%  (major 3.7%, minor 1.9%) | NR | NR | 0.628  (HPPR vs no HPPR)  [chi-square test] | NR | NR |  |
|  |  |  |  |  |  | no HPPR (n=512) |  | 5.1% (major 1.7%, minor 3.4%) |  |  |  |  |  |  |
| Campo, 2010{Campo, 2010 58 /id} 20951320 10 sites in Italy, Belgium, France, Sprain 3T/2R trial | Clopidogrel LD 300 or 600 mg or maintaining 75mg daily | VerifyNowP2Y12 | TIMI major bleeding | TIMI major bleeding | 1-year | Full responder  (n=289) | TIMI major bleeding | 2 (0.6) | NR | NR | 0.8  (full vs poor responder)  [chi-square test] | NR | NR |  |
|  |  |  |  |  |  | Poor responder  (n=179) |  | 1 (0.5) |  |  |  |  |  |  |
|  | Clopidogrel LD 300 or 600 mg or maintaining 75mg daily | VerifyNowP2Y12 | TIMI minor bleeding | TIMI minor bleeding | 1-year | Full responder  (n=289) | TIMI minor bleeding | 9 (3.1) | NR | NR | 0.4  (full vs poor responder)  [chi-square test] | NR | NR |  |
|  |  |  |  |  |  | Poor responder  (n=179) |  | 4 (2.2) |  |  |  |  |  |  |
| Campo, 2011{Campo, 2011 13 /id} 21679849 Italy NR | Clopidogrel + aspirin | VerifyNow | Major or minor TIMI bleeding |  | 1 year | Poor response at baseline (N=107) |  | 6 |  |  | 0.8  (poor vs fuill responders)  [Fisher's exact] |  |  |  |
|  |  |  |  |  |  | Full response at baseline (n=193) |  | 13 |  |  |  |  |  |  |
|  | Clopidogrel + aspirin | VerifyNow | Superficial bleeding according to BleedScore |  |  | Poor response at baseline (N=107) |  | 9 | OR (calculated)= 0.75 |  | P= 0.495  (poor vs full responder)  [Fisher's exact] |  |  |  |
|  |  |  |  |  |  | Full response at baseline (n=193) |  | 21 |  |  |  |  |  |  |
|  | Clopidogrel + aspirin | VerifyNow | Internal or alarming bleeding according to BleedScore | intracranial, needing transfusion, melema, hematuria, hematemesis, or epistaxis |  | Poor response at baseline (N=107) |  | 8 |  |  | 0.3  (poor vs full responder)  [Fisher's exact] |  |  |  |
|  |  |  |  |  |  | Full response at baseline (n=193) |  | 18 |  |  |  |  |  |  |
|  | Clopidogrel + aspirin | VerifyNow | Major or minor TIMI bleeding |  |  | Poor response at 1 mo (n=40) |  | 1 |  |  | 0.5  (poor vs full responder)  [Fisher's exact] |  |  |  |
|  |  |  |  |  |  | Full response at 1 mo (n=260) |  | 18 |  |  |  |  |  |  |
|  | Clopidogrel + aspirin | VerifyNow | Superficial bleeding according to BleedScore |  |  | Poor response at 1 mo (n=40) |  | 3 |  |  | NR |  |  |  |
|  |  |  |  |  |  | Full response at 1 mo (n=260) |  | 27 |  |  |  |  |  |  |
|  | Clopidogrel + aspirin | VerifyNow | Internal or alarming bleeding according to BleedScore | intracranial, needing transfusion, melema, hematuria, hematemesis, or epistaxis |  | Poor response at 1 mo (n=40) |  | 1 |  |  | 0.2 (poor vs full responder)  [Fisher's exact] |  |  |  |
|  |  |  |  |  |  | Full response at 1 mo (n=260) |  | 25 |  |  |  |  |  |  |
|  | Clopidogrel + aspirin | VerifyNow | Bleeding |  |  | Enhanced response (PRU ≤85) at 1 mo (n=75) |  | 15 |  |  | ? |  |  |  |
|  |  |  |  |  |  | Normal response (PRU 86-238) at 1 mo (N=185) |  | 3 |  |  |  |  |  |  |
|  |  |  |  |  |  | Poor response (PRU ≥239) at 1 mo (n=40) |  | 1 |  |  |  |  |  |  |
|  | Clopidogrel + aspirin | VerifyNow | Bleeding endpoints (details NR) |  |  |  |  |  | Difference in AUC for 1 mo vs baseline, 0.2 | 0.1-0.3 | <0.01 |  |  |  |
|  |  |  |  |  | Baseline | </=95 PRU cutoff  (n=NR) |  |  | AUC 0.63 | 0.58-0.69 |  |  |  |  |
|  |  |  |  |  |  |  |  |  | Sensitivity 46%, specificity 85%, PPV 17%, NPV 96% |  |  |  |  |  |
|  |  |  |  |  | 1 mo | </=85 PRU cutoff  (n=NR) |  |  | AUC 0.84 | 0.79-0.88 |  |  |  |  |
|  |  |  |  |  |  |  |  |  | Sensitivity 81%, specificity 80%, PPV 21%, NPV 98% |  |  |  |  |  |
| Huczek, 2011{Huczek, 2011 239 /id} 21443410 Poland NR | Clopidogrel 600mg LD and 75mg MD  Aspirin: 300 mg LD & 75 mg MD | VerifyNow P2Y12 assay | Bleeding events | Bleeding defined as the occurrence  of either TIMI major or TIMI minor bleeding | 30 days | Low PR  (n=124) | Bleeding | 18 | 3.5  2.78 | 1.3‑9.42  1.5‑5.15 | 0.014 (Low vs medium)  0.001 (Low vs High)  [] | YES  female sex, BMI, diabetes,  ejection fraction | NR | Kaplan–Meier time-to-event curves in Fig 2 |
|  |  |  |  |  |  | Medium PR  (n=124) | Bleeding | 5 | Ref group vs low | Ref group vs low | Ref group vs low |  |  |  |
|  |  |  |  |  |  | High PR  (n=126) | Bleeding | 3 | Ref group vs low | Ref group vs low | Ref group vs low |  |  |  |
|  | Clopidogrel 600mg LD and 75mg MD  Aspirin: 300 mg LD & 75 mg MD | VerifyNow P2Y12 assay | Bleeding events | Bleeding defined as the occurrence  of either TIMI major or TIMI minor bleeding | 30 days | PRU ≤161  (n=NR) | Bleeding | NR | Sensitivity: 88.5%  specificity: 65.8%  Area under the curve (AUC): 0.77 | sensitivity of (69.8–97.6)  specificity (60.6–70.8)  0.72–0.81 | P<0.0001 | NR | NR | ROC curve Fig 3 |
| Mangiacapra 2010{Mangiacapra, 2010 83 /id} 20298992 Italy NR | Clopidogrel 300 mg LD, 75 mg MD with aspirin | verifyNow | major bleeding | NR | NR | HPR  (n=78) | major bleeding | 0 (0%) | NR | NR | NR | NO | NR | Secondary outcome |
|  |  |  |  |  |  | No HPR  (n=172) |  | 0 (0%) |  |  |  |  |  |  |
| Patti 2011{Patti, 2011 22 /id} 21256470 Italy Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (ARMYDA)–Bleeding Study (ARMYDA-BLEEDS) | Clopidogrel + aspirin | VerifyNow | 30-day incidence of major TIMI bleeding |  |  | PRU</=189 (high inhibition)  (n=NR) |  | 11.6% | AUC 0.76  Sensitivity 87%  Specificity 70% | For AUC, 0.66-0.87 | For AUC, P=0.001  For incidence, <0.001 vs. next row | NR | NR |  |
|  |  |  |  |  |  | PRU>189 (low inhibition)  (n=NR) |  | 1.9% | NR | NR | NR | NR | NR |  |
|  |  |  | 30-day incidence of minor TIMI bleeding |  |  | PRU</=189 (high inhibition)  (n=NR) |  | 13.7% | NR | NR | <0.001  (high vs low inhibition)  [] | NR | NR |  |
|  |  |  |  |  |  | PRU>189 (low inhibition)  (n=NR) |  | 5.1% | NR | NR | NR | NR | NR |  |
| Price, 2011{Price, 2011 23 /id} 21406646 USA Gauging Responsiveness with A VerifyNow assay—Impact on Thrombosis And Safety (GRAVITAS) | Clopidogrel 75 mg/d MD+ Aspirin 75-162 mg/d MD | VerifyNow | Severe or moderate  bleeding | As per Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) definition | 6 months | High on-treatment reactivity was  defined (PRU≥230)  (n= 1092) | Severe or moderate  bleeding | 25 (2.3%) | HR=0.51 | 0.22-1.19 | P=0.12  (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=586) |  | 7 (1.2%) |  |  |  |  |  |  |
|  | Clopidogrel 75 mg/d MD+ Aspirin 75-162 mg/d MD | VerifyNow | Any bleeding | As per Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) definition | 6 months | High on-treatment reactivity was  defined (PRU≥230)  (n=1105) | Any  bleeding | 113/1105 (10.2%) | HR=1.02 | 0.75-1.39 | P=0.87  (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=586) |  | 62/586 (10.6%) |  |  |  |  |  |  |
| Saw, 2008{Saw, 2008 242 /id} 19463380 Canada BRIEF-PCI | Clopidogrel 300 or 600 mg LD and maintaining 75 mg daily | VerifyNow P2Y12 | Major bleeding | REPLACE-2 major bleeding | 30 day | Low-responder  (n=51) | Major bleeding | 2 (3.9%) | NR | NR | 0.667  (low vs normal responder)  [chi square] | NR | NR |  |
|  |  |  |  |  |  | responder  (n=147) |  | 4 (2.7) | NR |  |  |  |  |  |
|  | Clopidogrel 300 or 600 mg LD and maintaining 75 mg daily | VerifyNow P2Y12 | Minor bleeding | REPLACE-2 minor bleeding | 30 day | Low-responder  (n=51) | Minor bleeding | 9 (17.6) | NR | NR | 0.125  (low vs normal responder)  [chi square] | NR | NR |  |
|  |  |  |  |  |  | responder  (n=147) |  | 43  (29.3) | NR |  |  |  |  |  |
| 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 | Clopidogrel | VerifyNow | Major TIMI bleeding | NR | 30 days | Clopidogrel nonresponders (<40% inhibition)  (n=147) | Major bleeding | 0 | OR (calculated)= 0.18 | NR | P= 0.39  (<40% vs ≥ 40%)  [Fisher's exact] | NR | NR | NONE |
|  |  |  |  |  |  | Dual (clopidogrel and aspirin) nonresponders  (n=26) |  | 0 | NR | NR | NR | NR | NR | NONE |
| Park, 2011 {Park, 2011 1 /id} 22152948  Korea  NR | clopidogrel LD 300 or 600 mg>=12h before PCI, MD 75mg/day  aspirin LD 200mg, MD 100-200 mg/day | VeryfyNow | bleeding | all type bleeding according to TIMI criteria | 2-year | HTPR (PRU >235 and/or a % inhibition <15%) | bleeding | high 62/1660  (3.3) | HR=1.31 | 0.87-1.98 | 0.20  comparing with normal  cox proportional model | NR | NR |  |
|  |  |  |  |  |  |  |  | normal  36/1189  (2.6) |  |  |  |  |  |  |
| Mangiacapra, 2012{Mangiacapra, 2012 18179 /id}  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 | VerifyNow | All bleeding events | Major bleed, & hematoma >10 cms | 30 days | Low PR (PRU ≤178)  n = 248 | All bleeding events | 26 (10.5%) | NR | NR | P for trend <0.0001 | No | NR |  |
|  |  |  |  |  |  | Normal PR (PRU between ≥179 and ≤238)  n = 244 |  | 7 (2.9%) | OR=0.53 (calculate) | 0.21-1.33 | normal vs other |  |  |  |
|  |  |  |  |  |  | High PR (PRU ≥239)  n = 240 |  | 3 (1.3%) |  |  |  |  |  |  |
|  |  |  | Major bleed | Major bleed | 30 days | Low PR (PRU ≤178)  n = 248 | Major bleed | 7 (2.8%) | NR | NR | P for trend =0.003  [fishers exact test] | No | NR |  |
|  |  |  |  |  |  | Normal PR (PRU between ≥179 and ≤238)  n = 244 |  | 1 (0.4%) |  |  |  |  |  |  |
|  |  |  |  |  |  | High PR (PRU ≥239)  n = 240 |  | 3 (0%) |  |  |  |  |  |  |
| Yu, 2012 {Yu, 2012 18231 /id}  22787468  Korea  NR | LD 300mg aspirin and 300 mg clopidogrel, | VerifyNow P2Y12 | major bleeding | major bleeding | 12 months | responder  n=109 | major bleeding | 1/109=0.9% | OR=0.70 | 0.04-11.42 | 0.802 comparing with low responder  chi square test or Fisher’s exact test | **No** | **No** | **no** |
|  |  |  |  |  |  | low responder n=77 |  | 1/77=1.3% |  |  |  |  |  |  |
| Ari, 2011  {Ari, 2012 18246 /id}  21239075  Turkey  EFFICIENT | clopidogrel 75 mg/day | VerifyNow P2Y12 | TIMI major bleeding | TIMI major bleeding | 6 month | group 1  platelet inhibition >40% | TIMI major bleeding | 98 | absolute risk difference 0 | -14.5 to 14.2 | 1 group 1 comparing with group 2 | NR | NR | **no** |
|  | clopidogrel 75 mg/day | VerifyNow P2Y12 | TIMI major bleeding | TIMI major bleeding | 6 month | group 2  platelet inhibition <40% | TIMI major bleeding | 47 | absolute risk difference 2.1% | -1.9 to 11.0 | 0.32 group 1 comparing with group 3 | NR | NR | **no** |
|  | clopidogrel 150 mg/day | VerifyNow P2Y12 | TIMI major bleeding | TIMI major bleeding | 6 month | group 3  platelet inhibition <40% | TIMI major bleeding | 1/47=2.1% | absolute risk difference 2.1 % | -5.5 to 11.1 | 0.32 group 2 comparing with group 3 | NR | NR | **no** |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | clopidogrel 75 mg/day | VerifyNow P2Y12 | TIMI minor bleeding | TIMI minor bleeding | 6 month | group 1  platelet inhibition >40% | TIMI minor bleeding | 4/98=4.1% | absolute risk difference 2% | -7.2 to 8.0 | 0.54 group 1 comparing with group 2 | NR | NR | **no** |
|  | clopidogrel 75 mg/day | VerifyNow P2Y12 | TIMI minor bleeding | TIMI minor bleeding | 6 month | group 2  platelet inhibition <40% | TIMI minor bleeding | 1/47=2.1% | absolute risk difference 2.3% | -4.3 to 13.2 | 0.54 group 1 comparing with group 3 | NR | NR | **no** |
|  | clopidogrel 150 mg/day | VerifyNow P2Y12 | TIMI minor bleeding | TIMI minor bleeding | 6 month | group 3  platelet inhibition <40% | TIMI minor bleeding | 3/47=6.4% | absolute risk difference 4.3 % | -2.0 to 15.1 | 0.30 group 2 comparing with group 3 | NR | NR | **no** |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | clopidogrel 75 mg/day | VerifyNow P2Y12 | total bleeding | TIMI major or minor bleeding | 6 month | group 1  platelet inhibition >40% | TIMI minor bleeding | 4/98=4.1% | absolute risk difference 2% | 1.0 to 11.8 | 0.54 group 1 comparing with group 2 | NR | NR | **no** |
|  | clopidogrel 75 mg/day | VerifyNow P2Y12 | total bleeding | TIMI major or minor bleeding | 6 month | group 2  platelet inhibition <40% | TIMI minor bleeding | 1/47=2.1% | absolute risk difference 4% | -6 to 16.1 | 0.27 group 1 comparing with group 3 | NR | NR | **no** |
|  | clopidogrel 150 mg/day | VerifyNow P2Y12 | total bleeding | TIMI major or minor bleeding | 6 month | group 3  platelet inhibition <40% | TIMI minor bleeding | 4/47=8.1% | absolute risk difference 6 % | -3.6 to 17.9 | 0.16 group 2 comparing with group 3 | NR | NR | **no** |