**Appendix Table E34. Results from studies assessing the ability of VerifyNow to predict myocardial infarction 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)** |
| Breet, 2010{Breet, 2010 86 /id}20179285NetherlandsPOPULAR | maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily | VerifyNow P2Y12 | MI | MI  | 1-year  | High OTPR | MI | 40/406 (9.9) | OR=2.96 | 1.74-5.02 | <0.001 | No  | NR |  |
|  |  |  |  |  |  | Normal OTPR |  | 23/646 (3.6) |  |  |  |  |  |  |
| Kim, 2010{Kim, 2010 241 /id}20449634KoreaNR | 300-600mg LD and 75 mg maintain dose clopidogrel  | VerifyNow P2Y12 (PRU) | non-fatal myocardial infarction  | non-fatal myocardial infarction | 6 months |  <240 | non-fatal myocardial infarction | 1.7% | OR=2.62 | 1.13-6.06 | 0.019 | NR | NR |  |
|  |  |  |  |  |  | ≥240 |  | 4.3% |  |  |  |  |  |  |
| Ko, 2011{Ko, 2011 26 /id}21315223KoreaNR | 75 mg/d clopidogrel & 100 mg/d aspirin  | VerifyNow P2Y12 Assay | Periprocedural MI  | Postprocedural ↑ of troponin or CK-MB >3 times the 99th percentile of the ULN in patients with normal baseline levels (or >3 times in pts with elevated baseline levels) | From PCI to 30 days | Hyporesponsiveness (PRU>274) | MI+ | NR | Sens=0.923Spec=0.479 | NR | NR | NR | NR | Prev. of CKMB>3x and moderate/severe bleeding were reported by clopidogrel response; These were not extracted |
|  | 75 mg/d clopidogrel & 100 mg/d aspirin | VerifyNow P2Y12 Assay | Periprocedural MI  | Postprocedural ↑ of troponin or CK-MB >3 times the 99th percentile of the ULN in patients with normal baseline levels (or >3 times in pts with elevated baseline levels). | From PCI to 30 days | NR | MI+ | NR | NR | NR | NR | NR | NR | AUC=0.680; P=0.024(Fig2d) |
| Campo, 2010{Campo, 2010 58 /id}2095132010 sites in Italy, Belgium, France, Sprain3T/2R trial | Clopidogrel LD 300 or 600 mg or maintaining 75mg daily | VerifyNowP2Y12 | Myocardial infarction  | Myocardial infarction | 1-year | Full responder | Myocardial infarction | 13/289 (4.5) | NR | NR | 0.001 | NR | NR |  |
|  |  |  |  |  |  | Poor responder |  | 29/179 (16.2) |  |  |  |  |  |  |
|  | Clopidogrel LD 300 or 600 mg or maintaining 75mg daily | VerifyNowP2Y12 | MI by CK-MB | 55 MIs, 6.6% using≥3xULN of CK-MB definition  | 0-3 days  | Full responder | MI by CK-MB | 55 | HR=1.19 | 1.09-1.28 | <0.01 | NR | NR |  |
|  | Clopidogrel LD 300 or 600 mg or maintaining 75mg daily | VerifyNowP2Y12 | MI by CK-MB | 55 MIs, 6.6% using≥3xULN of CK-MB definition | 0-3 days  | Full responder | MI by CK-MB | NR | HR=1.15 | 1.05-1.35 | 0.01 | Yes, variables with p-value>0.2  | NR |  |
|  | Clopidogrel LD 300 or 600 mg or maintaining 75mg daily | VerifyNowP2Y12 | MI by troponin I/T | 114 MIs, 6.6% using≥3xULN of troponin I/T definition  | 0-3 days  | Full responder | MI by troponin I/T | NR | HR=1.39 | 1.28-1.5 | <0.01 | NR | NR |  |
|  | Clopidogrel LD 300 or 600 mg or maintaining 75mg daily | VerifyNowP2Y12 | MI by troponin I/T | 114 MIs, 6.6% using≥3xULN of troponin I/T definition | 0-3 days  | Full responder | MI by troponin I/T | NR | HR=1.30 | 1.07-1.56 | 0.01 | Yes, variables with p-value>0.2  | NR |  |
| Cuisset, 2008{Cuisset, 2008 168 /id}18549843BelgiumNR | clopidogrel 600 mg + aspirin 500 mg LD | VerifyNow P2Y12 | Periprocedural MI | postprocedural increase in troponin T 3 times the 99th percentile (>0.03 ng/ml). | NR | nonresponder (Quartile 1) | Periprocedural MI | 14/32 (44%) | OR=4.6OR=3.9 | 1.9‑11.51.6‑8.7 | P=0.001(Q1 vs Q2-4)P<0.01(Q1 vs Q2-4) | NOYES;For confounding variable (list NR) | NRNR |  |
|  |  |  |  |  |  | responder (Quartile 2) |  | 4/30 (13%) |  |  |  |  |  |  |
|  |  |  |  |  |  | responder (Quartile 3) |  | 5/30 (17%) |  |  |  |  |  |  |
|  |  |  |  |  |  | responder (Quartile 4) |  | 4/30 (13%) |  |  |  |  |  |  |
| Kim, 2011{Kim, 2011 5 /id}21786434South KoreaCiLostazol administration before pErcutaneous coronAry intervention for Reduction of periprocedural myonecrosis trial (CLEAR trial) | Clopidogrel+aspirin | VerifyNow | MI |  | 6 mo | Clopidogrel resistance |  | 1/37 (1%) |  |  | NS vs. next row (chi-square statistics or Fisher ’s exact test) |  |  |  |
|  |  |  |  |  |  | Normal response |  | 0/73 (0%) |  |  |  |  |  |  |
|  |  |  | periprocedural MI | CK-MK elevation >/=3 times UNL | 6 mo | Clopidogrel resistance | YES event | 2/37 (5%) | NR | NR | NS vs. next row (chi-square statistics or Fisher ’s exact test) | NR | NR | NONE |
|  |  |  |  |  |  | Normal response |  | 4/73 (5%) |  |  |  |  |  |  |
|  |  |  | large periprocedural MI | CK-MK elevation >/=10 times UNL |  | Clopidogrel resistance |  | 1/37 (3%) |  |  | NS vs. next row (chi-square statistics or Fisher ’s exact test) |  |  |  |
|  |  |  |  |  |  | Normal response |  | 2/73 (3%) |  |  |  |  |  |  |
|  |  |  | cTnI elevation >/=3 times UNL |  |  | Clopidogrel resistance |  | 5/37 (14%) |  |  | NS vs. next row (chi-square statistics or Fisher ’s exact test) |  |  |  |
|  |  |  |  |  |  | Normal response |  | 14/73 (19%) |  |  |  |  |  |  |
|  |  |  | cTnI elevation >/=10 times UNL |  |  | Clopidogrel resistance |  | 3/37 (8%) |  |  | NS vs. next row (chi-square statistics or Fisher ’s exact test) |  |  |  |
|  |  |  |  |  |  | Normal response |  | 7/73 (10%) |  |  |  |  |  |  |
| Mangiacapra 2010{Mangiacapra, 2010 83 /id}20298992ItalyNR | Clopidogrel 300 mg LD, 75 mg MD with aspirin | verifyNow | Periprocedural myocardial infarction | periprocedural myocardial infacrction as per CPK-MB: increases of biomarkers >3x ULN | NR | HPR | periprocedural MI by CK-MB | 10/78 (13%) | OR= 3.47 | 1.27‑9.48 | p=0.011(HPR vs no HPR)[logistic regression] | No | NR | Secondary outcome |
|  |  |  |  |  |  | No HPR |  | 7/172 (4%) |  |  |  |  |  |  |
|  | Clopidogrel 300 mg LD, 75 mg MD with aspirin | verifyNow | Periprocedural myocardial infarction | periprocedural myocardial infacrction as per Tropinin I increases of biomarkers >3x ULN | NR | HPR | periprocedural MI by Troponin I | 25/78 (32%) | OR= 2.06 | 1.12-3.80 | p=0.019(HPR vs no HPR)[logistic regression] | No | NR | Secondary outcome |
|  |  |  |  |  |  | No HPR |  | 33/172 (19%) |  |  |  |  |  |  |
|  | Clopidogrel 300 mg LD, 75 mg MD with aspirin | verifyNow | Periprocedural myocardial infarction | periprocedural myocardial infacrction as per CPK-MB: increases of biomarkers >3x ULN | NR | HPR | periprocedural MI by CK-MB | 10/78 (13%) | OR= 3.21 | 1.11‑9.32 | p=0.032(HPR vs no HPR)[logistic regression] | YES;multivessel intervention, lesion type B2/C, multivessel disease, diabetes, total stent length, left ventricle ejection fraction <40% | NR | Secondary outcome |
|  |  |  |  |  |  | No HPR |  | 7/172 (4%) |  |  |  |  |  |  |
|  | Clopidogrel 300 mg LD, 75 mg MD with aspirin | verifyNow | Periprocedural myocardial infarction | periprocedural myocardial infacrction as per Tropinin I increases of biomarkers >3x ULN | NR | HPR | periprocedural MI by Troponin I | 25/78 (32%) | OR= 2.25 | 1.24-4.13 | p=0.019(HPR vs no HPR)[logistic regression] | YES;multivessel intervention, lesion type B2/C, multivessel disease, diabetes, total stent length, left ventricle ejection fraction <40% | NR | Secondary outcome |
|  |  |  |  |  |  | No HPR |  | 33/172 (19%) |  |  |  |  |  |  |
| Mangiacapra, 2010{Mangiacapra, 2010 94 /id}20129566BelgiumNR | clopidogrel 600 mg and aspirin 500 mg | VerifyNow | Periprocedural MI | post-procedural Troponin-T increase more than 3 times the 99th percentile of the upper reference limit | NR | HPR | Periproicedural MI | 42 (41.2%) | 1.92 | 1.18‑3.13 | P=0.008 | NO | Bonferroni  |  |
|  |  |  |  |  |  | Normal platelet reactivity |  | 63 (26.7%) |  |  |  |  |  |  |
|  | clopidogrel 600 mg and aspirin 500 mg | VerifyNow | Periprocedural MI | post-procedural Troponin-T increase more than 3 times the 99th percentile of the upper reference limit | NR | HPR | Periproicedural MI | 42 (41.2%) | 1.684 | 1.016‑2.789 | P=0.043(high PR vs normal PR)[multivariable logistic regression model] | YES;All clinical and procedural variables that showed a significant univariate association with periprocedural MI (p<0.05)  | Bonferroni  |  |
| Mangiacapra, 2010{Mangiacapra, 2010 65 /id}20723634ItalyNR | Clopidogrel 600 mg LD + 75 mg MD + aspirin 100 mg LD & MD | VerifyNow | Periprocedural MI | postprocedural increase in creatine kinase-MB x3 times the 99th percentile of the upper reference limit (with baseline negative myocardial necrosis markers) or subsequent increase≥50% the baseline value (in patients with increased baseline levels of creatine kinase MB)  | NR | HPR | Periprocedural MI | 11/77 (14%) | NR | NR | P=0.0008(P for trend)[chi square test] | NO | NR | Data calculated from Fig 3 and Fig 1 |
|  |  |  |  |  |  | No HPR |  | 16/208 (7.7%) |  |  |  |  |  |  |
|  | Clopidogrel 600 mg LD + 75 mg MD + aspirin 100 mg LD & MD | VerifyNow | Periprocedural MI | postprocedural increase in creatine kinase-MB x3 times the 99th percentile of the upper reference limit (with baseline negative myocardial necrosis markers) or subsequent increase≥50% the baseline value (in patients with increased baseline levels of creatine kinase MB)  | NR | HPR | Periprocedural MI | 11/77 (14%) | OR=8.34 | 2.6-26.76 | P=0.0003(HPR vs no HPR)[multivariate logistic regression] | YES;All variables listed in Tables 1 and 2 showing a significant univariate association with periprocedural MI (p<0.05) and HPR | NR | Data calculated from Fig 3 and Fig 1 |
| Marcucci, 2009{Marcucci, 2009 144 /id}19118249ItalyNR | clopidogrel 600 mg LD + 75 mg MD & ASA 500 mg IV LD + 100-325 mg MD | VerifyNow | Nonfatal MI | Nonfatal MI **Error! Bookmark not defined.** | 12 months | high residual platelet reactivity (PRU≥240) | Nonfatal MI | 16 (7.3)  | HR=2.73 | 1.54–5.01 | P=0.006(RPR vs no RPR) | NO | NR |  |
|  |  |  |  |  |  | No residual platelet reactivity (PRU<240) |  | 11 (2.4) |  |  |  |  |  |  |
|  | clopidogrel 600 mg LD + 75 mg MD & ASA 500 mg IV LD + 100-325 mg MD | VerifyNow | Nonfatal MI | Nonfatal MI **Error! Bookmark not defined.** | 12 months | high residual platelet reactivity (PRU≥240) | Nonfatal MI | 16 (7.3)  | HR=3.36 | 1.49–7.58 | P=0.034(RPR vs no RPR) | YES;cardiovascular risk factors, renal failure, left ventricular ejection fraction <40%, multivessel disease, total stent length, bifurcation lesions, number of lesions treated, type of stent used, and use of glycoprotein IIb/IIIa inhibitors | NR |  |
|  |  |  |  |  |  | No residual platelet reactivity (PRU<240) |  | 11 (2.4) |  |  |  |  |  |  |
|  | clopidogrel 600 mg LD + 75 mg MD & ASA 500 mg IV LD + 100-325 mg MD | VerifyNow | Nonfatal MI | Nonfatal MI **Error! Bookmark not defined.** | 12 months | high residual platelet reactivity (PRU≥235) | Nonfatal MI | NR | HR=2.94 | 1.37–6.34 | P=0.006(RPR vs no RPR) | NO | NR |  |
|  |  |  |  |  |  | No residual platelet reactivity (PRU<235) |  | NR |  |  |  |  |  |  |
|  | clopidogrel 600 mg LD + 75 mg MD & ASA 500 mg IV LD + 100-325 mg MD | VerifyNow | Nonfatal MI | Nonfatal MI **Error! Bookmark not defined.** | 12 months | high residual platelet reactivity (PRU≥235) | Nonfatal MI | NR | HR=3.12 | 1.38–7.02 | P=0.006(RPR vs no RPR) | YES;cardiovascular risk factors, renal failure, left ventricular ejection fraction <40%, multivessel disease, total stent length, bifurcation lesions, number of lesions treated, type of stent used, and use of glycoprotein IIb/IIIa inhibitors | NR |  |
|  |  |  |  |  |  | No residual platelet reactivity (PRU<235) |  | NR |  |  |  |  |  |  |
| Price, 2011{Price, 2011 23 /id}21406646USAGauging Responsiveness with A VerifyNow assay—Impact on Thrombosis And Safety (GRAVITAS) | Clopidogrel 75 mg/d MD+ Aspirin 75-162 mg/d MD | VerifyNow | Nonfatal MI | Nonfatal MI83 | 6 months | High on-treatment reactivity wasdefined (PRU≥230) | Nonfatal MI | 18 (1.6%) | HR=1.93 | 0.72-5.21 | P=0.19(high vs not high)[log-rank test stratified by acute coronary syndromes status] | NO | NR | Secondary analysis |
|  |  |  |  |  |  | Not High On-Treatment Reactivity (PRU<230) |  | 5 (0.9%) |  |  |  |  |  |  |
| Price, 2008{Price, 2008 174 /id}18263931USANR | Clopidogrel LD 600 mg and maintaining 75mg daily | VerifyNow P2Y12 assay | Non-fatal MI | Non-fatal MI | 6-months | Lower reactivity | Non-fatal MI | 2/209(1.0) | NR | NR | 0.6 comparing with the following row  | NR | NR |  |
|  |  |  |  |  |  | High reactivity  |  | 2/108 (1.9) |  |  |  |  |  |  |
|  |  |  |  |  |  | Total  |  | 4/317 (1.3) |  |  |  |  |  |  |
|  | Clopidogrel LD 600 mg and maintaining 75mg daily | VerifyNow P2Y12 assay | Non-fatal MI | Non-fatal MI | 6-months follow-up with a minimal of 3 months post-procedure | Lower reactivity | Non-fatal MI | 2/252(0.8) | NR | NR | 0.6 comparing with the following row  | NR | NR |  |
|  |  |  |  |  |  | High reactivity  |  | 2/121(1.7) |  |  |  |  |  |  |
|  |  |  |  |  |  | Total  |  | 4/373 (1.1) |  |  |  |  |  |  |
| Valgimigli , 2009{Valgimigli, 2009 244 /id}1952833710 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 | periprocedural MI | elevation of troponin I/T ratio >/=3xULN | 48 hr after PCI | Clopidogrel nonresponders, 21% to <40% inhibition |  | NR | NR | NR | 0.35 for interaction between tirofiban or placebo for this and next row | NR | NR | Risk ratios and CIs are in Fig. 4 (all are <1) |
|  |  |  |  |  |  | Clopidogrel nonresponders, <21% inhibition |  | NR | NR | NR | 0.78 for interaction between tirofiban and placebo and clopidogrel vs. aspirin nonresponder | NR | NR | Risk ratios and CIs are in Fig. 4 (all are <1) |
|  |  |  |  |  |  | Dual (clopidogrel and aspirin) nonresponders |  | NR | NR | NR | NR | NR | NR | Risk ratios and CIs are in Fig. 4 (all are <1) |
| Breet, 2011{Breet, 2011 15 /id}21478385The NetherlandsPOPular | Clopidogrel LD 300 or 600mg or maintaining 75 mg daily | VerifyNow | MI | MI | 1 year | HCPR(high on-clopidogrel platelet reactivity) or dual PR | MI | 12/168 | NR | NR | 0.0033comparing with NPR(normal on-treatment platelet reactivity) | NR | NR |  |
| Saw, 2008{Saw, 2008 242 /id}19463380CanadaBRIEF-PCI | Clopidogrel LD 600 mg and maintaining 75mg daily | VerifyNow P2Y12 | MI  | Tr-I > 3x ULN with normal baseline Tr-I | 30 day  | Low-responder(n=51) | 30-day death, MI, urgent TVR | 12 (24%) | NR | NR | 0.433(low vs normal responder)[Fisher’s exact] | NR | NR |  |
|  |  |  |  |  |  | Responder(n=147) |  | 43 (29.3%) | NR |  |  |  |  |  |
|  |  |  | MI | CK-MB > 3x ULN with high baseline Tr-I | 30 day  | Low-responder(n=51) | 30-day death, MI, urgent TVR | 2 (3.9%) | NR | NR | 0.467(low vs normal responder)[Fisher’s exact] | NR | NR |  |
|  |  |  |  |  |  | Responder(n=147) |  | 3 (2%) | NR |  |  |  |  |  |
| Park, 2011 {Park, 2011 1 /id} 22152948KoreaNR | clopidogrel LD 300 or 600 mg>=12h before PCI, MD 75mg/dayaspirin LD 200mg, MD 100-200 mg/day | VerifyNow | MI | MI | 2-year | HTPR (PRU >235 and/or a % inhibition <15%) | MI | high 6/1660 (0.3) | HR=1.34 | 0.37-4.83 | 0.66comparing with normal cox proportional model  | NR | NR |  |
|  |  |  |  |  |  |  |  | normal4/1189(0.3) |  |  |  |  |  |  |
| Park, 2011{Park, 2011 18181 /id}21880289KoreaCROSS-VERIFY | clopidogrel LD 300 or 600 mg, MD 75mg/day; aspirin MD 100 mg/day | VerifyNow | Periproedural MI | cardiac enzyme(creatine kinase-MB or troponin I) elevation >3 timesthe 99th percentile upper limit | 1 year | high OPR (HOPR) ≥235 PRUn=407 | Periprocedural MI | NR | NR | NR | P=0.435(HOPR vs no HOPR)[Log rank test] | NR | NR |  |
|  |  |  |  |  |  | No HOPR <235 PRUn=402 |  | NR |  |  |  |  |  |  |
|  |  |  |  |  |  | high OPR (HOPR) ≥275 PRUn=247 | Periprocedural MI | 42(17%) | OR=1.23 | 0.82-1.86 | P=0.311(HOPR vs no HOPR)[Chi-square test] | NR | NR |  |
|  |  |  |  |  |  | No HOPR <275 PRUn=562 |  | 80 (14.2%) |  |  |  |  |  |  |
|  |  |  | Nonfatal MI | Nonfatal MI | 1 year | high OPR (HOPR) ≥275 PRUn=247 | MI | 4(1.6%) | OR=3.07 | 0.68-13.81 | P=0.124(HOPR vs no HOPR)[Log rank test] | NR | NR |  |
|  |  |  |  |  |  | No HOPR <275 PRUn=562 |  | 3 (0.5%) |  |  |  |  |  |  |
| Mangiacapra, 2012{Mangiacapra, 2012 18179 /id}22440493Italy & BelgiumARMYDA-PROVE | Clopidogrel LD: 600 mg loading dose ≥6 h before PCI or 75 mg/d x 5 daysClopidogrel MD: 75 mg/d from 4 weeks to 12 monthsAspirin 80-100 mg/day | VerifyNow | MI | MI (including periprocedural MI) | 30 days | Low PR (PRU ≤178)n = 248  | MI | 9 (3.6%) |  |  | P<0.001 P for trend  | No | NR |  |
|  |  |  |  |  |  | Normal PR (PRU between ≥179 and ≤238) n = 244 |  | 11 (4.5%) | OR=0.48 | 0.24-0.94 | normal vs other |  |  |  |
|  |  |  |  |  |  | High PR (PRU ≥239)n = 240 |  | 35 (14.6%) |  |  |  |  |  |  |
|  |  |  | Periprocedural MI | Periprocedural MI | 30 days | Low PR (PRU ≤178)n = 248  | Periprocedural M | 8 (3.2%) |  |  | P<0.001 P for trend | No | NR |  |
|  |  |  |  |  |  | Normal PR (PRU between ≥179 and ≤238) n = 244 |  | 11 (4.5%) | OR=0.53 (calculated) | 0.27-1.05 | normal vs other |  |  |  |
|  |  |  |  |  |  | High PR (PRU ≥239)n = 240 |  | 32 (13.3%) |  |  |  |  |  |  |
| Jin, 2012 {Jin, 2012 18230 /id} KoreaNR | 600mg clopidogrel and 300 mg aspirin LD, 75 mg clopidogrel and 100 mg aspirin as MD | VerifyNow P2Y12 | nonfatal MI | nonfatal MI | 12 months | no HPR  | nonfatal MI  | 1/127=0.8% | HR=10.08 | 1.11-92.40 | 0.041comparing with HPRcox-model | **yes** | **No** |  |
|  |  |  |  |  |  | HPR | nonfatal MI  | 4/54=7.4% |  |  |  |  |  |  |
| Yu, 2012 {Yu, 2012 18231 /id}22787468KoreaNR | LD 300mg aspirin and 300 mg clopidogrel, | VerifyNow P2Y12 | non-fatal MI | non-fatal MI | 12 months | respondern=109 | non-fatal MI | 5/109=4.6% | OR=1.8 | 0.34-9.54 | 0.515comparing with low responderchi square test or Fisher’s exact test | **No** | **No** | **no** |
|  |  |  |  |  |  | low responder n=77 |  | 2/77=2.6% |  |  |  |  |  |  |