**Appendix E. Appendix Tables for Key Question 2**

**Appendix Table E1. Descriptive characteristics of studies reporting analytic validity information**

| **Author**  **Year**  **Country**  **PMID** | **Patient population** | **Assays evaluated**  **(agonist)**  **[brand name, manufacturer]** | **Test timing** | **Treatment preceding testing** | **Study design for the assessment of analytic validity** | **Sample size**  **(measurements performed and included in analyses)** | **Results** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Michelson  2009  USA  19435740 | Patients with ACS scheduled for PCI in the TRITON-TIMI 38 trial. Patients who had received abciximab within 30 d, or tirofiban or eptifibatide within 7 d of testing, were excluded from the LTA component of the study. | VASP phosphorylation assay  (PGE1 ± ADP, concentration not reported)  [BioCytex, Marseilles, France]; using flow cytometry [FACSCalibur, Becton Dickinson, San Jose, California]  LTA  (ADP 5 μmol/L and 20 μmol/L)  [not reported] | Samples were collected at 3 timepoints: at baseline (pre-PCI, pre-study drug); 1-2 h post PCI (at least 1 h after dosing); and at 30 d post-PCI. | A loading dose of the study medication (1:1 randomization; prasugrel 60 mg or clopidogrel 300 mg) was administered between randomization and 1 h after leaving the catheterization laboratory. Pretreatment with the study drug was permitted for up to 24 h pre-PCI. Adjunctive medication was left at the discretion of the treating physician. After PCI patients received maintenance doses of prasugrel (10 mg) or clopidogrel (75 mg). Aspirin use was required (recommended 325-500 mg loading dose; 75-162 mg maintenance dose). | All 13 participating sites sent samples for the VASP phosphorylation assay; 3 pre-selected sites performed LTA on site. | 125 using the VASP assay; of these 31 were also evaluated with LTA (both ADP concentrations). Measurements at baseline, 1-2 h post PCI, and 30 days (clopidogrel and prasugrel treated subjects) were analyzed together and observations were treated as independent. | Relative risk for identifying responders between VASP assay and MPA (20 μmol/L) = 5.25 (95% CI 2.34, 11.75) |
| Paniccia  2009  Italy  19461090 | Patients admitted to the coronary care of a single center unit for ACS; all patients underwent coronary angiography and PCI | Impedance aggregometry  (ADP, 10 μmol/L)  [Multiplate analyzer, Dynabyte, Munich, Germany]  LTA  (ADP, 10 μmol/L)  [APACT-4004 aggregometer, LABiTec, Ahrensburg, Germany]  High shear platelet function  (collagen/ADP)  [PFA-100, Dade-Behring, Marburg, Germany] | Samples were collected 24-48 h after PCI. | A loading dose of aspirin (500 mg IV) and oral clopidogrel (600 mg), followed by daily aspirin (325 mg) and clopidogrel (75 mg). During the procedure patients received UFH. | Measurements of samples with 3 techniques and different agonists; ROC analysis to identify optimal cut-offs for the Multiplate analyzer and PFA-100, using LTA as the reference method; 50 datapoints (10 measurements in each of 5 patient samples) for LTA | Multiplate analyzer and LTA (ADP as agonist): 297  Multiplate analyzer and PFA-100 (ADP as agonist): 111 | Agreement for residual platelet reactivity between the Multiplate analyzer and LTA (ADP as agonist): kappa = 0.74 (95% CI 0.64, 0.84); P<0.001  Agreement for residual platelet reactivity between the Multiplate analyzer and PFA-100 (ADP as agonist): kappa = 0.19; P = NS  Multiplate analyzer analytic test performance (using LTA as the reference test, ADP as the agonist): sensitivity = 0.78 (95% CI 0.68, 0.89); specificity = 0.95 (95% CI 0.92, 0.98); accuracy = 0.92 (95% CI NR); PPV = 0.80 (95% CI 0.69, 0.90); NPV = 0.95 (95% CI 0.92, 0.97)  ROC analysis for the Multiplate analyzer for detecting residual platelet reactivity on LTA (ADP as agonist): AUC = 0.93 (95% CI 0.89, 0.96); P<0.001 |
| Oestreich  2009  USA  19318928 | Patients with CAD from a single center outpatient cardiology clinic on dual antiplatelet therapy | LTA  (ADP, 5 and 20 μM)  [570VS aggregometer, Chrono-Log, Havertown, Pennsylvania]  Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, additional details NR] | At baseline; days 30 and 60 after enrollment | At baseline patients were receiving daily clopidogrel (75 mg) and aspirin (81-325 mg); clopidogrel was then increased to 150 mg for 30 d; after that, clopidogrel dosing at 75 mg was resumed for another 30 d (total duration of the study = 60 d) | Agreement between assays and different agonists, using predefined cut-offs for poor response | 20 subjects measured 3 times (different timepoints) | Agreement between PRU and MPA (LTA, ADP 5 μM): kappa = 0.85  Agreement between PRU and MPA (LTA, ADP 20 μM): kappa = 0.46  Agreement between PRU and RPA (LTA, ADP 5 μM): kappa = 1.00  Agreement between PRU and RPA (LTA, ADP 20 μM): kappa = 0.30  Agreement between MPA (LTA, ADP 5 μM) and MPA (LTA, 20 μΜ): kappa = 0.62  Agreement between MPA (LTA, ADP 5 μM) and RPA (LTA, 5 μΜ): kappa = 0.85  Agreement between MPA (LTA, ADP 5 μM) and RPA (LTA, 20 μΜ): kappa = 0.43  Agreement between MPA (LTA, ADP 20 μM) and RPA (LTA, 5 μΜ): kappa = 0.46  Agreement between MPA (LTA, ADP 20 μM) and RPA (LTA, 20 μΜ): kappa = 0.33  Agreement between RPA (LTA, ADP 5 μM) and RPA (LTA, 20 μΜ): kappa = 0.30 |
| Marcucci  2007  Italy  17938810 | Consecutive patients with STE MI admitted to a single center coronary care unit | LTA  (ADP, 2 and 10 μM)  [APACT 4 aggregometer, Helena Laboratories Italia s.p.a., Milan, Italy] | 12-15 h after PCI for patients receiving aspirin + clopidogrel; 24 h after the infusion of abciximab for patients receiving aspirin + clopidogrel + IIb/IIIa inhibitor | All patients underwent angiography and primary PCI; 200 patients received aspirin (500 mg loading dose; 100 mg maintenance) + clopidogrel (300 mg loading dose; 75 mg maintenance) and 167 received aspirin (500 mg loading dose; 100 mg maintenance) + clopidogrel (300 mg loading dose; 75 mg maintenance) + IIb/IIIa inhibitor (abciximab bolus 0.25 mg/kg of body weight, followed by continuous infusion 0.125 μg/kg/minute for 12 hours). All patients received UFH. | Agreement between LTA using alternative ADP concentrations | 367 subjects measured with two agonist concentrations | Agreement between LTA with ADP 2μM and ADP 10 μM: out of 367 measurements, 17 were positive by both tests; 279 were negative by both tests; 71 were positive with ADP 10 μM but not ADP 2 μM; none were positive with ADP 2 μM but not ADP 10 μM. |
| Frere  2007  France  17938809 | Consecutive patients with NSTE ACS admitted to the department of cardiology in a single center, following successful coronary stenting. | LTA  (ADP 10 μmol/L)  [PAP4, Biodata Corporation, Wellcome, Paris, France]  VASP phosphorylation assay  (PGE1 ± ADP, concentration not reported)  [Platelet VASP, Diagnostica Stago (BioCytex), Asnieres, France]; using flow cytometry [EPICS XL-MCL, Beckman Coultronics, Margency, France] | Before the PCI, at least 12 h after the loading dose of clopidogrel and aspirin; before the administration of tirofiban (if needed) | Clopidogrel (600 mg loading; 75 mg maintenance) + aspirin (250 mg loading; 75 mg maintenance); LMWH or UFH was used for anticoagulation | Agreement between LTA and VASP for determining low clopidogrel response | 195 patients measured with both tests | Weighted kappa for agreement between methods = 0.32 |
| Paniccia  2007  Italy  17723123 | Consecutive adult patients admitted to the coronary care units of a single center for ACS (STE MI, NSTE MI, UA), who underwent coronary angiography and PCI | LTA  (ADP, 2 μmol/L and 10 μmol/L)  [APACT-4 aggregometer, LABiTec, Ahrensburg, Germany]  High shear platelet function  (collagen/ADP)  [PFA-100, Dade-Behring, Marburg, Germany]  Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] | 24-48 h after PCI; assays performed within 2 h of blood sampling | Acetylsalicylic acid (500 mg loading; 100-325 mg maintenance) + clopidogrel orally (300 mg loading; 75 mg maintenance). UFH was used as the anticoagulant. Patients receiving IIb/IIIa inhibitors were excluded. | Measurements of samples from the same patient with multiple methods to assess agreement | For analyses of agreement, 626 to 1267 samples measured with the tests of interest (specific sample sizes reported by specific comparisons) | USING CUT-OFFS DERIVED FROM STUDY DATA  Agreement between LTA (ADP 2μml/L) and PFA-100 (collagen/ADP cartridge) for residual platelet reactivity: out of 626 measurements, 22 were positive by both tests; 393 were negative by both tests; 80 were positive with LTA (ADP 2μml/L) but not PFA-100 (collagen/ADP cartridge); 131 were positive with PFA-100 (collagen/ADP cartridge) but not LTA (ADP 2μml/L). ***NOTE:*** discrepant numbers are reported in the text of the paper for the same comparison: out of 626 measurements, 41 were positive by both tests; 335 were negative by both tests; 138 were positive with LTA (ADP 2μml/L) but not PFA-100 (collagen/ADP cartridge); 112 were positive with PFA-100 (collagen/ADP cartridge) but not LTA (ADP 2μml/L). Agreement between LTA (ADP 2μmol/L) with PFA-100 (collagen/ADP cartridge) for residual platelet reactivity: kappa = -0.02; P = NS.  Agreement between LTA (ADP 10μml/L) and PFA-100 (collagen/ADP cartridge) for residual platelet reactivity: out of 626 measurements, 35 were positive by both tests; 345 were negative by both tests; 128 were positive with LTA (ADP 10μml/L) but not PFA-100 (collagen/ADP cartridge); 118 were positive with PFA-100 (collagen/ADP cartridge) but not LTA (ADP 10μml/L). Agreement between LTA (ADP 10μmol/L) with PFA-100 (collagen/ADP cartridge) for residual platelet reactivity: kappa = -0.04; P = NS  Agreement between LTA (ADP 2μml/L) and VerifyNow (P2Y12 assay) for residual platelet reactivity: out of 1267 measurements, 159 were positive by both tests; 795 were negative by both tests; 159 were positive with LTA (ADP 2μml/L) but not VerifyNow (P2Y12 assay); 154 were positive with VerifyNow (P2Y12 assay) but not LTA (ADP 2μml/L). Agreement between LTA (ADP 2μmol/L) with VerifyNow (ADP assay) for residual platelet reactivity: kappa = 0.34; 95% CI 0.29, 0.35; P<0.001.  Agreement between LTA (ADP 10μml/L) and VerifyNow (P2Y12 assay) for residual platelet reactivity: out of 1267 measurements, 171 were positive by both tests; 831 were negative by both tests; 123 were positive with LTA (ADP 10μml/L) but not VerifyNow (P2Y12 assay); 142 were positive with VerifyNow (P2Y12 assay) but not LTA (ADP 10μml/L). Agreement between LTA (ADP 10μmol/L) with VerifyNow (ADP assay) for residual platelet reactivity: kappa = 0.43; 95% CI 0.36, 0.42; P<0.001.  Agreement between VerifyNow (P2Y12 assay) and PFA-100 (collagen/ADP cartridge) for residual platelet reactivity: out of 626 measurements, 53 were positive by both tests; 315 were negative by both tests; 158 were positive with VerifyNow (P2Y12 assay) but not PFA-100 (collagen/ADP cartridge); 100 were positive with PFA-100 (collagen/ADP cartridge) but not VerifyNow (P2Y12 assay). Agreement between PFA-100 (collagen/ADP cartridge) with VerifyNow (ADP assay) for residual platelet reactivity: kappa = -0.01; P=NS.  Analytic performance of VerifyNow, using LTA (ADP 2 μml/L) as the reference standard (cut-off based on study data): sensitivity = 50.0%; specificity = 83.8%; PPV = 50.8%; NPV = 83.3%.  Analytic performance of VerifyNow, using LTA (ADP 10 μml/L) as the reference standard (cut-off based on study data): sensitivity = 58.2%; specificity = 85.4%; PPV = 54.6%; NPV = 87.1%.  USING CUT-OFFS DERIVED FROM PRIOR LITERATURE  Agreement between LTA (ADP 10 μml/L) and VerifyNow (P2Y12 assay) for residual platelet reactivity: out of 1267 measurements, 142 were positive by both tests; 858 were negative by both tests; 96 were positive with LTA (ADP 10μml/L) but not VerifyNow (P2Y12 assay); 171 were positive with VerifyNow (P2Y12 assay) but not LTA (ADP 10μml/L). Agreement between LTA (ADP 10μmol/L) with VerifyNow (ADP assay) for residual platelet reactivity: kappa = 0.38; 95% CI 0.33, 0.39; P<0.001.  Analytic performance of VerifyNow, using LTA (ADP 10 μml/L) as the reference standard (70% cut-off, based on prior literature): sensitivity = 59.7%; specificity = 83.4%; PPV = 45.5%; NPV = 89.9%. |
| Van Werkum  2006  Netherlands  16938130 | Consecutive patients undergoing elective PCI with stenting referred to a single center | LTA  (ADP, 20 μmol/L)  [NR]  Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] | Variable (based on patient referral patterns) | Clopidogrel pre-treatment varied by center (maintenance therapy of 75mg for >5 d, n = 116; loading dose 300mg at least 24 h before PCI, n = 75; loading dose 600 mg at least 4 h before PCI, n = 20). All patients were on aspirin ≥80mg of aspirin for at least 7 days. | Assessment of agreement between measurements using both assays | 211 patients | Bland-Altman analysis “did not show proportional or systematic bias, with minimal clustering of values” for the following pairs of measurements:  “Peak aggregation” with LTA versus VerifyNow PRU units, and  “Late aggregation” with LTA versus VerifyNow PRU units |
| Mobley  2004  USA  14969622 | Patients scheduled for cardiac catheterization at a single center | Optical platelet aggregometry  (ADP, 1 μM)  [Dual Channel Aggregometer; Chrono-Log Corp., Havertown, PA]  TEG  (ADP, 1 μM)  [Thromboelastograph assay, Hemoscope, additional details NR]  PlateletWorks  (ADP, 1 μM)  [PlateletWorks assay, Ichor, additional detaisl NR] | “After a variable number of days on therapy” | 300 mg loading doses administered at the clinicians discretion; orally 75 mg maintenance; samples drawn to monitor platelet inhibition were obtained before treatment with additional anticoagulants or antiplatelet agents | Assessment of agreement between measurements with different assays | 50 patients | Agreement between was 89% for optical platelet aggregation; 91% for TEG; 76% for PlateletWorks; agreement was judged against an average of % change from baseline across all analyzers. |
| Ren  2011  China  21518592 | Patients with high-risk ACS undergoing elective PCI | TEG  (ADP, 2 μmol/L)  [Thromboelastograph mapping assay in TEG5000, Hemoscope Corp., USA] | Blood samples were obtained after 5 days of using omeprazole. | Clopidogrel (600 mg loading dose; 75 mg daily maintenance) + aspirin (300 mg loading dose; 100 mg daily maintenance); no patients received IIb/IIIA inhibitors. At the beginning of elective PCI patients were randomized to omeprazole (20 mg) or placebo for 30 days. | Not reported (for analytic validity assessment) | Not reported (for analytic validity assessment) | Analytic sensitivity for the ADP pathway = 80%  Analytic specificity for the ADP pathway = 86% |
| Godino  2009  Italy  19419580 | Consecutive patients with evidence of stable coronary artery disease undergoing elective PCI | ADP-stimulated IIb/IIIa receptor AND P-selectin expression (considered jointly as the reference standard)  (ADP, 20 μM and collagen, 5 μg/mL)  Using flow cytometry  [FC500; Beckman Coulter, S.p.A., Cassina De’ Pecchi, Milan, Italy]  Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] | Patients had to have been under treatment for 7 or d prior to testing; 2 samples were obtained within 1 hour; analyzed at least 10 min and within 2 h of sampling | Clopidogrel (75 mg) and aspirin (100 mg), daily, foe at least 7 days prior to testing. Patients who had received heparin, abciximab, tirofiban, or eptifibatide in the previous week were excluded from the study. | Samples from patients measured with 2 assays; flow cytometry used as the reference standard to determine analytic sensitivity and specificity for identifying non-responders using cut-offs determined by measurements in control individuals | 52 patients measured with both tests | Using % inhibition and a cut-off of ≤15% inhibition, derived from ROC analysis (AUC = 0.94; 95% CI 0.84, 0.98; P<0.0001):  Analytic sensitivity of VerifyNow, using ADP-stimulated IIb/IIIa receptor and P-selectin expression as the reference standard = 100%  Analytic specificity, using ADP-stimulated IIb/IIIa receptor and P-selectin expression as the reference standard = 89.1%  Using absolute PRU values and a cut-off of >213 units of inhibition, derived from ROC analysis (AUC = 0.85; 95% CI 0.72, 0.93; P<0.005):  Analytic sensitivity of VerifyNow, using ADP-stimulated IIb/IIIa receptor and P-selectin expression as the reference standard = 83.3%  Analytic specificity, using ADP-stimulated IIb/IIIa receptor and P-selectin expression as the reference standard = 84.4%  Agreement between ADP-stimulated IIb/IIIa receptor and P-selectin expression: out of 52 measurements, 6 were positive by both tests; 23 were negative by both tests; 2 were positive based on P-selectin expression but not IIb/IIIa receptor expression; 21 were positive based on IIb/IIIa receptor expression but not P-selectin expression. |
| Paniccia  2011  Italy  21192314 | Patients with CAD admitted to a single center’s coronary care unit for ACS. All patients underwent coronary angiography and PCI. | LTA  (ADP, 2 μmol/L, 5 μmol/L, 10 μmol/L, and 20 μmol/L)  [APACT-4004 aggregometer, LABiTec, Ahrensburg, Germany]  Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] | Samples were collected 24 or 48 h after the end of PCI; all assays were performed within 2 h of blood sampling. | Acetylsalicylic acid (500 mg IV) followed by aspirin (maintenance dose 100-325 mg) + clopidogrel (300 mg loading dose; followed by maintenance dosing at 75 mg daily). Patients receiving IIb/IIIa receptor inhibitors were excluded. | Measurements of samples with 2 assays (and different agonist concentrations for LTA) for the assessment of agreement and the derivation of limits of agreement; for the assessment of reliability, repeat measurements on samples from smaller groups of patients were performed (only for LTA) | Samples from 466 patients for assessment of agreement | Agreement between LTA (ADP 2 μmol/L) and LTA (ADP 5 μmol/L): kappa = 0.69 (95% CI 0.59, 0.79); P < 0.0001; percentage agreement = 93.1%  Agreement between LTA (ADP 2 μmol/L) and LTA (ADP 10 μmol/L): kappa = 0.63 (95% CI 0.53, 0.73); P < 0.0001; percentage agreement = 90.3%  Agreement between LTA (ADP 2 μmol/L) and LTA (ADP 20 μmol/L): kappa = 0.61 (95% CI 0.51, 0.71); P < 0.0001; percentage agreement = 89.2%  Agreement between LTA (ADP 5 μmol/L) and LTA (ADP 10 μmol/L): kappa = 0.68 (95% CI 0.59, 0.77); P < 0.0001; percentage agreement = 91.6%  Agreement between LTA (ADP 5 μmol/L) and LTA (ADP 20 μmol/L): kappa = 0.65 (95% CI 0.56, 0.74); P < 0.0001; percentage agreement = 90.6%  Agreement between LTA (ADP 10 μmol/L) and LTA (ADP 20 μmol/L): kappa = 0.86 (95% CI 0.80, 0.92); P < 0.0001; percentage agreement = 95.9%  Agreement between VerifyNow and LTA (ADP 10 μmol/L): kappa = 0.51 (95% CI 0.43, 0.60); P < 0.0001; percentage agreement = 82.4%  Agreement between VerifyNow and LTA (ADP 20 μmol/L): kappa = 0.44 (95% CI 0.35, 0.53); P < 0.0001; percentage agreement = 79.6%  Bland-Altman limits of agreement comparing LTA with ADP 10 μmol/L and 20 μmol/L: mean difference = -0.70% ±4.6% (CI, -9.7%, 8.3%). The difference in platelet reactivity between assays using these ADP concentrations was >20% in 3 samples (out of 466) |
| Koessler  2011  Germany  20873965 | Patients with stable coronary artery disease under dual antiplatelet therapy who underwent PCI | High shear platelet function  (collagen/ADP)  [INNOVANCE PFA-100 P2Y\*, Dade Behring (now Siemens), Marburg, Germany]  VASP phosphorylation assay  (PGE1 ± ADP, concentration not reported)  [Platelet VASP/P2Y12, BioCytex, Marseille, France]; using flow cytometry [FACScan, Becton Dickinson, Heidelberg, Germany] | The intended timing of measurements was not reported for the patient group; in the total population (n=50) samples were obtained on average 1.4 days post PCI | Patients were on dual antiplatelet treatment (aspirin + clopidogrel). | Agreement between the PFA-100 assay (at different thresholds) and VASP phosphorylation assay; analytic sensitivity and specificity of PFA-100 against VASP phosphorylation assay | 50 patients measured with both tests; alternative cut-offs applied to the PFA-100 measurements | Analytic sensitivity of INNOVANCE PFA-100 (cut-off 106 sec) against VASP (cut-off of PRI 50%) = 100% (among 31 responders)  Analytic specificity of INNOVANCE PFA-100 (cut-off 106 sec) against VASP (cut-off of PRI 50%) = 42% (among 19 non-responders)  Highest agreement between INNOVANCE PFA-100 and VASP assay was achieved using a cut-off of 200 sec for the former and 55% for the latter (Cohen’s kappa = 0.66). Using these cut-offs the analytic sensitivity of PFA-100 is 97% and specificity = 65%. Results at additional thresholds (where agreement was lower) are presented in Figure 5 of the paper. |
| Paniccia  2010  Italy  20458439 | Adult patients referred to a single vascular disease center enrolled in a registry of ACS; patients underwent PCI with stent implantation | LTA  (ADP, 10 μM)  [APACT-4004 aggregometer, LABiTec, Ahrensburg, Germany]  Impedance aggregometry  (ADP, 10 μM final concentration)  [Multiplate analyzer, Dynabyte, Munich, Germany]  Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] | Samples were collected 24 or 48 h after the end of PCI; PCI was performed 3-6 h after the ACS. All assays were performed within 2 h of blood sampling. | Acetylsalicylic acid (500 mg IV) followed by aspirin (maintenance 100-325 mg) + clopidogrel (300-600 mg loading dose) followed by maintenance dosing (75 mg daily). None of the investigated patients received other platelet function inhibitors (including IIb/IIIa receptor inhibitors). | Measurement of samples with 3 assays for assessment of agreement; cut-offs for residual platelet reactivity were based on prior literature. For the assessment of reliability, repeat measurements on samples from smaller groups of patients were performed (adequate information for the assessment of reliability was provided for LTA only) | 801 samples for the assessment of agreement; 5 samples from each of 10 patients of the assessment of reliability | Agreement between Multiplate analyzer and LTA: out of a total of 801 samples, 102 samples were positive with both tests; 609 samples were negative with both tests; 27 samples were positive by LTA but not the Multiplate analyzer; 63 samples were positive by the Multiplate analyzer but not LTA. Agreement kappa = 0.63 (95% CI 0.56, 0.70); P < 0.0001.  Agreement between Multiplate analyzer and VerifyNow: out of a total of 801 samples, 132 samples were bositive by both tests; 521 samples were negative by both tests; 33 samples were positive by Multiplate analyzer but negative by VerifyNow; 115 samples were positive by VerifyNow but not Multiplate analyzer. Agreement kappa = 0.52 (95% CI 0.46, 0.58); P < 0.0001.  Agreement between VerifyNow and LTA: out of a total of 801 samples, 105 samples were positive by both tests; 635 samples were negative by both tests; 24 samples were positive by LTA but not VerifyNow; 142 samples were positive by VerifyNow but not LTA. Agreement kappa = 0.44 (95% CI 0.38, 0.50); P < 0.0001 |
| Ko  2011  Korea  21315223 | Consecutive CAD patients undergoing PCI in two university hospitals; all patients received drug eluting stents | Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, additional details not reported]  Impedance aggregometry  (ADP, concentration not reported)  [Multiplate analyzer, Dynabyte, additional details not reported] | Samples were obtained in the catheterization room through the femoral catheter, before the administration of heparin | Patients were pre-treated with aspirin (100 mg/d) and clopidogrel (75 mg/d) ≥ 5 d before the procedure, or received oral loading doses of aspirin (250 mg) and clopidogrel (300 mg) 12-24 h before the procedure. | Measurement of samples using both tests to calculate limits of agreement | Data from both tests were available from 222 patients | Bland-Altman\* limits of agreement between VerifyNow PRU and Multiplate analyzer = -17.1 (SD = 232.1) with 95% limits of agreement from -472.0 to 437.8 |
| Aradi  2010  Hungary  20642320 | Prospectively recruited clopidogrel-naïve stable angina patients with planned PCI | LTA  (ADP, 5 μM and epinephrine, 10 μM)  [CARAT TX4 aggregometer, Carat Diagnostics, Budapest, Hungary]  VASP phosphorylation assay  (PGE1 ± ADP, concentration not reported)  [Platelet VASP/P2Y12 kit, BioCytex, Marseille, France]; using flow cytometry [Beckman Coulter flow cytometer, no additional details reported] | Samples were obtained 12-18 h post-clopidogrel loading and at 25 ± 2 d after PCI | All patients received clopidogrel (600 mg) and aspirin (300 mg) loading doses after angiography and immediately before PCI. | Measurement of samples with both assays (and different reactivity indexes from the same assay) to obtain limits of agreement; repeat measurements were obtained after clopidogrel loading and 25 ± 2 d after PCI but were treated as independent | 242 samples from 121 patients, all assessed with both assays | Bland-Altman analysis comparing maximal aggregation by LTA and PRI VASP measurements = +1.3  Bland-Altman analysis comparing late aggregation by LTA and PRI VASP measurements; bias = -10.6  Bland-Altman analysis comparing disaggregation by LTA and PRI VASP measurements; bias = -19.9  Bland-Altman analysis comparing LTA AUC of the light transmission curve and PRI VASP; bias measurements = -15.1  The authors noted the presence of substantial heteroscedasticity in the Bland-Altman plots for the last three of the four analyses listed above.†  Analytic accuracy using PRI VASP (50% cut-off) as the reference standard:  - Maximal aggregation by LTA (34.5% cut-off, based on ROC analysis):  Specificity = 79.4%  Sensitivity = 61.3%  Concordant pairs = 71.1%  Discordant pairs = 28.9%  Kappa = 0.4 (P<0.001)  AUC (95% CI) = 0.75 (0.68, 0.81); P<0.0001  - Late aggregation by LTA (12% cut-off, based on ROC analysis):  Specificity = 83.2%  Sensitivity = 62.2%  Concordant pairs = 73.1%  Discordant pairs = 26.9%  Kappa = 0.45; P<0.001  AUC (95% CI) = 0.73 (0.67, 0.80)  - Disaggregation by LTA (63.5% cut-off, based on ROC analysis):  Specificity = 80.2%  Sensitivity = 63.1%  Concordant pairs = 72.7%  Discordant pairs = 27.3%  Kappa = 0.44; P<0.001  AUC (95% CI) = 0.71 (0.64, 0.78); P<0.0001  - AUC of LTA light transmission curve (82xmin cut-off, based on ROC analysis):  Specificity = 86.7%  Sensitivity = 60.8%  Concordant pairs = 72.3%  Discordant pairs = 27.7%  Kappa = 0.44; P<0.001  AUC (95% CI) = 0.76 (0.69-0.82); P<0.0001 |
| Woo  2010  Korea  20890076 | Patients with CAD scheduled to undergo PCI with DES placement in a single center. | LTA  (ADP, 10 μM)  [Chronolog impedance aggregometer Series 590, Probe and Co., Endingen Germany]  Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]  Impedance aggregometry  (ADP, 20 μM)  [Multiplate analyzer, Dynabyte Medical,Munich, Germany]  VASP phosphorylation assay  (PGE1 ± ADP, concentration not reported)  [Platelet VASP/P2Y12 kit, BioCytex, Marseille, France]; using flow cytometry [no additional details reported] | Samples were collected “just before” PCI | All patients were administered lading doses of aspirin (300 mg), clopidogrel (300 mg), and cilostazol (200 mg) ≥ 12 h before stenting. | Measurements with 4 assays to assess agreement | 66 patients | Agreement between LTA and VerifyNow, kappa = 0.25  Agreement between LTA and Multiplate analyzer, kappa = 0.21  Agreement between LTA and PRI VASP assay, kappa = 0.14 |
| Madsen  2010  Canada  20224050 | Patients undergoing PCI at a single center | LTA  (ADP, 5 μM)  [Chrono-Log Lumi Aggregometer, model 810; Chrono-Log Corporation, no additional details provided]  Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, no additional details provided]  TEG  (ADP, 2 μmol/L)  [TEG Hemostasis Analyzer, Haemonetics Corporation, no additional details provided] | Before PCI and on 1 d, 1 mo, 6 mo, and 12 mo, post-treatment | “Just before” PCI patients received 600 mg of clopidogrel; during the procedure use of tirofiban or eptifibatide was permitted but their administration was to be stopped ≥ 10 h before blood was drawn; abciximab was not permitted. Aspirin (325 mg/d) and clopidogrel (75 mg/day) were administered for a year post-PCI. | Measurement of samples with all three techniques and comparison of measurements for agreement | 33 patients, 26 of whom completed all study visits. Patients contributed samples at multiple timepoints and measurements were considered independent. The total number of measurements for each comparison was not reported; as such data are incomplete for the assessment of agreement. | Agreement between absolute maximal ADP aggregation (50% cut-off) and change in aggregation (cut-off 10%) by LTA: “low response” by both tests, 1; “normal response” by change in aggregation but not absolute aggregation, 6; “normal response” by absolute aggregation but not change in aggregation, 14.  Agreement between VerifyNow and change in aggregation (cut-off 10%) by LTA: “low response” by both tests, 1; “normal response” by change in aggregation but not VerifyNow, 3; “normal response” by VerifyNow but not change in aggregation, 8.  Agreement between TEG and change in aggregation (cut-off 10%) by LTA: “low response” by both tests, 1; “normal response” by change in aggregation but not TEG, 12; “normal response” by TEG but not change in aggregation, 8.  Agreement between VerifyNow and absolute maximal aggregation (cut-off 50%) by LTA: “low response” by both tests, 3; “normal response” by absolute aggregation but not VerifyNow, 1; “normal response” by VerifyNow but not change in aggregation, 5.  Agreement between TEG and absolute aggregation (cut-off 50%) by LTA: “low response” by both tests, 2; “normal response” by absolute aggregation but not TEG, 15; “normal response” by TEG but not change in aggregation, 4.  Agreement between VerifyNow and TEG: “low response” by both tests, 1; “normal response” by TEG but not VerifyNow, 1; “normal response” by VerifyNow but not TEG, 14. |
| Siller-Matula  2010  Austria  19943879 | Single center prospective observational study of patients undergoing PCI with stent implantation ≥2 hours after clopidogrel loading. The majority of patients were undergoing elective PCI. | VASP phosphorylation assay  (PGE1 ± ADP, concentration not reported)  [Platelet VASP/P2Y12 kit, BioCytex, Marseille, France]; using flow cytometry [FACSCalibur System, BD Biosciences, Vienna, Austria]  Impedance aggregometry  (ADP, concentration not reported)  [Multiplate analyzer, Dynabyte Medical, Munich, Germany] | Blood samples were obtained in the catheterization laboratory “directly after” PCI and at least 5 min after the IV administration of aspirin | 326 patients were on chronic clopidogrel treatment; 90 patients received a clopidogrel loading dose (600mg) within 2 d before PCI, followed by a maintenance dose of 75 mg. All patients received 250 mg of IV acetylsalicylic acid directly after stent placement, followed by a daily dose of 100 mg. Patients receiving IIb/IIIa inhibitors were excluded from analyses with the Multiplate analyzer. | Measurement of samples with both assays | 402 patients with results available from both assays | Agreement between Multiplate analyzer and VASP assay: “non-responders” by both tests, 54 (13%); “responders” by both tests, 138 (34%); “non-responders” by Multiplate analyzer but “responders” by VASP, 7 (2%); “responders” by Multiplate analyzer but “non-responders” by VASP assay, 203 (51%)  Bland-Altman analysis for agreement between VASP assay and Multiplate analyzer\*: average difference (bias) = 21; 95% limits of agreement, -34 to 78 |
| Cuisset  2010  France  20142119 | Consecutive patients admitted to a single institution for NSTE ACS | LTA  (ADP 10 μmol/L)  [PAP4, Biodata Corporation, Wellcome, Paris, France]  VASP phosphorylation assay  (PGE1 ± ADP, concentration not reported)  [Platelet VASP-FCM kit, Diagnostic Stago (BioCytex), Asnieres, France]; using flow cytometry [no additional details reported]  Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] | Samples were drawn 1 mo after discharge | Patients received oral loading doses of aspiring (250 mg) and clopidogrel (600 mg) at least 12 h before stenting | Measurement of patient samples with all three assays to determine limits of agreement and kappa statistics | 70 patients, assessed with all 3 assays | Bland-Altman analysis comparing aggregation by LTA versus PRI VASP\*: bias = 10.6; 95% limits of agreement, -23.3, 44.4  Bland-Altman analysis comparing aggregation by LTA versus VerifyNow PRU\*: bias = -146.4; 95% limits of agreement, -331.6, 39.0  Bland-Altman analysis comparing PRI VASP versus VerifyNow PRU\*: bias = -156.9; 95% limits of agreement, -342.1, 28.3  Agreement between LTA (cut-off 70%) and VASP PRI: kappa = 0.35  Agreement between VerifyNow PRU and LTA (cut-off 70%): kappa = 0.36  Agreement between VASP PRI and VerifyNow PRU: kappa = 0.46  Additional analysis using a different threshold:  Agreement between LTA (cut-off 50%) and VASP PRI: kappa = 0.42  Agreement between VerifyNow PRU and LTA (cut-off 50%): kappa = 0.52 |
| Smit  2009  Netherlands  19200163 | Patients participating in a multicenter trial of tirofiban vs. placebo (On-TIME 2 study) for STEMI requiring PCI | Fe-induced platelet aggregation [samples were added to tubes containing 100 mg of steel wool (Haemoscan, Groningen, Netherlands)] and a platelet counter was use to assess platelet aggregation (against a control tube no containing iron).  Plateletworks  (ADP, 20 μM/L)  [PlateletWorks, Helena Laboratories, Beaumont, TX] | Samples were obtained before PCI, but after the patients received the study medication (tirofiban or placebo) and antiplatelets | Before testing, patients received clopidogrel (600 mg orally) and acetylsalicylic acid (500 mg IV); blood was drawn at the “start of catheterization” | Measurement of samples with three assays to assess limits of agreement | 111 patients (53 randomized to tirofiban and 58 randomized to placebo) | Bland-Altman comparison between duplicate measurements using the iron-based assay: the mean was close to 0 (exact result not reported) and in ~6/111 samples were outside “limits of agreement of ±20%” (see also Figure 2 of the paper).  Bland-Altman comparison of the iron-based assay versus Plateletworks (ADP as the agonist): ~4/111 samples were outside limits of agreement of ±40% (see also Figure 4 of the paper). |
| Gremmel  2009  Austria  19190818 | Patients with peripheral, coronary, or carotid artery disease after elective percutaneous intervention with endovascular stent implantation | LTA  (ADP 10 μΜ)  [ΑPACT 4S Plus aggregometer, LABiTec, Ahrensburg, Germany]  Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]  VASP phosphorylation assay  (PGE1 ± ADP, concentration not reported)  [Platelet VASP kit, Diagnostica Stago, BioCytex, Marseille, France]; using flow cytometry [FACSCalibur system, Becton Dickinson, BD Biosciences, Vienna, Austria]  Impedance aggregometry  (ADP, 6.4 μM)  [Multiplate analyzer, Dynabyte Medical, Munich, Germany]  Cone and plate analyzer  (ADP 1.36 μM)  [Impact-R test, DiaMed, Cressier, Switzerland] | Samples were obtained 24 h after the percutaneous intervention | Patients had received acetylsalicylic acid (100 mg/d) at least 2 w prior to the percutaneous intervention. All patients received a loading dose of clopidogrel (300 mg) 24 h prior to the intervention, followed by a maintenance dose of 75 mg/day | Measurement of samples with 5 methods; assessment of correlations between methods, agreement between methods, and analytic sensitivity and specificity using LTA as the reference standard test (treated as a gold standard) | 80 patients assessed with 5 assays | Analytic performance, using LTA as the reference standard (20 positive samples):  Analytic sensitivity  -VerifyNow, 55%  - VASP assay,45%  -Multiplate analyzer, 35%  - Impact-R, 40%  Analytic specificity  -VerifyNow, 85%  - VASP assay, 81.7%  -Multiplate analyzer, 78.3%  - Impact-R, 78.3%  Analytic positive predictive value  -VerifyNow, 55%  - VASP assay, 45%  -Multiplate analyzer, 35%  - Impact-R, 38.1%  Analytic negative predictive value  -VerifyNow, 85%  - VASP assay, 81.7%  -Multiplate analyzer, 78.3%  - Impact-R, 79.7%  Agreement between LTA and VerifyNow: concordant positive samples = 11; concordant negative samples = 51; positive with LTA but not VerifyNow = 9; positive with VerifyNow but not LTA = 9  Agreement between LTA and VASP assay: concordant positive samples = 9; concordant negative samples = 49; positive with LTA but not VASP assay = 11; positive with VASP assay but not LTA = 11  Agreement between LTA and Multiplate analyzer: concordant positive samples = 7; concordant negative samples = 47; positive with LTA but not Multiplate analyzer = 13; positive with Multiplate analyzer but not LTA = 13  Agreement between LTA and Impact-R: concordant positive samples = 8; concordant negative samples = 47; positive with LTA but not Impact-R = 12; positive with Impact-R but not LTA = 13  Cut-offs for all assays were based on quartiles of the observed measurement distribution (most extreme reactivity quartile vs. all others). |
| Schafer  2008  Germany  18841284 | Consecutive patients with CAD admitted to a single center | LTA  (ADP 20 μΜ)  [PAP-8, BioData, Horsham, PA]  VASP phosphorylation assay  (PGE1 ± ADP, 20 μM)  [Platelet VASP Test kit, American Diagnostica, Pfungstadt, Germany]; using flow cytometry [FACSCalibur, Becton Dickinson, Heidelberg, Germany] | Samples were obtained 2-4 h after drug intake | Patients had been on maintenance dose clopidogrel (75 mg/d) for ≥5 d after a loading dose of 300-600 mg (on the first day); patients not on clopidogrel were used as controls (no data extracted) | Measurement of samples using 3 assays for assessment of agreement | 100 patients on clopidogrel | Agreement between VASP assay (cut-off 50%) and LTA (cut-off 50%): concordant positive results, 44%; concordant negative results, 28%; positive by VASP but not LTA, 25%; positive by LTA but not VASP assay, 3%.  Subgroup analysis by diabetic status:  Diabetic patients (n=30): agreement between VASP assay (cut-off 50%) and LTA (cut-off 50%): concordant positive results, 41%; concordant negative results, 24%; positive by VASP but not LTA, 34%; positive by LTA but not VASP assay, 0%.  Non-diabetic patients (n=70): agreement between VASP assay (cut-off 50%) and LTA (cut-off 50%): concordant positive results, 44%; concordant negative results, 28%; positive by VASP but not LTA, 23%; positive by LTA but not VASP assay, 5%. |
| Shenkman  2008  Israel  18155752 | Consecutive ACS patients who underwent PCI with stent implantation | LTA  (ADP, 5.5 μM)  [PACKS-4 aggregometer, Helena Laboratories, Beaumont, TX]  Impact-R  (ADP 1.38 μM)  [DiaMed, Cressier, Switzerland] | In one group of patients (n=114) blood samples were obtained before and 4 d after clopidogrel administration. In a second group (n=290) samples were obtained only 4 d after clopidogrel treatment. | All patients received aspirin 300 mg on admission and 200 mg/d thereafter. Eptifibatide was administered before PCI and for at least 12 h after the procedure. Clopidogrel was administered at a loading dose of 300 mg on completion of PCI, followed by a maintenance dose of 75 mg/d. | Measurement of samples with both assays to determine agreement and analytic sensitivity and specificity. For the later analyses LTA results were treated as a “gold standard” | 114 patients contributed measurements before and after clopidogrel administration; 290 patients only contributed measurements after clopidogrel administration. Only results from the second groups of patients were used for ROC and agreement analyses. | Analytic performance using LTA as the reference standard (cut-off 70%)  Optimal cut-off value for Impact\_r = 2.8  Analytic sensitivity = 71%  Analytic specificity = 83%  Analytic positive predictive value = 72%  Analytic negative predictive = 83%  AUC = 0.867  Agreement between LTA and Impact-R for non-response using the cut-offs identified through ROC analysis: concordant positive results, 78; concordant negative results, 151; non-responders by LTS but responders by Impact-R, 32; non-responders by Impact-R but responders by LTA, 29. |
| Lordkipanidze  2008  Canada  18520610 | Patients with CAD requiring eletive diagnostic coronary angiography with or without PCI from a single center. Patients were participants in a prospective, randomized, double-blind, placebo controlled trial | Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]  Comparisons were performed between a before-after assessment of the clopidogrel effect (based on two measurements using VerifyNow, pre- and post-clopidogrel administration) and a single on-clopidogrel measurement with VerifyNow where the TRAP channel of the assay is used to “approximate” the pre-clopidogrel reactivity level. | Blood was drawn “before clopidogrel initiation” (pre-clopidogrel measurement) and “just before” elective angiography | Patients were allocated randomly to 4 groups: 300 or 600 mg on the day before angiography, or 300 mg loading followed by 75 or 150 mg maintenance daily dose, started 1 w before angiography. All patients received aspirin (80 mg). Patients receiving IIb/IIIa inhibitors were excluded. | Two measurements with VerifyNow (before and after clopidogrel) to compare the before-after contrast versus as “estimated” contrast using the post-clopidogrel measurement and the TRAP channel of the same device | 68 patients contributing data for both timepoints | Bland-Altman analysis: bias = 8%; limits of agreement from -49% to 65% |
| Lordkipanidze  2009  Canada  19840560 | Consecutive patients with stable CAD treated with aspirin and clopidogrel selected from the outpatient cardiology clinic of a single center | LTA  (ADP 5, 10, and 20 μΜ)  [Chrono-Log aggregometer 540 model, Chrono-Log, Havertown, PA]  Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] | Samples were obtained 2-12 h after the last aspirin and clopidogrel dose. | All patients were on aspirin (≥80 mg/d) and clopidogrel (≥75 mg/d) for ≥ 3 mo. | Measurements were obtained with both assays (and using different concentrationsof ADP for LTA) to compare agreement | 85 patients contributed measurements with LTA, using ADP 5 and 20 μM concentrations, and VerifyNow; 77 patients were also assessed with LTA using an ADP concentration of 10 μM | Agreement between VerifyNow and LTA ADP 5 μΜ: kappa = 0.487; P<0.0001  Agreement between VerifyNow and LTA ADP 10 μΜ: kappa = 0.309; P=0.004  Agreement between VerifyNow and LTA ADP 20 μΜ: kappa = 0.661; P<0.0001 |
| Lordkipanidze  2009  Canada  19419755 | Patients presenting at a single center outpatient cardiology department with symptomatic CAD requiring diagnostic coronary angiography. Patients were participants in a prospective, randomized, double-blind, placebo controlled trial. | LTA  (ADP 5 and 20 μΜ)  [ChronoLog aggregometer 540 model, Havertown, PA] | Samples were obtained before clopidogrel initiation and “just before” elective angiography. | Patients were allocated randomly to 4 groups: 300 or 600 mg on the day before angiography, or 300 mg loading followed by 75 or 150 mg maintenance daily dose, started 1 w before angiography. All patients received aspirin (80 mg). Patients receiving IIb/IIIa inhibitors were excluded | Measurements obtained with both ADP concentrations to assess agreement | 120 patients contributed measurements | Bland-Altman analysis of peak versus late aggregation using LTA ADP 5 μM: bias = 10.8%; limits of agreement from -5.8% to 27.3%  Bland-Altman analysis of peak versus late aggregation using LTA ADP 20 μM: bias = 10.3%; limits of agreement from -8.5% to 29.2%  Analyses of inhibition of platelet reactivity (i.e., change from baseline)  Bland-Altman analysis of peak versus late absolute inhibition using LTA ADP 5 μM: bias = 3.4%; limits of agreement from -18% to 25%  Bland-Altman analysis of peak versus late absolute inhibition using LTA ADP 20 μM: bias = 5.9%; limits of agreement from -18% to 30%  Bland-Altman analysis of peak versus late relative inhibition using LTA ADP 5 μM: bias = -16.3%; limits of agreement from -59% to 26%  Bland-Altman analysis of peak versus late relative inhibition using LTA ADP 20 μM: bias = -12.3%; limits of agreement from -49% to 23% |
| Collet  2008  France  18765393 | Adult patients on maintenance clopidogrel for > 7 d scheduled to undergo cardiac catheterization because of unstable CAD or stable angina. Patients were participants in a prospective trial of alternative clopidogrel loading doses.‡ | LTA  (ADP 5, 10, 20, and 50 μmol/L)  [Chronolog Aggregometer model 490-4D, Chrono-Log Corp., Kordia, Netherlands]  Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] | Samples were obtained before the first and second loading doses and 24 h after the first loading dose (see adjacent cell for details). Agreement was assessed using the baseline measurements only (i.e., reflective of patients’ reactivity on maintenance clopidogrel) | All patients were on clopidogrel maintenance (75 mg/d) for > 7 d. They were alternately allocated to clopidogrel loading doses of 300, 600, or 900 mg (first loading dose). Depending on the initial assignment, patients then received a second loading dose, such that the total clopidogrel amount received would be 900 mg. Thereafter, all patients received maintenance clopidogrel (75 mg/d) and aspirin (≤100 mg/d). Only baseline measurements were used for the assessment of agreement. | Agreement regarding baseline on-clopidogrel non-responsiveness between assays | 166 patients measured at baseline | Agreement for poor response between LTA (cut-off 50% for residual platelet reactivity) and VerifyNow (cut-off 15%): kappa = 0.20; 95% CI 0.06, 0.40 |
| Von Beckerath  2010  Germany  19823079 | Consecutive patients without clopidogrel treatment within the last 4 week, scheduled for coronary angiography | LTA  (ADP 5 μmol/L)  [PAP 8 aggregometer, Molab, Berlin, Germany]  Impedance aggregometry  (ADP 6.4 μmol/L ± PGE1 9.4 μmol/L)  [Multiplate analyzer, Dynabyte Medical, Munich, Germany]  Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]  VASP phosphorylation assay  (PGE1 ± ADP, 20 μM)  [Platelet VASP, Biocytex, Marseille, France]; using flow cytometry [no additional details provided] | Samples were obtained before the administration of clopidogrel and immediately after stent placement (post-clopidogrel loading) | All patients received a single clopidogrel loading dose (600 mg), which was recommended to be given ≥ 2 h before catheterization. Patients treated with IIb/IIIa inhibitors within 28 d were excluded. | Assessment of samples with all 3 assessment and assessment of agreement for identifying “lack of response”. Lack of response was defined as values in the top quintile of measurements obtained from each assay. | Samples from 60 patients measured with 4 assays (2 different agonist types were used for the Multiplate analyzer) | 12 patients were in the upper quintile of the Multiplate analyzer using ADP as the agonist; of those 7 were in the upper quintile of VerifyNow (P<0.001), 6 in the upper quintile if Multiplate analyzer using ADP+ PGE1 as the agonist (P=0.004), and 3 were in the upper quintile of VASP PRI (P=0.63). P-values were from a “chi-square test”; it was unclear whether the paired nature of the measurements was accounted for in the analysis.  The authors stated that “comparisons of categorical classifications (upper quintiles) yielded a poor agreement of post-clopidogrel values” [no additional statistics were reported] |
| Varenhorst  2009  Sweden  19249429 | Patients with stable CAD participating in a parallel-group randomized trial of prasugrel versus clopidogrel, both in combination with aspirin | Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]  VASP phosphorylation assay  (PGE1 ± ADP, concentrations NR)  [Platelet VASP kit, BioCytex, Marseille, France]; using flow cytometry [samples were analyzed on different flow-cytometers in 2 participating centers: Epics XL, Beckman Coulter, Fullurton, CA; and FACScan, Becton Dickinson, Franklin Lakes, NJ]. The authors reported that “synchronization between the flow cytometers was performed”.  Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] | Samples were obtained before the loading dose, 2h and 24h post-loading, and the 14th and 29th day of clopidogrel maintenance treatment | Patients received aspirin 75mg/d for 5-21 d before randomization and were then assigned to clopidogrel (600 mg loading, 75 mg maintenance dose) or prasugrel (60 mg loading; 10 mg maintenance) groups, while continuing the same aspirin regimen | Two measurements with VerifyNow (before and after antiplatelet treatment) to compare the before-after contrast versus an “estimated” contrast using the post-clopidogrel measurement and the TRAP channel of the same device | 110 patients (1:1 randomized to clopidogrel or prasugrel) measured at 5 timepoints (not clear if all measurements were available for all patients and timepoints) | Lin’s concordance correlation coefficient between observed and estimated % inhibition = 0.97; P<0.0001 (the authors indicated that there is “modest underestimation by the device-reported %inhibition”)  Agreement for high platelet inhibition (quartile 1 vs. quartiles 2-4 for each assay), 95% CI  Agreement between VASP PRI and PRU, during loading phase = 0.35 (0.20, 0.49)  Agreement between VASP PRI and PRU, during maintenance phase = 0.55 (0.42, 0.68)  Agreement between late reactivity by LTA and PRU, during loading phase = 0.54 (0.41, 0.67)  Agreement between late reactivity by LTA and PRU, during maintenance phase = 0.52 (0.39, 0.66)  Agreement for low platelet inhibition (quartile 4 vs. quartiles 1-3 for each assay), 95% CI  Agreement between VASP PRI and PRU, during loading phase = 0.79 (0.69, 0.89)  Agreement between VASP PRI and PRU, during maintenance phase = 0.66 (0.54, 0.78)  Agreement between late reactivity by LTA and PRU, during loading phase = 0.75 (0.64, 0.85)  Agreement between late reactivity by LTA and PRU, during maintenance phase = 0.66 (0.54, 0.77) |
| Lordkipanidze  2008  Canada  18826988 | Patients with suspected CAD requiring elective diagnostic coronary angiography, recruited from the pre-angiography outpatient clinic of a single center. The current study was a pre-specified analysis nested within a prospective randomized trial of alternative clopidogrel dosing regimens | LTA  (ADP 5 and 20 μM)  [ChronoLog 540 model, Havertown, PA]  Impedance aggregometry  (ADP 5 and 20 μM)  [ChronoLog 560 model, Havertown, PA]  Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] | Blood was drawn at two time points: before clopidogrel initiation and “just before” coronary angiography | Patients were allocated randomly to 4 groups: 300 or 600 mg on the day before angiography, or 300 mg loading followed by 75 or 150 mg maintenance daily dose, started 1 w before angiography. All patients received aspirin (80 mg). Patients receiving IIb/IIIa inhibitors were excluded | Measurement of samples with all assays to assess agreement | 116 patients contributed samples to the analyses; only 72 patients had measurements with VerifyNow | Data were extracted only for on-clopidogrel measurements.  Bland-Altman analyses  Agreement between LTA ADP 5 μM and 20 μM: bias = 4.5% (95% CI, 1.3%, 7.7%); P=0.006 by paired t-test; limits of agreement: -26% to 38%.  Agreement between LTA ADP 20 μM and impedance aggregometry ADP 5 μM: bias = 13% (95% CI, 2.6%, 24.0%; overestimation by impedance aggregometry); P=0.01 by paired t-test; limits of agreement: -97% to 124%.  Agreement between LTA ADP 20 μM and impedance aggregometry ADP 20 μM: bias = -11% (95% CI, -20.7%, -1.8%; underestimation by impedance aggregometry); P=0.02 by paired t-test; limits of agreement: -110% to 87%.  Agreement between LTA ADP 20 μM and VerifyNow: bias = 6.3% (95% CI, -1.6%, 14.2%; non-significant overestimation by VerifyNow); P=0.117 by paired t-test; limits of agreement: -54.4% to 67.0%.  Agreement using a cut-off of 50%  Agreement between LTA ADP 5 μM and LTA ADP 20 μM: kappa = 0.679; P<0.05  Agreement between LTA ADP 5 μM and impedance aggregometry ADP 5 μM: kappa = -0.117; P=NS  Agreement between LTA ADP 5 μM and impedance aggregometry ADP 20 μM: kappa = 0.057; P=NS  Agreement between LTA ADP 5 μM and VerifyNow: kappa = 0.295; P<0.05  Agreement between LTA ADP 20 μM and impedance aggregometry ADP 5 μM: kappa = -0.187; P<0.05  Agreement between LTA ADP 20 μM and impedance aggregometry ADP 20 μM: kappa = 0.101; P=NS  Agreement between LTA ADP 20 μM and VerifyNow: kappa = 0.364; P<0.05  Agreement between impedance aggregometry ADP 5μM and impedance aggregometry ADP 20 μM: kappa = 0.308; P<0.05  Agreement between impedance aggregometry ADP 5μM and VerifyNow: kappa = -0.047; P=NS  Agreement between impedance aggregometry ADP 20 μM and VerifyNow: kappa = 0.132; P=NS  (exact p-values were not reported) |
| Jeong  2008  S. Korea  18617479 | Consecutive patients undergoing PCI with DES implantation at a single center | LTA  (ADP 5 μM)  [ChronoLog 540 model, Havertown, PA]  Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] | “from the arterial sheath” | Unclear (on-clopidogrel) | Measurements with both assays to assess analytic performance using LTA as the reference standard | 300 patients provided measurements with both assays | Optimal VerifyNow cut-off for HPR using LTA (with 50% cut-off) as the reference standard = 239 PRU; AUC = 0.794; 95% CI 0.736, 0.851; P<0.001  At this cut-off analytic sensitivity = 83.6%; analytic specificity = 68.3%  The authors also reported the analytic sensitivity and specificity of LTA % inhibition as 76.2% and 83.6% respectively, presumably against LTA on-treatment reactivity. For this analysis the optimal LTA cut-off was determined to be 20% (AUC = 0.841; 95% CI 0.790, 0.891). |
| Kim  2010  S. Korea  20449634 | Unselected patients treated with coronary stenting for symptomatic coronary artery disease, including AMI | LTA  (ADP 5 and 20 μM)  [AggRam aggregometer, Helena Laboratories Corp., Beaumont, TX]  Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] | “Pre-discharge” measurement, either ≥3 d after coronary stenting in patients not treated with tirofiban or at ≥5 d post-procedure in patients treated with tirofiban | In cases of scheduled coronary stenting, clopidogrel-naive patients received clopidogrel 300-mg (loading) at least 12 h pre-PCI. In patients already on chronic clopidogrel therapy, no loading dose was used. All AMI patients received clopidogrel 600 mg loading, followed by  75 mg/d maintenance. Tirofiban was the only IIb/IIIa inhibitor allowed. | Measurements with both assays to assess agreement and analytic performance | 1058 patients contributed measurements | Agreement between maximal reactivity by LTA ADP 5 μmol/L (50% cut-off) and VerifyNow (PRU 240 cut-off): kappa = 0.438; P<0.001; 29.1% concordant positives; 42.5% concordant negatives; 5.9% positive by LTA but not VerifyNow; 22.5% positive by VerifyNow but not LTA; overall concordance = 71.6%  Agreement between maximal reactivity by LTA ADP 20 μmol/L (50% cut-off) and VerifyNow (PRU 240 cut-off): kappa = 0.505; P<0.001; 35.0% concordant positives; 40.2% concordant negatives; 8.2% positive by LTA but not VerifyNow; 16.6% positive by VerifyNow but not LTA; overall concordance = 75.1%  Analytic performance using LTA as the reference standard test (however, with different thresholds for each analysis)  Analytic performance of VerifyNow against maximal reactivity by LTA ADP 5 μmol/L (cut-off 50%): optimal cut-off for VerifyNow = 241; AUC = 0.822 (95% CI 0.797, 0.847); analytic sensitivity = 0.830; analytic specificity = 0.660  Analytic performance of VerifyNow against maximal reactivity by LTA ADP 20 μmol/L (cut-off 62%): optimal cut-off for VerifyNow = 241; AUC = 0.840 (95% CI 0.816, 0.863); analytic sensitivity = 0.807; analytic specificity = 0.714  Analytic performance of VerifyNow against maximal reactivity by LTA ADP 20 μmol/L (cut-off 50%): optimal cut-off for VerifyNow = 195; AUC = 0.851 (95% CI 0.827, 0.875); analytic sensitivity = 0.889; analytic specificity = 0.635  Analytic performance of VerifyNow against late reactivity by LTA ADP 5 μmol/L (cut-off 14%): optimal cut-off for VerifyNow = 194; AUC = 0.826 (95% CI 0.796, 0.856); analytic sensitivity = 0.829; analytic specificity = 0.683  The paper also includes a table (see Table 2 in the manuscript for additional details) reporting comparisons between LTA (both maximal and late reactivity and 5 and 20 μmol/L ADP concentration) and VerifyNow using different thresholds for each test. Kappa statistics for all combinations assessed ranged between 0.260 and 0.734; concordance rates ranged between 56.7% and 87.2%; analytic sensitivities ranged between 68.8% and 100%; analytic specificities ranged between 34.4% and 83.9%. |
| Lordkipanidze  2009  Canada  19250657 | Patients with CAD receiving aspirin and clopidogrel§ were recruited from a single center’s pre-angiography clinic | LTA  (ADP 5 and 20 μM)  [ChronoLog Aggregometer, 540 model, Havertown, PA]  “Platelet count drop method” using impedance platelet counting before and after exposure to the agonist  (ADP 5 and 20 μM)  Using a Coulter ACT Series Analyzer, Beckman Coulter Inc., Fullerton, CA] | NR | Patients were on aspirin (80 mg/d) and clopidogrel (varying dosing schemes) | Measurements with both methods to assess agreement | 91 patients on clopidogrel + aspirin | Bland-Altman analysis comparing LTA (ADP 5 μM) and platelet count drop method (ADP 5 μM): bias = 13% (overestimation by platelet count drop); limits of agreement -27% to 52%.  Bland-Altman analysis comparing LTA (ADP 20 μM) and platelet count drop method (ADP 20 μM): bias = 18% (overestimation by platelet count drop); limits of agreement -30% to 65%.  Agreement between LTA (ADP 5 μM) and platelet count drop method (ADP 5 μM) using a cut-off of 50% for both: kappa = 0.192; P = 0.02  Agreement between LTA (ADP 20 μM) and platelet count drop method (ADP 20 μM) using a cut-off of 50% for both: kappa = 0.281; P = 0.002  Agreement between LTA (ADP 5 μM) and platelet count drop method (ADP 5 μM) using a cut-off of 70% for both: kappa = 0.207; P = 0.001  Agreement between LTA (ADP 20 μM) and platelet count drop method (ADP 20 μM) using a cut-off of 70% for both: kappa = 0.089; P = 0.191 |
| Pettersen  2011  Norway  21426546 | Patients with symptomatic CAD randomized to the aspirin + clopidogrel arm of a randomized trial | VASP phosphorylation assay  (PGE1 ± ADP, concentration not reported)  [PLT VASP/P2Y12 assay, Biocytex, France]; using flow cytometry [FACS Calibur System, Becton Dickinson, Plymouth, UK]  Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] | One month post-randomization to the clopidogrel arm | Aspirin (160 mg/d) + clopidogrel (75 mg/day) treatment for ≥ 1 mo; patients on aspirin only were used to derive the cut-off for “clopidogrel resistance” | Measurements with both assays to determine agreement | 219 patients were on aspirin + clopidogrel; 155 were analyzed successfully with the VASP assay and 212 with the VerifyNow assay | Agreement between VASP assay and VerifyNow: kappa = 0.379; P<0.001; concordance rate = 74.5% |
| Sibbing  2008  Germany  18217143 | Consecutive patients scheduled for coronary angiography; patients were required to not have received clopidogrel within 4 w of enrollment | LTA  (ADP 5 or 20 μM)  [PAPA 8 aggregometer, Bio/Data, no additional information reported]  Impedance aggregometry  (ADP, 6.4 μM)  [Multiplate analyzer, Dynabyte, Munich, Germany] | Samples were obtained from a subset of 60 patients at baseline (pre-clopidogrel loading) and from all participating patients (n=149) during catheterization (post-loading dose) | Patients received a loading dose of clopidogrel of 600 mg, recommended to be given ≥ 2 h before catheterization | Measurements with both methods to assess agreement | 149 patients contributed on-clopidogrel measurements; 60 patients also had baseline (pre-clopidogrel) measurements available | Agreement between LTA and Multiplate analyzer for lowest quartile of inhibition (n = 60): concordant positives = 7 (12%); concordant negatives = 35 (58%); positives by LTA but not Multiplate analyzer = 8 (13%); positives by Multiplate analyzer but not LTA = 10 (17%)  Agreement between LTA and Multiplate analyzer for lowest quartile of inhibition (n=149): concordant positives = 21 (14%); concordant negatives = 94 (63%); positives by LTA but not Multiplate analyzer = 17 (11%); positives by Multiplate analyzer but not LTA = 17 (11%) |
| Gaglia  2011  USA  21919956 | Patients undergoing urgent or elective PCI in a single center | LTA  (ADP 5 or 20 μM)  [ChronoLog, Havertown, PA]  VASP phosphorylation assay  (PGE1 ± ADP, concentration not reported)  [PLT VASP/P2Y12 assay, BioCytex, Marseille, France]; using flow cytometry [FACSCalibur flow cytometer, BD Biosciences, San Jose, CA]  Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] | Measurements of on-treatment platelet reactivity were obtained between 6 and 24 h following PCI and ≥ 6 hours following clopidogrel loading | Patients received clopidogrel loading (600 mg) ≥ 2 h prior to platelet testing or where on clopidogrel maintenance (75 mg) ≥ 5 d prior | Measurements with 3 assays to assess agreement | 200 patients | “All kappa statistics had P values <0.001” and “ranged from 0.33-0.53”  Agreement between LTA ADP 5 μM and LTA ADP 20 μM: kappa = 0.53 (95% CI 0.37, 0.68)  Agreement between VASP and LTA ADP 5 μM: kappa = 0.33 (95% CI 0.19, 0.47)  [agreement results were not reported for other pairs of assays]  “Overall, the level of agreement between assays was in the moderate to poor range” |
| McGlasson  2011  USA  21799401 | Patients scheduled to receive clopidogrel for cardiovascular or cerebrovascular disase, or with ≥ 2 risk factors for vascular disease (AHA criteria) | High shear platelet function  (ADP/PGE1 cartridges and collagen/ADP)  [INNOVANCE PFA P2Y and PFA-100 collagen/ADP cartridges, Siemens Healthcare Inc., Deerfield, IL]; the INNOVANCE assay was used on samples anticoagulated with 3.2% and 3.8% citrate  Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]  LTA  (ADP 20 μmol/L)  [ChronoLog 700 aggregometer, Chrono-Log, Havertown, PA]  Whole blood aggregometry  (ADP 5 and 10 μmol/L)  [ChronoLog 700 aggregometer, Chrono-Log, Havertown, PA] | Blood was collected 6-24 h post-clopidogrel loading or ≥ 7 d of maintenance therapy | Patients scheduled to receive clopidogrel; patients receiving non-clopidogrel platelet function inhibitors were excluded. 96 patients were receiving clopidogrel maintenance treatment (75 mg/day for ≥7 d); 5 received clopidogrel loading with 300-600 mg. | Measurements with multiple assays and using different anti-coagulants to assess agreement | 101 patients | concordance between PFA P2Y (3.2% citrate) and %inhibition = 71%  concordance between PFA P2Y (3.2% citrate) and P2Y12 PRU = 74%  concordance between PFA P2Y (3.2% citrate) and whole-blood aggregometry (5 μmol/L) = 64%  concordance between PFA P2Y (3.2% citrate) and whole-blood aggregometry (10 μmol/L) = 65%  concordance between PFA P2Y (3.2% citrate) and LTA = 69%  concordance between PFA P2Y (3.8% citrate) and VerifyNow P2Y12 %inhibition = 72%  concordance between PFA P2Y (3.8% citrate) and P2Y12 PRU = 62%  concordance between PFA P2Y (3.8% citrate) and whole-blood aggregometry (5 μmol/L) = 90%  concordance between PFA P2Y (3.8% citrate) and whole-blood aggregometry (10 μmol/L) = 90%  concordance between PFA P2Y (3.8% citrate) and LTA = 76%  concordance between VerifyNow P2Y12 %inhibition and whole-blood aggregometry (5 μmol/L) = 68%  concordance between VerifyNow P2Y12 %inhibition and whole-blood aggregometry (10 μmol/L) = 67%  concordance between VerifyNow P2Y12 %inhibition and LTA = 72%  concordance between VerifyNow P2Y12 PRU and whole-blood aggregometry (5 μmol/L) = 60%  concordance between VerifyNow P2Y12 PRU and whole-blood aggregometry (10 μmol/L) = 59%  concordance between VerifyNow P2Y12 PRU and LTA = 69% |
| Park  2012  Korea  21942752 | Consecutive patients admitted to a single academic cardiology department to undergo non-emergent PCI | LTA  (ADP 5 and 20 μM and ADP 5 μM + 5 nM PGE1)  [AggRAM aggregometer, Helena Laboratories Corp., Beaumont, TX]  Impedance aggregometry  (ADPtest 6.4 μΜ ADP and high-sensitivity ADPtest 6.4 μΜ ADP + 9.4 nM PGE1)  [Multiplate analyzer, Dynabyte, Munich, Germany] | Blood samples were obtained from the arterial sheath at the catheterization laboratory (pre-PCI) | Patients were pre-treated with aspiring (100 mg/d) and clopidogrel (75 mg/d) for ≥ 5 d pre-PCI or received loading doses of aspirin (300 mg) and clopidogrel (600 mg); patients receiving IIb/IIIa inhibitors were excluded | Testing of samples with two assays, and different agonists/ agonist concentrations, to assess agreement | 246 patients | Cut-offs for the assessment of agreement and analytic performance (summarized below) were obtained using ROC analysis with the ADPtest treated as the reference standard; cut-offs were chosen to maximize the sum of analytic sensitivity and specificity.  *Analytic performance for high on-clopidogrel reactivity*  Analytic performance of LTA maximal platelet reactivity (5 μM ADP) AUC = 0.836, 95% CI: 0.777, 0.896; P<0.001. At the cut-off of ≥46%, analytic sensitivity = 70.6% and analytic specificity = 89.3%  Analytic performance of LTA maximal platelet reactivity (20 μM ADP) AUC = 0.846, 95% CI: 0.785, 0.908; P<0.001. At the cut-off of ≥59%, analytic sensitivity = 75.0% and analytic specificity = 88.2%  *Agreement for high on-clopidogrel reactivity*  Agreement between ADPtest (≥47 U), and LTA maximal platelet aggregation (5 μM ADP) ≥46%: kappa =0.537; P<0.001 and concordance = 80.5%  Agreement between ADPtest (≥47 U) and LTA maximal platelet aggregation (20 mM ADP) ≥59%: kappa = 0.564; P<0.001 and concordance = 81.7%  *Analytic performance for low on-clopidogrel reactivity*  Analytic performance of LTA maximal platelet reactivity (5 μM ADP) AUC = 0.714, 95% CI: 0.618, 0.809; P<0.001. At the cut-off of ≤26.6%, analytic sensitivity = 64.0% and analytic specificity = 76.2%  Analytic performance of LTA maximal platelet reactivity (20 μM ADP) AUC = 0.796, 95% CI: 0.714, 0.879; P<0.001. At the cut-off of ≤35.3%, analytic sensitivity = 64.0% and analytic specificity = 88.9%  *Agreement for low on-clopidogrel reactivity*  Agreement between ADPtest (≤19 U), and LTA maximal platelet aggregation (5 μM ADP) ≤26.6%: kappa = 0.152; P<0.001 and concordance = 65.0%  Agreement between ADPtest (≤19 U) and LTA maximal platelet aggregation (20 μM ADP) ≤35.3: kappa = 0.152; P<0.001 and concordance = 65.0%  Bland-Altman analysis  Agreement between LTA maximal platelet aggregation (ADP 5 μM) and ADPtest: difference = -3.0; SD of difference = 17.6; 95% limits of agreement = -37.4 to 31.4  Agreement between LTA final platelet aggregation (ADP 5 μM) and ADPtest: difference = -14.9; SD of difference = 19.2; 95% limits of agreement = -52.5 to 22.6  Agreement between LTA maximal platelet aggregation (ADP 5 μM + PGE1) and ADPtest: difference = -9.4; SD of difference = 16.0; 95% limits of agreement = -40.8 to 21.9  Agreement between LTA final platelet aggregation (ADP 5 μM + PGE1) and ADPtest: difference = -18.5; SD of difference = 17.4; 95% limits of agreement = -52.7 to 15.6  Agreement between LTA maximal platelet reactivity (20 μM) and ADPtest: difference = 5.4; SD of difference = 18.8; 95% limits of agreement = -31.5 to 42.3  Agreement between LTA final platelet reactivity (20 μM) and ADPtest: difference = -7.3; SD of difference = 22.4; 95% limits of agreement = -51.2 to 36.6  Agreement between ADPtest HS and ADPtest: difference = -15.3; SD of difference = 11.4; 95% limits of agreement = -37.6 to 7.0  Agreement between LTA maximal platelet reactivity (5 μM) and ADPtest HS: difference = 12.3; SD of difference = 18.4; 95% limits of agreement = -23.8 to 48.3  Agreement between LTA final platelet reactivity (5 μM) and ADPtest HS: difference = 0.3; SD of difference = 20.1; 95% limits of agreement = -39.1 to 39.8  Agreement between LTA maximal platelet reactivity (5 μM + PGE1) and ADPtest HS: difference = 5.9; SD of difference = 16.5; 95% limits of agreement = -26.4 to 38.1  Agreement between LTA final platelet reactivity (5 μM + PGE1) and ADPtest HS: difference = -3.2; SD of difference = 17.4; 95% limits of agreement = -37.3 to 30.8  Agreement between LTA maximal platelet reactivity (20 μM) and ADPtest HS: difference = 20.7; SD of difference = 20.1; 95% limits of agreement = -18.8 to 60.2  Agreement between LTA final platelet reactivity (20 μM) and ADPtest HS: difference = 8.0; SD of difference = 24.5; 95% limits of agreement = -40.1 to 56.1 |
| Zhang  2012  Korea  22774770 | Patients with CAD undergoing PCI in a single center | LTA  (ADP 10 μM)  [additional information NR]  Impedance aggregometry  (ADP, 6.4 μM, sample anticoagulated with hirudin or citrate)  [Multiplate analyzer, Dynabyte Medical, Munich, Germany]  Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] | Blood samples were obtained from the arterial sheath at the catheterization laboratory (pre-PCI) and then 24-36 h post PCI | Patients were on clopidogrel maintenance treatment (75 mg/d for ≥ 5 d) or received clopidogrel loading (300 or 600 mg) ≥ 4 h pre-PCI; all patients were on aspirin maintenance treatment (100mg/d) or receive aspirin loading (300 mg) ≥ 4 h pre-PCI; patients receiving IIb/IIIa inhibitors were excluded | Measurement of samples with three assays to assess analytic performance at 2 timepoints (at PCI and post-PCI); assessments performed with samples treated with different anti-coagulants (pre-analytically) | 119 patients | *Using LTA as the reference standard and citrate anticoagulated samples at PCI*  Analytic sensitivity = 68.6%  Analytic specificity = 56.1%  AUC = 0.71 (95% CI 0.62, 0.79)  *Using LTA as the reference standard and hirudin anticoagulated samples at PCI*  Analytic sensitivity = 86.5%  Analytic specificity = 71.8%  AUC = 0.72 (95% CI 0.63, 0.80)  *Using LTA as the reference standard and citrate anticoagulated samples post-PCI*  Analytic sensitivity = 64.0%  Analytic specificity = 80.7%  AUC = 0.75 (95% CI 0.66, 0.83)  *Using LTA as the reference standard and hirudin anticoagulated samples post-PCI*  Analytic sensitivity = 64.0%  Analytic specificity = 80.7%  AUC = 0.77 (95% CI 0.68, 0.85)  *Using VerifyNow as the reference standard and citrate anticoagulated samples at PCI*  Analytic sensitivity = 56.8%  Analytic specificity = 87.5%  AUC = 0.74 (0.65–0.82)  *Using VerifyNow as the reference standard and hirudin anticoagulated samples at PCI*  Analytic sensitivity = 72.6%  Analytic specificity = 66.7%  AUC = 0.69 (95% CI 0.60, 0.78)  *Using VerifyNow as the reference standard and citrate anticoagulated samples post-PCI*  Analytic sensitivity = 60.0%  Analytic specificity = 92.7%  AUC = 0.79 (95% CI 0.71, 0.87)  *Using VerifyNow as the reference standard and hirudin anticoagulated samples post-PCI*  Analytic sensitivity = 58.0%  Analytic specificity = 80.5%  AUC = 0.74 (95% CI 0.65, 0.82) |
| Tsantes  2012  Greece  22646492 | Consecutive patients with coronary angiography-documented CAD, hospitalized after ACS, undergoing elective coronary angiography at a single cardiology department | LTA  (ADP 10 μM)  [Biodata-PAP-4 aggregometer, Bio/  Data Corporation, Horsham, PA]  High shear platelet function  (PFA-100 ADP/PGE1 cartridges)  [INNOVANCE PFA P2Y, Siemens Healthcare Diagnostics  Products GmbH, Marburg, Germany]  Impedance aggregometry  (ADP 6.5 μM)  [Multiplate analyzer, Dynabyte Medical, Munich, Germany] | Blood samples were obtained 1-24 h after the last dose of antithrombotic medication | Patients were on clopidogrel maintenance therapy (75 mg/d for >5 d) in combination with aspirin (100 mg/d) | Measurement of samples with two assays to assess agreement | 90 patients  [Note: data were also presented from analyses using the VASP assay; however this information did not meet the sample size requirement for our review; N<50] | *Based on cut-offs suggested by manufacturers*  Agreement between LTA and INNOVANCE PFA-100 P2Y: kappa = 0.31; SE = 0.08; P<0.05 [exact p-value not reported]; concordance = 74.4%  Agreement between Multiplate analyzer and INNOVANCE PFA-100 P2Y: kappa = 0.37; SE = 0.09; P<0.05 [exact p-value not reported] concordance = 75.6%  Agreement between Multiplate analyzer and LTA: kappa = 0.30; SE = 0.10; P<0.05 [exact p-value not reported] concordance = 85.6%  *Based on cut-offs associated with thrombotic risk (from previous publications)*  Agreement between LTA and INNOVANCE PFA-100 P2Y: kappa = 0.24; SE = 0.07; P<0.05 [exact p-value not reported] concordance = 72.2%  Agreement between Multiplate analyzer and INNOVANCE PFA-100 P2Y: kappa = 0.20; SE = 0.06; P<0.05 [exact p-value not reported] concordance = 71.1%  Agreement between Multiplate analyzer and LTA: kappa = 0.13; SE = 0.10; P=NS [p-value not reported] concordance = 90.0% |
| Liang  2012  Canada  22797934 | Stable patients with established CAD on dual antiplatelet treatment; patients were participants in a factorial RCT designed to explore the possibility of an interaction between clopidogrel and aspirin treatment | LTA  (ADP 5 μmol/L)  [Chrono-log aggregometer, Model 560-Ca]  Impedance aggregometry  (ADP 6.5 μM)  [Multiplate analyzer, Dynabyte Medical, Munich, Germany]  VASP phosphorylation assay  (PGE1 ± ADP, concentration not reported)  [PLT VASP/P2Y12 assay, BioCytex, Marseille, France]; using flow cytometry [FACSCaliber Flow Cytometer, Becton-Dickinson, San  Jose, CA] | Blood samples were  collected 6 h post-loading on d 1 and 1 h post-treatment on d 7 and 14 | Participants where on “regular” dual antiplatelet treatment; they were randomized  to clopidogrel 600 mg loading followed by  150 mg/d for 1 wk and 75 mg/d thereafter, or to clopidogrel 300 mg loading followed by  75 mg/d, and were also randomized to aspirin 325 mg/d or 81 mg/d (2x2 factorial design); all treatments were continued for 2 wk | Measurements with 3 assays to assess concordance (ICC) | 82 patients measured at measured at 6 h post-loading on d 1 and 1 h post-treatment on d 7 and 14 | *6 h post-loading on day 1*  ICC between VASP-PRI and LTA = 0.6446  ICC between VASP-PRI and Multiplate = 0.4720  ICC between LTA and MEA = 0.4693  *1 h post-treatment, d 7*  ICC between VASP-PRI and LTA = 0.5570  ICC between VASP-PRI and Multiplate = 0.4212  ICC between LTA and MEA = 0.5041  *1 h post-treatment, d 14*  ICC between VASP-PRI and LTA = 0.4724  ICC between VASP-PRI and Multiplate = 0.3965  ICC between LTA and MEA = 0.5022  No significant difference between each pair of ICCs on any day |
| Jang  2012  Korea  22811359 | Patients undergoing PCI at a single cardiology center | High shear platelet function  (PFA-100 ADP/PGE1 cartridges)  [INNOVANCE PFA P2Y, Siemens Healthcare Diagnostics  Products GmbH, Marburg, Germany]  Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] | Blood samples were collected at 48 h post clopidogrel loading | Patients were preliminarily treated with aspiring (100 mg/d), followed by co-administration of clopidogrel (loading dose, 600 mg; maintenance dose, 75 mg/d) | Measurement of samples with two assays to assess agreement | 255 patients | Agreement between INNOVANCE PFA P2Y and VerifyNow %inhibition: kappa = 0.52; % concordance = 85%  Agreement between INNOVANCE PFA P2Y and VerifyNow PRU: kappa = 0.44; % concordance = 79% |
| Park  2011  S. Korea  21880289 | Patients undergoing PCI with stent implantation for native coronary artery stenosis | Platelet agglutination assay  (ADP cartridges)  [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] | “After clopidogrel therapy” | Patients taking clopidogrel for >7 days underwent PCI without loading doses. Loading doses of clopidogrel (300 mg) were administered in patients who had been taking clopidogrel for <7 days. Patients who were expected to undergo PCI in <6 hours were given loading doses of 600 mg. Dual-antiplatelet therapy (aspirin 100 mg/day and clopidogrel 75 mg/day) was continued for ≥6 months post-PCI. | Measurement of samples with one assay and assessment of agreement between different measures of reactivity | 809 patients | Agreement between P2Y12 %inhibition (cut-off 5%) and P2Y12 PRU (cut-off 275 PRU): concordant positive, 126; concordant negative, 493; positive by PRU but not %inhibition, 121; positive by %inhibition but not PRU, 69. Kappa= 0.412 (95% CI 0.343, 0.481) [calculated value] |

\*The two tests report results in different units; thus Bland-Altman analysis is not strictly valid.  
†The interpretation of “bias” (or limits of agreement) from the Bland-Altman test is not straightforward in the presence of heteroscedasticity.  
‡The trial was described as “randomized,” however it appears to have been a alternate allocation design (often called, “pseudo-randomized” or “quasi-randomized” design).  
§The paper also reported on a cohort of patients receiving aspirin alone. We only extracted data from patients on clopidogrel.  
**Abbreviations:** ACS = acute coronary syndrome; ADP = adenosine diphosphate; CI = confidence interval; d = days; h = hour; ICC = intra-class correlation coefficient; LMWH = low molecular weight heparin; LTA = light transmittance aggregometry; MI = myocardial infarction; mo = month; MPA = maximal platelet aggregation; NPV = negative predictive value; NS = non-significant; NSTE = non-ST elevation; PCI = percutaneous coronary intervention; PGE1 = prostaglandin E1; PMID = PubMed identification number; PPV = positive predictive value; PRI = platelet reactivity index; PRU = platelet reactivity units; RPA = residual platelet aggregation; UA = unstable angina; UFH = unfractionated heparin; VASP = vasodilator-stimulated phosphoprotein. Percentages may not sum to 100% because of rounding.