Appendix Table E66. Phenotypic test details in studies assessing the predictive ability of Multiplate Analyzer in patients with ischemic heart disease

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| **Author, year [ref]****UID****Country****Study Name** | **Test/Device name** **Device category Device name & manufacturer\*** | **Agonist used** | **Sample Collection and Procurement****Anticoagulant used****Interval between clopidogrel doses and blood sampling (in days)** **Interval between sampling and testing (in days):** | **Grouping of Phenotypes\*\* [Definition]**  | **Rational for the grouping of phenotypes reported (Yes/No)** **[short description]** | **Frequency of phenotypes**  |
| Siller-Matula,2009{Siller-Matula, 2009 234 /id}19135705AustriaNR | Multiplate AnalyzerImpedance aggregometryDynabyte Medical, Munich,Germany | Adenosine diphosphate(ADP), prostaglandin (PGE1) | 1st blood sample: in catheterization laboratory, after PCI and after 250 mg IV aspirin 2nd blood sample: 20‑24 hours after PCI3.8% citrate, 3.2% citrate and recombinant hirudinNRClopidogrel came first0.04 days (1 hour) | Impedence between 16-88 unitsImpedence between <16 units | Based on Normal ranges as reported by manufacturer | Impedence between 16-88 units: 20 (67%)Impedence between <16 units:10 (33%) |
| Ko, 2011{Ko, 2011 26 /id}21315223KoreaNR | Multiple Electrode Platelet AggregometryWhole blood impedence aggregometryMultiplate analyzerDynabyte | ADP | Before PCI; 8 and 24 hrs after PCIlepirudin (25 μg/mL)5 days (clopidogrel came first)0.125 days (Within 3 hrs)  | Multiple electrode aggregometry with ADP was not used to classify clopidogrel response in patients | NR | NR |
| Sibbing, 2010{Sibbing, 2010 88 /id}19943882Sibbing, 2010{Sibbing, 2010 73 /id}20633826GermanyNR | multiple electrode aggregometryMultiplate analyzerDynabyte, Munich, Germany | 6.4 μmol/l ADP | Whole blood; after diagnostic angiography, before PCIlepirudin (25 μg/ml)0.08 days (2 hours)NR | Enhanced Responders (<188 aggregation units\*min)Remaining patients - Not enhanced responders (≥188 aggregation units\*min)From Sibbing 2010 PMID: 20633826Enhanced responder (AUC≤188)Normal responder (AUC189-467)Low responder (AUC≥468)For Stent thrombosis>468 aggregation units\*min≤468 aggregation units\*min | ROC curve of all participants in the study | Enhanced Responders (<188 aggregation units\*min): 975 (38.5%)Remaining patients -  Not enhanced responders (≥188 aggregation units\*min): 1558 (61.5%) From Sibbing 2010 PMID: 20633826Enhanced responder (AUC≤188): 975 (38%)Normal responder (AUC189-467): 1130 (45%)Low responder (AUC≥468): 428 (17%)For Stent thrombosis>468 aggregation units\*min: 428 (17%)≤468 aggregation units\*min: 1180 (83%) |
| Sibbing, 2009{Sibbing, 2009 135 /id} 19264241 Sibbing, 2010{Sibbing, 2010 100 /id}20062919GermanyNR | multiple electrode platelet aggregometrymultiple electrode platelet aggregometryMultiplateDynabyte, Munich, Germany | 6.4 μmol/l ADP | Whole blood; after diagnostic angiography, before PCI, and at least 2 min after administration of intravenous aspirin.lepirudin (25 μg/ml)0.08 days (2 hours)0.02 days (30 mins) | Low Responders (Quintile 5: >416 aggregation units\*min)Normal Responders (Quintile 1-4 ≤416 aggregation units\*min)By other quintilesHigh Responders (Quintile 1 ≤124 AU\*min)Normal Responders (Quintile 2 >124-≤192 AU\*min)Normal Responders (Quintile 3 >192-≤261 AU\*min)Normal Responders (Quintile 4 >261-≤416 AU\*min)Low Responders (Quintile 5: >416 AU\*min) | Based on literature | Low Responders (Quintile 5: >416 aggregation units\*min): 323 (20.1%)Normal Responders (Quintile 1-4 ≤416 aggregation units\*min): 1285 (79.9%)By other quintilesHigh Responders (Quintile 1 ≤124 AU\*min): 318 (19.8%)Normal Responders (Quintile 2 >124-≤192 AU\*min): 322 (20%)Normal Responders (Quintile 3 >192-≤261 AU\*min): 322 (20%)Normal Responders (Quintile 4 >261-≤416 AU\*min): 323 (20.1%)Low Responders (Quintile 5: >416 AU\*min): 323 (20.1%) |
| Schulz, 2010{Schulz, 2010 67 /id}20691843GermanyNR | multiple electrode platelet aggregometrymultiple electrode platelet aggregometryMultiplateDynabyte, Munich, Germany | ADP | After diagnostic angiographylepirudinNRNR | Low response (Upper quintile of MEA measurements [>416 AU\*min])Normal response (Lower 4 quintiles of MEA measurements [≤416 AU\*min]) | Based on literature – a previous study | Low response (Upper quintile of MEA measurements [>416 AU\*min]): 323 (20%)Normal response (Lower 4 quintiles of MEA measurements [≤416 AU\*min]): 1285 (80%) |
| Freynhofer, 2011{Freynhofer, 2011 1 /id}21614416AustriaNR | MEA/Impedence aggregometryMultiple Platelet Function AnalyzerDynabyte Medical, Munich, Germany | ADP 6.5 umol | Samples were incubated and stirred at 37°C for 3 min in the test cuvettes. Agonists were added and the increase in electrical impedance was recorded for 6 minLithium-heparin + 0.9% sodium chloride6-24 h (morning) after PCIWithin 30 min to 3 hr after blood collection | MEA result <47 U (high on-treatment platelet reactivity, poor response)MEA result >47 U (low reactivity, good response) | previous published literature | MEA result <47 U (high on-treatment platelet reactivity, poor response); 57/196 (29%)MEA result >47 U (low reactivity, good response); 139/196 (71%) |
| Siller-Matula, 2010{Siller-Matula, 2010 89 /id}19943879AustriaNR | Multiple electrode aggregometryMultiplate analyzerDynabyte Medical, Munich, Germany | ADP (6.4 uM) + PGE1 (9.4 nM) | Samples taken directly after PCI and at least 5 min after IV aspirin dose (250 mg).Hirudin and 0.9% NaClDose first (clopidogrel loading dose given at least 2 hr before PCI).NR | MEA (n=402; 14 pts not tested because of glycoprotein IIb/IIIa):No platelet hyperreactivity (<54U)Platelet hyperreactivity (≥54U) | ROC curve analysis | MEA (n=402; 14 pts not tested because of glycoprotein IIb/IIIa):346 (86%)No platelet hyperreactivity (<54U)Platelet hyperreactivity (≥54U)56 (14%) |
| Eshtehardi, 2010{Eshtehardi, 2010 78 /id}20435201SwitzerlandNR | whole blood impedance platelet aggregometrythe multiple electrode aggregometry Multiplate analyzerDynabyte, Munich, Germany | ADP 6.4 umol/L | peripheral venous blood samples were drawn from an antecubital vein using a 21-gauge needle and collected in a polyethylene tube containing a stabilized direct thrombin inhibitor (melagatran 15 μg/mL). Sample was diluted with NaCl 0.9% in a 1:1 ratioMelagatran12 to 18 hr after PCIwithin 30 to 60 minutes after the blood sampling | Low response to clopidogrel only= results of ADP test AUC within the upper quartile and results of aspirin test AUC below the upper quartile.Low response to ASA and clopidogrel (dual low response) =results of aspirin test AUC and ADP test AUC within the upper quartile.Controls (dual normal response)= results of aspiring test AUC and ADP test AUC below the upper quartile.[Also low response to asprin; this group ignored re data extraction since not relevant] | AUC plots in present study (see Fig. 4 and previous publications and findings [refs 7,14,16,17,27-30] | Low response to clopidogrel only= results of ADP test AUC within the upper quartile and results of aspirin test AUC below the upper quartile.: 33 (15%)Low response to ASA and clopidogrel (dual low response) =results of aspirin test AUC and ADP test AUC within the upper quartile: 19 (9%)Controls (dual normal response)= results of aspiring test AUC and ADP test AUC below the upper quartile: 133 (60%)[Also low response to asprin; this group ignored re data extraction since not relevant]: 34 (16%) |
| Ivandic, 2009{Ivandic, 2009 125 /id}19359538GermanyNR | whole-blood impedance aggregometryCA560 lumi-aggregometerChronoLog | 6.4 μmol/l ADP | NRNRNRthe day after clopidogrel loadingNR | Nonresponse, defined as impedance exceeded 5 ohms after 6 min of aggregation, to clopidogrelFull response (to aspirin and clopidogrel)Dual nonresponse (to aspirin and clopidogrel)Nonresponse to clopidogrel but full response to aspirin | Not explicitly reported | Nonresponse, defined as impedance exceeded 5 ohms after 6 min of aggregation, to clopidogrel: 34 (18.7%)Full response (to aspirin and clopidogrel):163 (73.6%)Dual nonresponse (to aspirin and clopidogrel): 19 (10.4%)Nonresponse to clopidogrel but full response to aspirin: 15 (8%) |
| Siller-matula, 2012{Siller-Matula, 2012 1 /id}22260716PEGASUS-PCI | multiple electrode aggregometry (MEA)impedanceaggregometer Multiplate Analyzer; Verum DiagnosticaGmbH, Munich, Germany | 6.4 uM ADP | Blood samples from patientswere obtained from the arterial sheath (6F) in the catheterizationlaboratory directly post-PCI and at least 5 min afterintravenous infusion of aspirin.3.8% sodium citrate NRperformed up to 24 h after blood sampling | Clopidogrelnon-responderaccording to MEA (≥ 48 U)Clopidogrel responderaccording to MEA(< 48 U)n = 321 (80%) | ref 16, 28 | non-respondern = 81 (20%)respondern = 321 (80%) |
| Codner, 2012{Codner, 2012 18241 /id}22534051IsraelNR | multiple electrode aggregometry (MEA)impedanceaggregometer Multiplate Analyzer; Verum DiagnosticaGmbH, Munich, Germany | 6.4 uM ADP | NR3.2% citrateNR1 hr | HTPR MEA (≥ 47 AU)Clopidogrel responder (< 47 U)  | Based on literature | HTPR : 13Clopidogrel responder: 44 |
| Gerotziafas, 2012{Gerotziafas, 2012 18243 /id}22311629FranceNR | multiple electrode aggregometry (MEA)impedanceaggregometer Multiplate Analyzer; Verum DiagnosticaGmbH, Munich, Germany | 6.4 uM ADP | NRr-hirudin 25μg/mLNR2 hrs | HTPR MEA (≥ 50 AU)Clopidogrel responder (< 50 U) | Based on ROC curve | HTPR MEA (≥ 50 AU): 3Clopidogrel responder (< 50 U): 103 |
| Johnston, 2012{Johnston, 2012 18242 /id} 22465351New ZealandNR | multiple electrode aggregometry (MEA)impedanceaggregometer Multiplate Analyzer; Verum DiagnosticaGmbH, Munich, Germany | 6.4 uM ADP | 2 hrs after loading doser-hirudin 2 hrs30-60 minutes | HTPR MEA (≥ 468 AU\*min)Clopidogrel responder (< 468 AU\*min) | Based on literature | HTPR MEA (≥ 468 AU\*min): 95Clopidogrel responder (< 468 AU\*min): 155 |
| Sibbing, 2012{Sibbing, 2012 18239 /id}22682553GermanyISAR-REACT 4 | multiple electrode aggregometry (MEA)impedanceaggregometer Multiplate Analyzer; Verum DiagnosticaGmbH, Munich, Germany | 6.4 uM ADP | Before PCI r-hirudin 25μg/mLNRNR | HTPR MEA (≥ 468 AU\*min)Clopidogrel responder (< 468 AU\*min) | Based on literature | Pts on Abciximab Plus UFH:HTPR MEA (≥ 468 AU\*min): 96Clopidogrel responder (< 468 AU\*min): 178Pts on Bivaluridin:HTPR MEA (≥ 468 AU\*min): 109Clopidogrel responder (< 468 AU\*min): 181 |
| Siller-Matula, 2012{Siller-Matula, 2012 18323 /id}22305813AustriaNR | multiple electrode aggregometry (MEA)impedanceaggregometer Multiplate Analyzer; Verum DiagnosticaGmbH, Munich, Germany | ADP: 6.4 μM or AA: 0.5 mM | Before PCI r-hirudin 25μg/mLNRImmediately after sampling | With only ADP high platelet reactivity (HPR) to ADP(ADP≥48U)No HPR to ADP(ADP<48U)With ADP & AAHPR to AA and ADP (ADP≥48U; AA≥14U)HPR to ADP(ADP≥48U;)HPR to AA (AA≥14U)No HPR (ADP<48U; AA<14U) | Based on ROC curve | high platelet reactivity (HPR) to ADP(ADP≥48U): 75 (19%)No HPR to ADP(ADP<47U): 328 (81%)With ADP & AAHPR to AA and ADP: 32(8%)HPR to ADP: 44 (11%)HPR to AA: 77 (19%)No HPR: 250 (62%) |

ADP= adenosine 5'-diphosphate; Ag= aggregation; PGE1=prostaglandin; ROC=receiver operating characteristic; AUC=area under the curve; IPA= inhibition of platelet aggregation; LTA= light transmission aggregometry; MEA= multiple electrode platelet aggregometry; PFA= platelet function analysis; TEG=thromboelastography; sTEG=short thromboelastography; VASP = vasodilator-stimulated phosphoprotein; VASP-FCT=vasodilator-stimulated phosphoprotein flow cytometry; CEPI=collagen-epinephrine ; CADP=collagen-ADP; CT=closure times; HCPR=high on-clopidogrel platelet reactivity; PCI = percutaneous coronary intervention; RPA= residual platelet aggregation; GP= glycoprotein; HRP=high platelet reactivity; NPR=normal on-treatment platelet reactivity; HPPR= high post-treatment platelet reactivity; MPA= maximum platelet aggregation; RPR= residual platelet reactivity; OTPR=on-treatment platelet reactivity; DPAI= degree of platelet aggregation inhibition; PRU=P2Y12 reaction units; CRP=C-reaction protein; PRI=platelet reactivity index; LR=low responder; IQR=interquartile range; AA= arachidonic acid; LD=loading dose; MD=maintain dose; SD=standard deviation; NR=not reported;