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}  19135705  Austria  NR | Multiplate Analyzer  Impedance aggregometry  Dynabyte 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 PCI  3.8% citrate, 3.2% citrate and recombinant hirudin  NR  Clopidogrel came first  0.04 days (1 hour) | Impedence between 16-88 units  Impedence 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}  21315223  Korea  NR | Multiple Electrode Platelet Aggregometry  Whole blood impedence aggregometry  Multiplate analyzer  Dynabyte | ADP | Before PCI; 8 and 24 hrs after PCI  lepirudin (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}  19943882  Sibbing, 2010{Sibbing, 2010 73 /id}  20633826  Germany  NR | multiple electrode aggregometry  Multiplate analyzer  Dynabyte, Munich, Germany | 6.4 μmol/l ADP | Whole blood; after diagnostic angiography, before PCI  lepirudin (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: 20633826  Enhanced 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: 20633826  Enhanced 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}  20062919  Germany  NR | multiple electrode platelet aggregometry  multiple electrode platelet aggregometry  Multiplate  Dynabyte, 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 quintiles  High 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 quintiles  High 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}  20691843  Germany  NR | multiple electrode platelet aggregometry  multiple electrode platelet aggregometry  Multiplate  Dynabyte, Munich, Germany | ADP | After diagnostic angiography  lepirudin  NR  NR | 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}  21614416  Austria  NR | MEA/Impedence aggregometry  Multiple Platelet Function Analyzer  Dynabyte 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 min  Lithium-heparin + 0.9% sodium chloride  6-24 h (morning) after PCI  Within 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}  19943879  Austria  NR | Multiple electrode aggregometry  Multiplate analyzer  Dynabyte 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% NaCl  Dose 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}  20435201  Switzerland  NR | whole blood impedance platelet aggregometry  the multiple electrode aggregometry Multiplate analyzer  Dynabyte, 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 ratio  Melagatran  12 to 18 hr after PCI  within 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}  19359538  Germany  NR | whole-blood impedance aggregometry  CA560 lumi-aggregometer  ChronoLog | 6.4 μmol/l ADP | NR  NR  NR  the day after clopidogrel loading  NR | Nonresponse, defined as impedance exceeded 5 ohms after 6 min of aggregation, to clopidogrel  Full 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}22260716  PEGASUS-PCI | multiple electrode aggregometry (MEA)  impedance  aggregometer  Multiplate Analyzer; Verum Diagnostica  GmbH, Munich, Germany | 6.4 uM ADP | Blood samples from patients  were obtained from the arterial sheath (6F) in the catheterization  laboratory directly post-PCI and at least 5 min after  intravenous infusion of aspirin.  3.8% sodium citrate  NR  performed up to 24 h after blood sampling | Clopidogrel  non-responder  according to MEA (≥ 48 U)  Clopidogrel responder  according to MEA  (< 48 U)  n = 321 (80%) | ref 16, 28 | non-responder  n = 81 (20%)  responder  n = 321 (80%) |
| Codner, 2012{Codner, 2012 18241 /id}  22534051  Israel  NR | multiple electrode aggregometry (MEA)  impedance  aggregometer  Multiplate Analyzer; Verum Diagnostica  GmbH, Munich, Germany | 6.4 uM ADP | NR  3.2% citrate  NR  1 hr | HTPR MEA (≥ 47 AU)  Clopidogrel responder  (< 47 U) | Based on literature | HTPR : 13  Clopidogrel responder: 44 |
| Gerotziafas, 2012{Gerotziafas, 2012 18243 /id}  22311629  France  NR | multiple electrode aggregometry (MEA)  impedance  aggregometer  Multiplate Analyzer; Verum Diagnostica  GmbH, Munich, Germany | 6.4 uM ADP | NR  r-hirudin 25μg/mL  NR  2 hrs | HTPR MEA (≥ 50 AU)  Clopidogrel responder  (< 50 U) | Based on ROC curve | HTPR MEA (≥ 50 AU): 3  Clopidogrel responder  (< 50 U): 103 |
| Johnston, 2012{Johnston, 2012 18242 /id}  22465351  New Zealand  NR | multiple electrode aggregometry (MEA)  impedance  aggregometer  Multiplate Analyzer; Verum Diagnostica  GmbH, Munich, Germany | 6.4 uM ADP | 2 hrs after loading dose  r-hirudin  2 hrs  30-60 minutes | HTPR MEA (≥ 468 AU\*min)  Clopidogrel responder  (< 468 AU\*min) | Based on literature | HTPR MEA (≥ 468 AU\*min): 95  Clopidogrel responder  (< 468 AU\*min): 155 |
| Sibbing, 2012{Sibbing, 2012 18239 /id}  22682553  Germany  ISAR-REACT 4 | multiple electrode aggregometry (MEA)  impedance  aggregometer  Multiplate Analyzer; Verum Diagnostica  GmbH, Munich, Germany | 6.4 uM ADP | Before PCI  r-hirudin 25μg/mL  NR  NR | HTPR MEA (≥ 468 AU\*min)  Clopidogrel responder  (< 468 AU\*min) | Based on literature | Pts on Abciximab Plus UFH:  HTPR MEA (≥ 468 AU\*min): 96  Clopidogrel responder  (< 468 AU\*min): 178  Pts on Bivaluridin:  HTPR MEA (≥ 468 AU\*min): 109  Clopidogrel responder  (< 468 AU\*min): 181 |
| Siller-Matula, 2012{Siller-Matula, 2012 18323 /id}  22305813  Austria  NR | multiple electrode aggregometry (MEA)  impedance  aggregometer  Multiplate Analyzer; Verum Diagnostica  GmbH, Munich, Germany | ADP: 6.4 μM or AA: 0.5 mM | Before PCI  r-hirudin 25μg/mL  NR  Immediately after sampling | With only ADP  high platelet reactivity (HPR) to ADP  (ADP≥48U)  No HPR to ADP  (ADP<48U)  With ADP & AA  HPR 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 & AA  HPR 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;