**Appendix Table E71. Results from the studies assessing the ability of Multiplate Analyzer to predict major adverse cardiovascular events in patients with ischemic heart disease**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author,year**  **UID**  **Country**  **Study name** | **Treatment** | **Phenotypic Test Used [index test]** | **Clinical Outcome** | **Outcome Definition** | **Timing of measurement** | **Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP** | **Outcome status (e.g., bleeding or no bleeding)** | **No. with outcome status within phenotype group** | **Comparative metric (OR, RR, HR)** | **95% CI** | **P (between which groups?)**  **[statistical test]** | **Adjusted?**  **[YES/NO/NR]**  **If YES, for what factors?** | **Procedures for multiple comparisons [YES, NO, NR]** | **Comments (e.g., additional data in figures)** |
| Ko, 2011{Ko, 2011 26 /id}  21315223  Korea  NR | 75 mg/d clopidogrel & 100 mg/d aspirin | Multiple Electrode Platelet Aggregometry (MEA-ADP) | Major adverse cardiovascular events (MACE) | Death, MI, stroke, and  target vessel revascularization | From PCI to 30 days | NR | MACE + | NR | NR | NR | NR | NR | NR | AUC=0.443; P=0.415  (Fig2b) |
| Sibbing 2010{Sibbing, 2010 88 /id}  19943882  Sibbing 2010{Sibbing, 2010 73 /id}  20633826  Germany  NR | Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD | Mutliplate analyzer | adverse event | Definite or probable stent thrombosis or in-hospital TIMI major bleeding | 30 days | AUC≤ 188  Enhanced responder (N=975) | adverse event | NR | incidence of adverse events | NR | 0.008 across all 3 groups  chi square test | NR | NR | Fig 1 |
|  |  |  |  |  |  | AUC 189-467 normal responders  n=1130 |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  | AUC ≥468  low responders  n=428 |  |  |  |  |  |  |  |  |
| Sibbing 2010{Sibbing, 2010 73 /id}  20633826  Germany  NR | Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD | Mutliplate analyzer | adverse event | Definite or probable stent thrombosis or in-hospital TIMI major bleeding | 30 days | Normal responder (N=1130) | adverse event | NR | OR=0.40 | 0.22-0.75 | 0.003 between normal responder and remaining patients  NR | NR | NR |  |
|  |  |  |  |  |  | Enhanced or low responder (N=1403) |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Sibbing 2009{Sibbing, 2009 135 /id}  19264241  Sibbing 2010{Sibbing, 2010 100 /id}  20062919  Germany  NR | Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD | MEA | MACE | Death or Stent thrombosis | 30 days | Low Responders (>416 aggregation units\*min) | MACE | 10 (3.1%) | OR=5.1 | 2.2- 11.6 | P<0.001  (low vs normal responder)  [log rank] | NO | NR | Secondary |
|  |  |  |  |  |  | Normal Responders (≤416 aggregation units\*min) |  | 8 (0.6%) |  |  |  |  |  |  |
| Sibbing 2010{Sibbing, 2010 100 /id}  20062919  Germany  NR |  | MEA | MACE | Death or Stent thrombosis | 6 months | Low Responders (>416 aggregation units\*min) | MACE | 16 (5%) | OR=5.1 | 2.2- 11.6 | P<0.001  (low vs normal responder)  [log rank] | NO | NR | Secondary |
|  |  |  |  |  |  | Normal Responders (≤416 aggregation units\*min) |  | 30 (2.3%) |  |  |  |  |  |  |
|  |  |  | MACE | Cardiac Death + Definite ST | 6 months | Low Responders (>416 aggregation units\*min) | MACE | 14 (4.4%) | OR=3.3 | 1.7- 6.5 | P<0.001  (low vs normal responder)  [log rank] | NO | NR | Secondary |
|  |  |  |  |  |  | Normal Responders (≤416 aggregation units\*min) |  | 17 (1.3%) |  |  |  |  |  |  |
|  |  |  | MACE | Death + ST As per Academic Research  Consortium criteria | 30 days | Low Responders (>416 aggregation units\*min) | Combined death/definite ST | 10 (3.1%) | OR=5.05 | 2.19- 11.64 | P<0.001  (low vs normal responder)  [log rank] | NO | NR | Secondary |
|  |  |  |  |  |  | Normal Responders (≤416 aggregation units\*min) |  | 8 (0.6%) |  |  |  |  |  |  |
|  |  |  | MACE | Death or definite Stent thrombosis | 6 months | Low Responders (>416 aggregation units\*min) | MACE | 16 (5%) | OR=2.2 | 1.2- 4.1 | P=0.008  (low vs normal responder)  [log rank] | NO | NR | Secondary |
|  |  |  |  |  |  | Normal Responders (≤416 aggregation units\*min) |  | 29 (2.3%) |  |  |  |  |  |  |
| Schulz 2010{Schulz, 2010 67 /id}  20691843  Germany  NR | Clopidogrel 75 mg/d + Aspirin 100 mg/d | MEA by Multiplate analyzer | MACE | Death or MI | 1 year | Low responder | MACE | 27 (8.4%) | HR=1.3 | 0.8-1.9 | 0. 298  (low vs normal)  cox proportional harzard model | NO | NR | Secondary outcome |
|  |  |  |  |  |  | Normal responder |  | 86 (6.7%) |  |  |  |  |  |  |
| Freynhofer 2011{Freynhofer, 2011 1 /id}  21614416  Austria  NR | 300 or 600mg LDClopidogrel and maintain dose 75 mg+aspirin 100mg | MEA | MACE | MACE included: 1) definite and probable ST according to the ARC-definition; 2) cardiovascular death, defined as death associated with ACS, significant arrhythmia, or congestive heart failure; and 3) non-fatal STEMI (STEMI: acute onset of prolonged typical ischaemic chest pains, ST-segment elevation of at least 1 mm in 2 or more contiguous electrocardiogram leads and increased biomarkers of myocardial necrosis) | 6 months | High reactivity/poor response  n=59 | MACE | 3 (5.4%) | OR=23.5 (calculate) | NR | 0.670 high vs. low reactivity  chi square | NR | NR | Fig 1 |
|  |  |  |  |  |  | Low reactivity/good response  n=137 |  | 4 (2.9%) |  |  |  |  |  | Get n’s from Fig 1 (pasted in on last page of this form) |
| Eshtehardi 2010{Eshtehardi, 2010 78 /id}  20435201  Switzerland  NR | 600 mg LD Clopidogrel+500 mg aspirin | Aggregometry | MACE | Composite of PCI-related MI, stent thrombosis, death, or MI | 30 days | Clopidogrel low response n=33 | MACE | 2 (6.1%) | OR=8.0 dual vs normal (calculate)  OR= 9.0  dual vs clopidogrel low response  (calculated) | 2.5-25.4  1.6-49.8 | <0.001 across this and next three rows; <0.001 for dual vs normal; 0.005 for dual vs clopidogrel (Fisher’s exact or chi-square) | NR | NR | none |
|  |  |  |  |  |  | Aspirin low response n=34 |  | 3 (8.8%) |  |  |  |  |  |  |
|  |  |  |  |  |  | Dual low response  n=19 |  | 7 (36.8%) | odds 7.35 | 2.21-24.42 | <0.001(Multivariable logistic regression analysis) |  |  |  |
|  |  |  |  |  |  | Normal response  n=133 |  | 9 (6.8%) |  |  |  |  |  |  |
| Ivandic 2009{Ivandic, 2009 125 /id}  19359538  Germany  NR | Clopidogrel600mg LD+aspires 0.5g | Aggregometry | Combined end point: | Combined end point: first occurrence of any of the following cardiovascular events: cardiovascular death, myocardial infarction, target vessel revascularization, or stent thrombosis occurring 30 days or later after PCI. | >/= 30 days after PCI | Clopidogrel nonresponder (n=34) | Combined end point | 8 (23.5%) | HR= 1.04 | 0.24-4.44 | NS non-responder vs. full (cox proportional hazard model)  Also NS vs full responders below | NR | NR | NONE |
|  |  |  |  |  |  | Nonresponse to clopidogrel but response to aspirin (n=15) |  | 2 (13.3%) |  |  |  |  |  |  |
|  |  |  |  |  |  | Full responders (n=134) |  | 18 (13.4%) |  |  |  |  |  |  |
|  |  |  |  |  |  | Dual nonresponder (n=19) |  | 6 (31.6%) | HR 2.57  HR in multivariate analysis, 2.9 | 1.18-5.61  In multivariate, 1.17-7.2 | 0.03 dual non-responder vs. any responders,  In multivariate, 0.02  (Cox regression) |  |  |  |
|  | Clopidogrel600mg LD+aspires 0.5g | Aggregometry | cardiovascular events | Freedom from combined end point myocardial infarction, target vessel revascularization, late stent thrombosis, or cardiac death in KM curve | >/= 30 days after PCI | Responders (n=163) | cardiovascular events | 40/163 | OR=5.3  (calculated) | 1.9-14.3 | 0.03 dual nonresponder vs. responder (log rank) | NR | NR | K-M curves are in Fig. 1 |
|  |  |  |  |  |  | Dual nonresponders (n=19) |  | 12/19 |  |  |  |  |  | K-M curves are in Fig. 1 |
|  | Clopidogrel600mg LD+aspires 0.5g | Aggregometry | Any cardiovascular event | Any cardiovascular event | >/= 30 days after PCI | Responders (n=163) | Any cardiovascular event | 20 (12.2%) | Relative risk 2.57  dual non-responder vs. responder | 1.18-5.61 | NR | NR | NR |  |
|  |  |  |  |  |  | Dual nonresponders (n=19) |  | 6 (31.5%) |  |  |  |  |  |  |
| Siller-matula, 2012{Siller-Matula, 2012 1 /id}22260716  PEGASUS-PCI | clopidogrel LD 600mg, MD 75mg | MEA | MACE | major adverse cardiac events | 12-month | non-responder | MACE | 15/81 (21) | HR=1.67 | 0.86-3.2 | NR | yes,CY  P2C19\*2 carrier status,BMI, CRP levels,DM, age, renal failure(creatine clearance<60mg mL,MI,sex,PPI | NR |  |
|  |  |  |  |  |  | responder |  | 37/321(12) |  |  |  |  |  |  |
|  | clopidogrel LD 600mg, MD 75mg | MEA | MACE | major adverse cardiac events | 12-month | non-responder | MACE | 15/81 (21) | HR=1.67 | 0.86-3.2 | NR | yes,CY  P2C19\*2 carrier status,BMI, CRP levels,DM, age, renal failure(creatine clearance<60mg mL,MI,sex,PPI | NR |  |
|  |  |  |  |  |  | responder |  | 37/321(12) |  |  |  |  |  |  |
|  | clopidogrel LD 600mg, MD 75mg | MEA-ADP-PGE1 | MACE | major adverse cardiac events | 12-month | NR | MACE | NR | sensitivity 0.3  specificity 0.81  AUC 0.63  cut-off 48 | AUC 0.55-0.71 | 0.042 | NR | NR |  |
|  | clopidogrel LD 600mg, MD 75mg | MEA-ADP | MACE | major adverse cardiac events | 12-month | NR | MACE | NR | sensitivity 0.5  specificity 0.64  AUC 0.62  cut-off 46 | AUC 0.54-0.70 | 0.039 | NR | NR |  |
|  | clopidogrel LD 600mg, MD 75mg | VASP (%PRI) | MACE | major adverse cardiac events | 12-month | NR | MACE | NR | sensitivity 0.68  specificity 0.37  AUC 0.54  cut-off 42 | AUC0.45-0.63 | 0.039 | NR | NR |  |
|  | clopidogrel LD 600mg, MD 75mg | PFA100:CADP-CT(s) | MACE | major adverse cardiac events | 12-month | NR | MACE | NR | sensitivity 0.44  specificity 0.62  AUC 0.56  cut-off 105 | AUC0.48-0.64 | 0.062 | NR | NR |  |
|  | clopidogrel LD 600mg, MD 75mg | CPA:ADP (SC%) | MACE | major adverse cardiac events | 12-month | NR | MACE | NR | sensitivity 0.72  specificity 0.36  AUC 0.54  cut-off 4.6 | AUC0.38-0.62 | 0.38 | NR | NR |  |
|  | clopidogrel LD 600mg, MD 75mg | CPA: ADP (ASum2) | MACE | major adverse cardiac events | 12-month | NR | MACE | NR | sensitivity 0.43  specificity 0.60  AUC 0.53  cut-off 43 | AUC  0.45-0.61 | 0.47 | NR | NR |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Gerotziafas, 2012{Gerotziafas, 2012 18243 /id}  22311629  Greece  NR | aspirin  100 mg and clopidogrel 75 mg once daily | MEA | MACE | acute coronary syndrome, ischemic stroke, and death  from cardiovascular cause | 90 days | High platelet reactivity MEA >50U  n=3 | HPR | 0 | OR (calculated)= 29.6 | NR | P=0.1  (HPR vs normal)  [Fisher’s exact] | No | NR |  |
|  |  |  |  |  |  | normal platelet reactivity  n=103 |  | 0 |  |  |  |  |  |  |
| Sibbing, 2012{Sibbing, 2012 18239 /id}  22682553  Germany  ISAR-REACT 4 | LD: 600 mg of clopidogrel and 500 mg aspirin MD: clopidogrel 75 mg x 12 months and aspirin 100 mg twice daily for an indefinite period | MEA | MACE | death, MI, or  urgent TVR at 30 days after PCI | 30 days | high on-treatment platelet reactivity  >468 AU\*min  n=205 | MACE | 33 | OR=3.1 | 1.73-5.5 | P<0.0001  (HTPR vs normal)  [Cox regression] | No | NR |  |
|  |  |  |  |  |  | normal platelet reactivity  ≤468 AU\*min  n=359 |  | 31 |  |  |  |  |  |  |
|  |  |  | MACE in pts on Abciximab Plus UFH | death, MI, or  urgent TVR at 30 days after PCI | 30 days | high on-treatment platelet reactivity  >468 AU\*min  n=96 | MACE | 9 | OR=1.43 | 0.6-3.5 | P=0.43  (HTPR vs normal)  [Cox regression] | No | NR |  |
|  |  |  |  |  |  | normal platelet reactivity  ≤468 AU\*min  n=178 |  | 12 |  |  |  |  |  |  |
|  |  |  | MACE in pts on Bivalirudin | death, MI, or  urgent TVR at 30 days after PCI | 30 days | high on-treatment platelet reactivity  >468 AU\*min  n=109 | MACE | 24 | OR=1.4 | 0.4-2.3 | P<0.001  (HTPR vs normal)  [Cox regression] | No | NR |  |
|  |  |  |  |  |  | normal platelet reactivity  ≤468 AU\*min  n=181 |  | 9 |  |  |  |  |  |  |
|  |  |  | MACE in pts on Abciximab Plus UFH | death or any recurrent MI | 30 days | high on-treatment platelet reactivity  >468 AU\*min  n=96 | MACE | 9 | OR=1.43 | 0.6-3.5 | P=0.43  (HTPR vs normal)  [Cox regression] | No | NR |  |
|  |  |  |  |  |  | normal platelet reactivity  ≤468 AU\*min  n=178 |  | 12 |  |  |  |  |  |  |
|  |  |  | MACE in pts on Bivalirudin | death or any recurrent MI | 30 days | high on-treatment platelet reactivity  >468 AU\*min  n=109 | MACE | 23 | OR=5.5 | 2.3-12.8 | P<0.001  (HTPR vs normal)  [Cox regression] | No | NR |  |
|  |  |  |  |  |  | normal platelet reactivity  ≤468 AU\*min  n=181 |  | 9 |  |  |  |  |  |  |
| Siller-Matula, 2012{Siller-Matula, 2012 18323 /id}  22305813  Austria  NR | LD clopidogrel 600 mg 2 h pre PCI, 100 mg aspirin intake ; Additionally 250 mg acetylsalicylic acid i.v. directly before stent placement  MD: 75 mg clopidogrel; 100 mg aspirin for 12 months | MEA | MACE | stent thrombosis, acute coronary syndrome,  death, stroke, repeated revascularization: percutaneous coronary intervention or coronary  artery bypass surgery | 12 monhts | high platelet reactivity (HPR) to ADP  (ADP≥48U): 75 (19%) | MACE | NR | AUC=0.6 | 0.53-0.66 | P=0.033 | No | NR |  |
|  |  |  |  |  |  | No HPR to ADP  (ADP<47U): 328 (81%) |  | NR |  |  |  |  |  |  |
|  |  |  | MACE | stent thrombosis, acute coronary syndrome,  death, stroke, repeated revascularization: percutaneous coronary intervention or coronary  artery bypass surgery | 12 monhts | HPR to AA and ADP: 32(8%) | MACE | K-M estimates: 12 (37.5%) | NR | NR | P=0.003  (dual nonresponders vs any or both responders)  [log rank test] | yes | Bonferroni correction |  |
|  |  |  |  |  |  | HPR to ADP: 44 (11%) |  | K-M estimates: 15 (33.3%) |  |  |  |  |  |  |
|  |  |  |  |  |  | HPR to AA: 77 (19%) |  | K-M estimates: 20 (25.6%) |  |  |  |  |  |  |
|  |  |  |  |  |  | No HPR: 250 (62%) |  | K-M estimates: 47 (18.6%) |  |  |  |  |  |  |
|  |  |  | MACE | stent thrombosis, acute coronary syndrome,  death, stroke, repeated revascularization: percutaneous coronary intervention or coronary  artery bypass surgery | 12 monhts | Any HPR  (ADP≥48U and/or AA>14U): n=153 | MACE | 48 | OR=1.75 | 1.1-2.9 | P=0.029  (Any HPR vs no HPR)  [Chi-squared Automatic Interaction Detection (CHAID) analysis] | No | NR |  |
|  |  |  |  |  |  | No HPR to ADP or AA  (ADP<48U, AA<14U): 250 |  | 47 |  |  |  |  |  |  |
|  |  |  | MACE in diabetic patients | stent thrombosis, acute coronary syndrome,  death, stroke, repeated revascularization: percutaneous coronary intervention or coronary  artery bypass surgery | 12 monhts | Any HPR  (ADP≥48U and/or AA>14U): | MACE | 37% | OR=2.18 | 1.2-3.95 | P=0.04  (Any HPR vs no HPR)  [Chi-squared Automatic Interaction Detection (CHAID) analysis] | No | NR |  |
|  |  |  |  |  |  | No HPR to ADP or AA  (ADP<48U, AA<14U): |  | 21% |  |  |  |  |  |  |
|  |  |  | MACE in non-diabetic patients | stent thrombosis, acute coronary syndrome,  death, stroke, repeated revascularization: percutaneous coronary intervention or coronary  artery bypass surgery | 12 monhts | Any HPR  (ADP≥48U and/or AA>14U): | MACE | 29% | OR=1.86 | 1.03-3.37 | P=0.048  (Any HPR vs no HPR)  [Chi-squared Automatic Interaction Detection (CHAID) analysis] | No | NR |  |
|  |  |  |  |  |  | No HPR to ADP or AA  (ADP<48U, AA<14U): |  | 18% |  |  |  |  |  |  |