**Appendix Table E70. Results from studies assessing the ability of Multiplate Analyzer to predict stent thrombosis 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)** |
| 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 | MEA | definite ST | Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis. | 30 days | >468 aggregation units\*min | definite ST | 9/428 (2.1%) | OR=3.6  (calculated) | 1.3-9.7 | P<0.001  (>468 AU\*min vs ≤ 468 AU\*min)  [chi square] | NO | NR | Secondary |
|  |  |  |  |  |  | ≤468 aggregation units\*min |  | 7/1180 (0.3) |  |  |  |  |  |  |
|  | 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 | Definite or probable stent thrombosis | Definite or probable stent thrombosis | 30 days (all outcomes) | Enhanced responder (AUC≤188) (N=975) | Yes thrombosis | NR | NR | NR | 0.38 enhanced responder vs. the remaining |  |  | Fig. 2 |
|  |  |  |  |  |  | Normal responder (AUC189-467) (N=1130) | Yes thrombosis | NR |  |  |  |  |  |  |
|  |  |  |  |  |  | Low responder (AUC≥468) (N=428) | Yes thrombosis | NR (2.8%) |  |  | <0.001 low responder vs the remaining two rows |  |  |  |
| 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 | definite ST | Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis. | 30 days | Low Responders (>416 aggregation units\*min) n=323 | definite ST | 7 (2.2%) | OR=9.4 | 3.1- 28.4 | P<0.0001  (low vs normal responder)  [log rank] | NO | NR | Primary |
|  |  |  |  |  |  | Normal Responders (≤416 aggregation units\*min) n=1285 |  | 3 (0.2%) |  |  |  |  |  |  |
| 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 | definite ST | Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis. | 6 months | Low Responders (>416 aggregation units\*min) n=323 | definite ST | 8 (2.5%) | OR=6.5 | 2.4- 17 | P<0.0001  (low vs normal responder)  [log rank] | NO | NR | Primary |
|  |  |  |  |  |  | Normal Responders (≤416 aggregation units\*min) n=1285 |  | 6 (0.4%) |  |  |  |  |  |  |
| Sibbing, 2009{Sibbing, 2009 135 /id}  19264241 | 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 | definite ST | Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis. | 30 days | Low Responders (>416 aggregation units\*min)  n=323 | definite ST | 7 (2.2%) | HR=10.95 | 2.31- 51.99 | P=0.003  (low vs normal responder)  [cox proportional hazards regression] | YES;  Diabetes mellitus, active smoking, body mass index, ejection fraction, platelet count, time from clopidogrel loading to blood sampling, and CAD presentation (including STEMI, NSTEMI, stable angina, and unstable angina) | NR | Primary |
|  |  |  |  |  |  | Normal Responders (≤416 aggregation units\*min) n=1285 |  | 3 (0.2%) |  |  |  |  |  |  |
|  | 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 | definite ST | Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis. | 6 months | Low Responders (>416 aggregation units\*min) | **definite ST** | **8 (2.5%)** | HR=5.3 | 2.3- 13.7 | P=0.0006  (low vs normal responder)  [cox proportional hazards regression] | YES;  Diabetes mellitus, active smoking, body mass index, ejection fraction, platelet count, time from clopidogrel loading to blood sampling, and CAD presentation (including STEMI, NSTEMI, stable angina, and unstable angina) | NR | Primary |
|  |  |  |  |  |  | Normal Responders (≤416 aggregation units\*min) |  | 6 (0.4%) |  |  |  |  |  |  |
|  | 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 | Probable Stent thrombosis | As per Academic Research  Consortium criteria | 30 days | Low Responders (>416 aggregation units\*min) | Probable Stent thrombosis | 2 (0.6%) | OR=4 | 0.65- 24.47 | P=0.13  (low vs normal responder)  [log rank] | NO | NR | Primary |
|  |  |  |  |  |  | Normal Responders (≤416 aggregation units\*min) |  | 2 (0.2%) |  |  |  |  |  |  |
|  | 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 | Probable Stent thrombosis | As per Academic Research  Consortium criteria | 6 months | Low Responders (>416 aggregation units\*min) | Probable Stent thrombosis | 5 (1.6%) | OR=5 | 1.5- 16.3 | P=0.008  (low vs normal responder)  [log rank] | NO | NR | Primary |
|  |  |  |  |  |  | Normal Responders (≤416 aggregation units\*min) |  | 4 (0.3%) |  |  |  |  |  |  |
|  | 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 | Possible stent thrombosis | As per Academic Research  Consortium criteria | 6 months | Low Responders (>416 aggregation units\*min) | Possible stent thrombosis | 0/323 | OR=0.4  (calculated) | 0-6.5 | P=0.26  (low vs normal responder)  [log rank] | NO | NR | Primary |
|  |  |  |  |  |  | Normal Responders (≤416 aggregation units\*min) |  | 5/1285 (0.4%) |  |  |  |  |  |  |
|  | 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 | Stent thrombosis | Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis. | 30 days | Low Responders (>416 aggregation units\*min) | Stent thrombosis | 9 (2.8%) | Sensitivity: 0.7  Specificity: 0.84  AUC=0.78 | 0.60-0.96 | P<0.001 | NR | NR | Primary |
|  |  |  |  |  |  | Normal Responders (≤416 aggregation units\*min) |  | 5 (0.4%) |  |  |  |  |  |  |
|  | 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 | Stent thrombosis | Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis. | 6 months | Low Responders (>425 aggregation units\*min) | Stent thrombosis | 13 (4.1%) | Sensitivity: 0.59  Specificity: 0.81  AUC=0.74 | 0.62-0.86 | P<0.0001 | NR | NR | Primary |
|  |  |  |  |  |  | Normal Responders (≤425 aggregation units\*min) |  | 9 (0.7%) |  |  |  |  |  |  |
|  | 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 | definite ST | Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis. | 30 days | High Responders (Quintile 1 ≤124 AU\*min) | definite ST | 1 (0.3%) | NR | NR | P=0.003  [Chi square] | NO | NR | Primary |
|  |  |  |  |  |  | Normal Responders (Quintile 2 >124-≤192 AU\*min) |  | 0 |  |  |  |  |  |  |
|  |  |  |  |  |  | Normal Responders (Quintile 3 >192-≤261 AU\*min) |  | 1 (0.3%) |  |  |  |  |  |  |
|  |  |  |  |  |  | Normal Responders (Quintile 4 >261-≤416 AU\*min) |  | 1 (0.3%) |  |  |  |  |  |  |
|  |  |  |  |  |  | Low Responders (Quintile 5: >416 AU\*min) |  | 7 (2.2%) |  |  |  |  |  |  |
|  | 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 | Probable/ definite ST | Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis. | 30 days | High Responders (Quintile 1 ≤124 AU\*min) | Probable/ definite ST | 1 (0.3%) | NR | NR | P=0.001  [Chi square] | NO | NR | Primary |
|  |  |  |  |  |  | Normal Responders (Quintile 2 >124-≤192 AU\*min) |  | 0 |  |  |  |  |  |  |
|  |  |  |  |  |  | Normal Responders (Quintile 3 >192-≤261 AU\*min) |  | 2 (0.6%) |  |  |  |  |  |  |
|  |  |  |  |  |  | Normal Responders (Quintile 4 >261-≤416 AU\*min) |  | 2 (0.6%) |  |  |  |  |  |  |
|  |  |  |  |  |  | Low Responders (Quintile 5: >416 AU\*min) |  | 9 (2.8%) |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | 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 | Combined probable/definite stent thrombosis | As per Academic Research  Consortium criteria | 30 days | Low Responders (>416 aggregation units\*min) | Combined probable/definite stent thrombosis | 9 (2.8%) | OR=7.26 | 2.86- 18.46 | P<0.0001  (low vs normal responder)  [log rank] | NO | NR | Landmark |
|  |  |  |  |  |  | Normal Responders (≤416 aggregation units\*min) |  | 5 (0.4%) |  |  |  |  |  |  |
|  | 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 | Combined probable/definite stent thrombosis | As per Academic Research  Consortium criteria | 6 months | Low Responders (>416 aggregation units\*min) | Combined probable/definite stent thrombosis | 13 (4.1%) | OR=5.8 | 2.8- 12.3 | P<0.0001  (low vs normal responder)  [log rank] | NO | NR | Landmark |
|  |  |  |  |  |  | Normal Responders (≤416 aggregation units\*min) |  | 9 (0.7%) |  |  |  |  |  |  |
|  | 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 | Combined probable/definite stent thrombosis | As per Academic Research  Consortium criteria | 30 days to 6 months | Low Responders (>416 aggregation units\*min) | Combined probable/definite stent thrombosis | 4 (1.2%) | OR=4.1 | 1.1- 14.7 | P=0.03  (low vs normal responder)  [log rank] | NO | NR | Landmark |
|  |  |  |  |  |  | Normal Responders (≤416 aggregation units\*min) |  | 4 (0.3%) |  |  |  |  |  |  |
| Schulz, 2010{Schulz, 2010 67 /id}  20691843  Germany  NR | Clopidogrel 75 mg/d + Aspirin 100 mg/d | MEA by Multiplate analyzer | Definite stent thrombosis | Based on definition of the Academic Research  Consortium (ARC) | 1 year | Low responder | Definite stent thrombosis | 8 (2.5%) | HR=5.4 | 1.9-15.6 | 0.02  (low vs normal)  cox proportional hazard model | NO | NR | Secondary outcome |
|  |  |  |  |  |  | Normal responder |  | 6 (0.5%) |  |  |  |  |  |  |
|  | Clopidogrel 75 mg/d + Aspirin 100 mg/d | MEA by Multiplate analyzer | Probable stent thrombosis | Based on definition of the Academic Research  Consortium (ARC) | 1 year | Low responder | Probable stent thrombosis | 5 (1.6%) | HR=3.4 | 1-11 | 0.046  (low vs normal)  cox proportional hazard model | NO | NR | Secondary outcome |
|  |  |  |  |  |  | Normal responder |  | 6 (0.5%) |  |  |  |  |  |  |
| Siller-Matula 2010{Siller-Matula, 2010 89 /id}  19943879  Austria  NR | 600 mg LD Clopidogrel followed by MD 75 mg daily+250 mg LD aspirin followed by 100 mg daily | MEA | Definite stent thrombosis | Defined by ARC as ACS with angiographic or pathologic confirmation of thrombosis | Within 6 mo after stenting | Platelet hyperreactivity vs. no hyperreactivity | Definite stent thrombosis | -- | AUC, 0.92 (SE 0.04)  ROC cutoff, 54U  Sensitivity 100% and specificity 86%; | For AUC, 0.85-0.99 | 0.012 from ROC | NR | NR | NONE |
|  |  |  |  |  |  | No platelet hyperreactivity | Definite stent thrombosis | 0/341 | NR | NR | NR | NR | NR | Data also given for MEA+VASP in Fig 3 |
|  |  |  |  |  |  | Platelet hyperreactivity |  | 3/61 | NR | NR | NR | NR | NR | Data also given for MEA+VASP in Fig 3 |
|  | 600 mg LD Clopidogrel followed by MD 75 mg daily+250 mg LD aspirin followed by 100 mg daily | MEA | Composite of definite or probable stent thrombosis | Probable defined any unexplained death within 30 days or target vessel MI without angiographic conﬁrmation of thrombosis or other identiﬁed culprit lesion |  | Platelet hyperreactivity vs. no hyperreactivity | Composite of definite or probable stent thrombosis | -- | AUC, 0 .81 (SE 0.10)  ROC cutoff, 54U  Sensitivity 86% and specificity 87% | For AUC, 0.61-1.02 | 0.004 from ROC | NR | NR | NONE |
|  |  |  |  |  |  | No platelet hyperreactivity |  | 1/341 | NR | NR | NR | NR | NR | Data also given for MEA+VASP in Fig 3 |
|  |  |  |  |  |  | Platelet hyperreactivity |  | 6/61 | NR | NR | NR | NR | NR | Data also given for MEA+VASP in Fig 3 |
|  | 600 mg LD Clopidogrel followed by MD 75 mg daily+250 mg LD aspirin followed by 100 mg daily | MEA | Probable stent thrombosis | Probable stent thrombosis |  | No platelet hyperreactivity | Probable stent thrombosis | 0/341 | NR | NR | NR | NR | NR | Data also given for MEA+VASP in Fig 3 |
|  |  |  |  |  |  | Platelet hyperreactivity |  | 3/61 | NR | NR | NR | NR | NR | Data also given for MEA+VASP in Fig 3 |
| Eshtehardi, 2010{Eshtehardi, 2010 78 /id}  20435201  Switzerland  NR | 600 mg LD Clopidogrel+500 mg aspirin | Aggregometry | Stent thrombosis (early definite) | Defined according to the Academic Research Consortium  Definitions [ref 26] |  | Clopidogrel low response |  | 0 | OR=6.6 (calculated) | 0.6-74.8 | 0.004 across this and next three rows (Fisher’s exact or chi-square) |  |  |  |
|  |  |  |  |  |  | Aspirin low response |  | 0 |  |  |  |  |  |  |
|  |  |  |  |  |  | Dual low response |  | 2 (10.5%) |  |  |  |  |  |  |
|  |  |  |  |  |  | Normal response |  | 1 (0.8%) |  |  |  |  |  |  |
| Siller-matula, 2012{Siller-Matula, 2012 1 /id}22260716  PEGASUS-PCI | clopidogrel LD 600mg, MD 75mg | MEA | stent thrombosis | stent  thrombosis (definite and probable) | 12-month | non-responder | stent thrombosis | 9/81 (12.5) | HR=36.9 | 4.3-31.9 | <0.001 between non-responder and responder  cox regression | yes,CY  P2C19\*2 carrier status,BMI, CRP levels,DM, age, renal failure(creatine clearance<60mg mL,MI,sex,PPI | NR |  |
|  |  |  |  |  |  | responder |  | 1/321(0.3) |  |  |  |  |  |  |
|  | clopidogrel LD 600mg, MD 75mg | MEA-ADP-PGE1 | stent thrombosis | stent thrombosis | 12-month | NR | stent thrombosis | NR | sensitivity 0.9  specificity 0.83  AUC 0.90  cut-off 48 | AUC 0.86-0.95 | <0.001 | NR | NR |  |
|  | clopidogrel LD 600mg, MD 75mg | MEA-ADP | stent thrombosis | stent thrombosis | 12-month | NR | stent thrombosis | NR | sensitivity 0.7  specificity 0.67  AUC 0.78  cut-off 46 | AUC 0.63-0.94 | 0.002 | NR | NR |  |
|  | clopidogrel LD 600mg, MD 75mg | VASP (%PRI) | stent thrombosis | stent thrombosis | 12-month | NR | stent thrombosis | NR | sensitivity 0.7  specificity 0.38  AUC 0.62  cut-off 42 | AUC  0.46-0.79 | 0.204 | NR | NR |  |
|  | clopidogrel LD 600mg, MD 75mg | PFA100:CADP-CT(s) | stent thrombosis | stent thrombosis | 12-month | NR | stent thrombosis | NR | sensitivity 0.70  specificity 0.61  AUC 0.66  cut-off 105 | AUC  0.48-0.84 | 0.084 | NR | NR |  |
|  | clopidogrel LD 600mg, MD 75mg | CPA:ADP (SC%) | stent thrombosis | stent thrombosis | 12-month | NR | stent thrombosis | NR | sensitivity 0.90  specificity 0.36  AUC 0.62  cut-off 4.6 | AUC  0.47-76 | 0.205 | NR | NR |  |
|  | clopidogrel LD 600mg, MD 75mg | CPA: ADP (ASum2) | stent thrombosis | stent thrombosis | 12-month | NR | stent thrombosis | NR | sensitivity 0.6  specificity 0.42  AUC 0.45  cut-off 43 | AUC  0.25-0.65 | 0.606 | NR | NR |  |
| Johnston, 2012{Johnston, 2012 18242 /id}  22465351  New Zealand  NR | aspirin ≥300 mg at and clopidogrel  ≥300 mg and/or aspirin (≥75 mg) and clopidogrel (≥75 mg) | MEA | stent thrombosis | stent thrombosis | 3 days | High on treatment platelet reactivity >468 AU\*min  n=95 | HTPR | 0 | OR (calculated)=1.63 | NR | P=0.81  (HTPR vs normal)  [Fisher’s exact] | No | NR |  |
|  |  |  |  |  |  | normal platelet reactivity  ≤468 AU\*min  n=155 |  | 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 | stent thrombosis in pts on Abciximab Plus UFH | definite stent thrombosis | 30 days | high on-treatment platelet reactivity  >468 AU\*min  n=96 | definite stent thrombosis | 0 | OR(calculated)=0.6 | 0.02-15.2 | P=0.46  (HTPR vs normal)  [Cox regression] | No | NR |  |
|  |  |  |  |  |  | normal platelet reactivity  ≤468 AU\*min  n=178 |  | 1 |  |  |  |  |  |  |
|  |  |  | stent thrombosis in pts on Bivalirudin | definite stent thrombosis | 30 days | high on-treatment platelet reactivity  >468 AU\*min  n=109 | definite stent thrombosis | 1 | OR(calculated)=5.02 | 0.2-124.3 | P=0.2  (HTPR vs normal)  [Cox regression] | No | NR |  |
|  |  |  |  |  |  | normal platelet reactivity  ≤468 AU\*min  n=181 |  | 0 |  |  |  |  |  |  |