**Appendix Table E15. Results from studies assessing the ability of LTA to predict myocardial infarction 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)** |
| Breet, 2010{Breet, 2010 86 /id}  20179285  Netherlands  POPULAR | maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily | ADP LTA 5µmol/L | MI | MI | 1-year | High OTPR | MI | 37/445 (8.3) | OR=2.19 | 1.29-3.72 | <0.003 | No | NR |  |
|  |  |  |  |  |  | Normal  OTPR |  | 24/604  (4) |  |  |  |  |  |  |
|  | maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily | ADP LTA 20 µmol/L | MI | MI | 1-year | High OTPR | MI | 37/392  (9.4) | OR=2.76 | 1.62-4.68 | <0.0001 | No | NR |  |
|  |  |  |  |  |  | Normal  OTPR |  | 24/659  (3.6) |  |  |  |  |  |  |
| Kim, 2010{Kim, 2010 241 /id}  20449634  Korea  NR | 300-600mg LD and 75 mg maintain dose clopidogrel | 5umol/L ADP LTA | non-fatal myocardial infarction | non-fatal myocardial infarction | 6 months | <50% | non-fatal myocardial infarction | 1.9% | OR=3.15 | 1.55-6.4 | 0.001 | NR | NR |  |
|  |  |  |  |  |  | ≥50% |  | 5.6% |  |  |  |  |  |  |
| Bliden  2007{Bliden, 2007 202 /id}  17291930  USA  NR | clopidogrel  75 mg qd | ADP-induced platelet reactivity | Myocardial infarction | Myocardial infarction | Day 0-30 | HPR n=22 | Myocardial infarction | 3/100 | OR(calculated)=17.1 | 1.8-162.4 | P=0.003  (HPR vs NPR)  [Fishers exact] | NR | NR |  |
|  |  |  |  |  | Day 0-30 | NPR  N=78 | Myocardial infarction | 1/100 | NR | NR | NR | NR | NR |  |
|  |  |  |  |  | Day 31-365 | HPR n=22 | Myocardial infarction | 1/100 |  |  |  |  |  |  |
|  |  |  |  |  | Day 31-365 | NPR  N=78 | Myocardial infarction | 0/100 |  |  |  |  |  |  |
| Breet, 2011{Breet, 2011 15 /id}  21478385  The Netherlands  POPular | Clopidogrel LD 300 or 600mg or maintaining 75 mg daily | LTA5 | MI | MI | 1 year | HCPR(high on-clopidogrel platelet reactivity) or dual HPR | MI | 31/385 | NR | NR | 0.023comparing with NPR(normal on-treatment platelet reactivity) | NR | NR |  |
|  | Clopidogrel LD 300 or 600mg or maintaining 75 mg daily | LTA20 | MI | MI | 1 year | HCPR(high on-clopidogrel platelet reactivity) or dual HPR | MI | 30/335 | NR | NR | 0.007comparing with NPR(normal on-treatment platelet reactivity) | NR | NR |  |
| Buonamici, 2007{Buonamici, 2007 200 /id}  17572245  Italy  NR | Clopidogre l LD 600 mg maintenance dose of 75 mg daily | LTA ADP | ST-segment elevation AMI | ST-segment elevation AMI | 6 months | Responders | ST-segment elevation AMI | 199/699 | NR | NR | <0.001 comparing with the following group | NR | NR |  |
|  |  |  |  |  |  | Non-responders |  | 18/105 |  |  |  |  |  |  |
| Campo, 2007{Campo, 2007 197 /id}  17868803  Italy  NR | Clopidogrel 300-mg loading dose, followed by 75 mg/day | LTA ADP | Reinfarction | Reinfarction | 6 months | Responder to both | Reinfarction | 0/25 | OR(calculated)=6.41 | 0.6-74.2 | P=0.15  (nonresponder vs responder)  [Fishers exact] | NR | NR |  |
|  |  |  |  |  |  | Clopidogrel –  Ticlopidine+ |  | 1/25 |  |  |  |  |  |  |
|  |  |  |  |  |  | Clopidogrel +  Ticlopidine - |  | 1/25 |  |  |  |  |  |  |
|  |  |  |  |  |  | Nonresponder to both |  | 1/25 |  |  |  |  |  |  |
| Cuisset, 2007{Cuisset, 2007 204 /id}  17264958  France  NR | Clopidogrel loading dose 600 mg | ADP LTA | Periprocedural MI | Periprocedural MI | NR | Non-responders | Periprocedural MI | 43% | OR=2.43 | 1.18-4.97 | 0.0143 comparing with the following group | NR | NR |  |
|  |  |  |  |  |  | responders |  | 24% |  |  |  |  |  |  |
| Geisler, 2006{Geisler, 2006 210 /id}  17005534  Germany  NR | Clopidogrel LD dose of 600 mg followed 75 mg daily | ADP LTA | Myocardial infarction | Myocardial infarction | 3-month | Adequate response | Myocardial infarction | 4/341 (1.2) | NR | NR | 0.29 | NR | NR |  |
|  |  |  |  |  |  | Low response |  | 1/22 (4.5) |  |  |  |  |  |  |
| Geisler 2010{Geisler, 2010 101 /id}  19812059  Germany  NR | Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 500 mg LD + 100 mg MD | LTA | MI | NR | 3 months | Low responder (Terrtile 3) | MI | 14 (2%) | OR=2.15 | 1.01-4.57 | p=0.04  (low responder vs responder)  [chi square] | NO | NR | Secondary outcome |
|  |  |  |  |  |  | Responders (Tertile 1&2) |  | 14 (4.3%) |  |  |  |  |  |  |
| Gurbel 2008{Gurbel, 2008 157 /id}  19012177  USA  None | Clopidogrel+aspirin | 5 uM ADP aggregation | MI |  | 1 mo | >46% platelet aggregation (HPR) |  | 1 | OR(calculated)=2.4 | 0.5-12.2 | P=0.37  (HPR vs NPR)  [Fishers exact] | NR | NR | NR |
|  |  |  |  |  | 2-24 mo |  |  | 2 | NR | NR | NR | NR | NR | NR |
|  |  |  |  |  | 1 mo | <=46% |  | 0 | NR | NR | NR | NR | NR | NR |
|  |  |  |  |  | 2-24 mo |  |  | 3 | NR | NR | NR | NR | NR | NR |
|  | Clopidogrel+aspirin | 20 uM ADP aggregation | MI |  | 1 mo | >46% platelet aggregation (HPR) |  | 1 | OR(calculated)=10.2 | 1.2-88.1 | P=0.012  (HPR vs NPR)  [Fishers exact] | NR | NR | NR |
|  |  |  |  |  | 2-24 mo |  |  | 4 | NR | NR | NR | NR | NR | NR |
|  |  |  |  |  | 1 mo | <=46% |  | 0 | NR | NR | NR | NR | NR | NR |
|  |  |  |  |  | 2-24 mo |  |  | 1 | NR | NR | NR | NR | NR | NR |
| Htun, 2011{Htun, 2011 20 /id}  21273381  Germany  NR | clopidogrel LD 600 mg then 75 mg/d and aspirin 100  mg/d | LTA ADP | myocardial infarction | myocardial infarction | 1 year | low-responder group1 | myocardial infarction | 17/165  (10.2) | NR | NR | 0.024 comparing with the lower row | NR | NR |  |
|  |  |  |  |  |  | responder group 1 |  | 20/396 (5.1) |  |  | 0.2 |  |  |  |
|  |  |  |  |  |  | low-responder group 2 |  | 9/161 (5.7) |  |  | comparing with the lower row |  |  |  |
|  |  |  |  |  |  | responder group 2 |  | 21/613 (3.4) |  |  |  |  |  |  |
| Saw, 2008{Saw, 2008 243 /id}  19038679  Canada  ELAPSE trial | Clopidogrel+aspirin | LTA | NSTEMI | NR | 12 mo | Clopidogrel resistant | YES event | 0 | OR(calculated)=0.62 | 0-14.2 | P=1.0  (resistant vs onresistant)  [chi square] | NR | NR | NR |
|  |  |  |  |  |  | Nonresistant |  | 3 |  |  |  |  |  |  |
| Trenk, 2008{Trenk, 2008 171 /id}  18482659  Germany  EXCELSIOR (Impact of Extent of Clopidogrel- Induced Platelet Inhibition During Elective Stent Implantation  on Clinical Event Rate) | 600 mg clopidogrel LD + 75 mg/day MD (for 30 d w/ bare-metal stents or 6 mth w/ atleast 1 drug-eluting stent | LTA | Nonfatal ST elevation MI | Nonfatal ST elevation MI | 1 year | high on-treatment platelet  reactivity (RPA>14%) | Nonfatal ST elevation MI | 2/217 (0.9%) | HR=2. 6 | 0.4-18.1 | P=0.33 (between high and not high residual platelet reactivity) | YES;  Age, HTN, DM, BMI, platelet count, verapamil, insulin and antidiabetic medication use, previous angioplasty and CABG, LV function, angina class, PCI, stent implantation, LAD affected, stenosis length ad diameter of stenosis | NR | Primary outcome |
|  |  |  |  |  |  | no high on-treatment platelet  reactivity (RPA≤ 14%) |  | 2/548 (0.4%) |  |  |  |  |  |  |
|  | 600 mg clopidogrel LD + 75 mg/day MD (for 30 d w/ bare-metal stents or 6 mth w/ atleast 1 drug-eluting stent | LTA | Nonfatal non-ST elevation MI | Nonfatal non-ST elevation MI | 1 year | high on-treatment platelet  reactivity (RPA>14%) | Nonfatal non-ST elevation MI | 4/217 (1.8%) | HR=1.7 | 0.5-6.1 | P=0.4 (between high and not high residual platelet reactivity) | YES;  Age, HTN, DM, BMI, platelet count, verapamil, insulin and antidiabetic medication use, previous angioplasty and CABG, LV function, angina class, PCI, stent implantation, LAD affected, stenosis length ad diameter of stenosis | NR | Primary outcome |
|  |  |  |  |  |  | no high on-treatment platelet  reactivity (RPA≤ 14%) |  | 6/548 (1.1%) |  |  |  |  |  |  |
| Wang, 2010{Wang, 2010 37 /id}  21171668  China  None | Clopidogrel+aspirin | LTA | MI |  |  | Clopidogrel resistance |  | 3 (9.38%) | OR=6.21(calculated) | 0.99-38.9 | 0.061 vs. next row | NR |  |  |
|  |  |  |  |  |  | nonresistance |  | 2 (1.64%) |  |  |  |  |  |  |
| Wang, 2009{Wang, 2009 130 /id}  19041120  China  NR | LD 300 mg clopidogrel and maintaining 75 mg daily | ADP-LTA | Non fatal-MI | nonfatal-MI | One year | Clopidogrel resistance | nonfatal-MI | 4/65 (6.2) | OR=2.56  (calculate) | 0.75-8.79) | 0.126 comparing with the following group | NO |  |  |
|  |  |  |  |  |  | Normal response |  | 8/321  (2.5) |  |  |  |  |  |  |
|  |  |  |  |  |  | Total |  | 12/386  (3.1) |  |  |  |  |  |  |
| Yong, 2009{Yong, 2009 146 /id}  19081397  Australia  Platelet Responsiveness to Aspirin and Clopidogrel and  Troponin Increment after Coronary intervention in Acute  coronary Lesions (PRACTICAL) Trial | 300-600 mg LD of clopidogrel | LTA using 4 , 10, 20μmol/L | Post-PCI myonecrosis | Postprocedure troponin I level above the preprocedure troponin I level and greater than 5 times the upper limit of the reference range (0.1 ng/mL). | 6 months | Quartile 1 | Post-PCI myonecrosis | NR | NR | NR | NR | NR | NR | Data presented in Fig 2A; no pvalues are reporter for all concentrations of ADP |
|  |  |  |  |  |  | Quartile 2 | NR |  |  |  |  |  |  |  |
|  |  |  |  |  |  | Quartile 3 | NR |  |  |  |  |  |  |  |
|  |  |  |  |  |  | Quartile 4 | NR |  |  |  |  |  |  |  |
| Gurbel, 2003{Gurbel, 2003 222 /id}  12796140  USA  NR | LD 300 mg clopidogrel and maintaining 75 mg daily | ADP-LTA | Q wave MI | Q wave MI | 30 days | Clopidogrel resistance | Q wave MI | 0 | NR | OR(calculated)=1.3 | NR | P=0.9  (HPR vs NPR)  [Fishers exact] | NO |  |
|  |  |  |  |  |  | Clopidogrel nonresistance |  | 0 |  |  |  |  |  |  |
| Aradi {Aradi, 2012 18248 /id}  21902692  Hungary  NR | LD clopidogrel 600mg and aspirin 300mg  MD clopidogrel 75 mg/day 4 weeks | LTA ADP | MI | Myocardio infarction | 12 months | NPR | MI | 1/122=0.8% | OR=10.37(calculate) | 1.05-102.85 | NR | NR | NR | NR |
|  |  |  |  |  |  | HPR+150 mg clopidogrel | MI | 0/36=0 |  |  | 0.08 comparing with the low row  log-rank test |  |  |  |
|  |  |  |  |  |  | HPR +75 mg clopidogrel | MI | 3/38=8.7% |  |  |  |  |  |  |
| Ge, 2012{Ge, 2012 18184 /id}  21602258  China  NR | Clopidogrel 600 mg loading; maintenance clopidogrel 75 mg/d + aspirin 100 mg/d | LTA (ADP) | MI | Myocardial infarction , including procedural MI requiring TVR | 6 mo | Resistance (drop in reactivity <10% post-loading) | MI events | 4/65 (6%) | OR (calculated) = 9.34 | 1.67, 52.17 | 0.015 [reported; Cox regression]; p = 0.012 [calculated, Fisher’s exact test] | Unclear (“relevant prognostic factors”) | NR | NR |
|  |  |  |  |  |  | Non-resistance (drop ≥10% post-loading) | MI events | 2/287 (1%) |  |  |  |  |  |  |