**Appendix Table E14. Results of studies assessing the ability of LTA to predict mortality 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 | Death | death, | 1-year | High OTPR  N=445 | Death | 11 (2.5) | OR=2.53 | 0.93-6.88 | <0.06  (high vs normal)  [logistic regression] | No | NR |  |
|  |  |  |  |  |  | Normal  OTPR  N=604 |  | 6 (1) |  |  |  |  |  |  |
|  | maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily | ADP LTA 20 µmol/L | Death | death, | 1-year | High OTPR  N=392 | Death | 6(12) | OR=0.92 | 0.34-2.50 | 0.86  (high vs normal)  [logistic regression] | No | NR |  |
|  |  |  |  |  |  | Normal  OTPR  N=659 |  | 11 (6.2) |  |  |  |  |  |  |
| Kim, 2010{Kim, 2010 241 /id}  20449634  Korea  NR | 300-600mg LD and 75 mg maintain dose clopidogrel | 5umol/L ADP LTA | cardiac death | cardiac death | 6 months | <50% | cardiac death | 0.2% | OR=9.61 | 1.15-80.11 | 0.016  (<50 vs ≥ 50%)  [logistic regression] | NR | NR |  |
|  |  |  |  |  |  | ≥50% |  | 1.5% |  |  |  |  |  |  |
| Bliden,  2007{Bliden, 2007 202 /id}  17291930  USA  NR | clopidogrel  75 mg qd | ADP-induced platelet reactivity | death | death | Day 0-30 | HPR n=22 | Death | 0 | OR (calculate)=3.5 | NR | P=0.535  (HPR vs NPR)  [Chi square] | NR | NR |  |
|  |  |  |  |  | Day 0-30 | NPR  N=78 | death | 0 | NR | NR | NR | NR | NR |  |
|  |  |  |  |  | Day 31-365 | HPR n=22 | death | 0 |  |  |  |  |  |  |
|  |  |  |  |  | Day 31-365 | NPR  N=78 | death | 0 |  |  |  |  |  |  |
| Breet, 2011{Breet, 2011 15 /id}  21478385  The Netherlands  POPular | Clopidogrel LD 300 or 600mg or maintaining 75 mg daily | LTA5 | Death | Death | 1 year | HCPR(high on-clopidogrel platelet reactivity) or dual HPR  N=385 | Death, | 9/385 | OR (calculate)=2.1 | 0.7-6.0 | P=0.19  (HPR vs NPR)  [Fishers exact] | NR | NR |  |
|  | Clopidogrel LD 300 or 600mg or maintaining 75 mg daily | LTA20 | Death | Death | 1 year | HCPR(high on-clopidogrel platelet reactivity) or dual HPR  N=335 | Death, | 5/335 | OR (calculate)=0.86 | 0.3-2.5 | P=1.0  (HPR vs NPR)  [Fishers exact] | NR | NR |  |
| Buonamici, 2007{Buonamici, 2007 200 /id}  17572245  Italy  NR | Clopidogre l LD 600 mg maintenance dose of 75 mg daily | LTA ADP | Cardic mortality | Cardic mortality | 6 months | Responders  N=699 | Cardic mortality | 10 (1.4) | NR | NR | <0.001 (responder vs nonresponder)  Chi-square | NR | NR |  |
|  |  |  |  |  |  | Nonresponders  N=105 |  | 9 (8.6) |  |  |  |  |  |  |
| Campo, 2007{Campo, 2007 197 /id}  17868803  Italy  NR | Clopidogrel 300-mg loading dose, followed by 75 mg/day | LTA ADP | Death | Death | 6 months | Responder to both | Death | 1/90 (1.1) | OR (calculate)=1.52 | 0.1-17.5 | P=1.0  (clopidogrel nonresponder +dual nonresponder vs other groups)  [Fishers exact] | NR | NR |  |
|  |  |  |  |  |  | Clopidogrel –  Ticlopidine+ |  | 0(0) |  |  |  |  |  |  |
|  |  |  |  |  |  | Clopidogrel +  Ticlopidine - |  | 1(4.3) |  |  |  |  |  |  |
|  |  |  |  |  |  | Nonresponder to both |  | 1(20) |  |  |  |  |  |  |
| Geisler, 2006{Geisler, 2006 210 /id}  17005534  Germany  NR | Clopidogrel LD dose of 600 mg followed 75 mg daily | ADP LTA | Death from cardiovascular cause | Death from cardiovascular cause | 3-month | Adequate response | Death from cardiovascular cause | 10/341 (2.9) | NR | NR | 0.006 | NR | NR |  |
|  |  |  |  |  |  | Low response |  | 4/22 (18.2) |  |  |  |  |  |  |
|  | Clopidogrel LD dose of 600 mg followed 75 mg daily | ADP LTA | Death from any cause | Death from any cause | 3-month | Adequate response | Death from any cause | 14/341  (4.1) | NR | NR | 0.003 | NR | NR |  |
|  |  |  |  |  |  | Low response |  | 5/22 (22.7) |  |  |  |  |  |  |
| 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 | cardiovascular death | cardiovascular death | 3 months | Low responder (Terrtile 3) | cardiovascular death | 10 (1.4%) | OR=3.02 | 1.33-6.88 | p=0.02  (low responder vs responder)  [chi square] | NO | NR | Secondary outcome |
|  |  |  |  |  |  | Responders (Tertile 1&2) |  | 14 (4.3%) |  |  |  |  |  |  |
| Gori 2008 {Gori, 2008 164 /id}  18718420  Italy  RECLOSE study  (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis) | 600 mg clopidogrel LD + 75-mg MD & Aspirin 325 mg MD | LTA | Cardiac death | Cardiac death | 6 months | Clopidogrel responder and Aspirin responder | Cardiac death | 9 (1.6) | NR | NR | p <0.05 (dual clopidogrel and aspirin nonresponders versus aspirin nonresponders)  p <0.0001 (dual clopidogrel and aspirin nonresponders versus aspirin nonresponders) | NO | NR | Secondary endpoint |
|  |  |  |  |  |  | Clopidogrel nonresponder and aspirin nonresponder |  | 4 (8.9) | OR (calculate)=4.54 | 1.6-12.8 | P=0.008  (dual and single clopidogrel nonresponder vs responders)  [Fishers exact] |  |  |  |
|  |  |  |  |  |  | Clopidogrel nonresponder and aspirin responder |  | 2 (4.4) |  |  |  |  |  |  |
|  |  |  |  |  |  | Clopidogrel responder and aspirin nonresponder |  | 1 (1.2) |  |  |  |  |  |  |
| Gurbel, 2008{Gurbel, 2008 157 /id}  19012177  USA  None | Clopidogrel+aspirin | 5 uM ADP aggregation | Death |  | 1 mo | >46% platelet aggregation (HPR) |  | 0 | OR (calculate)=2.4 | 0.1-38.7 | P=0.505  (HPR vs NPR over 1-24 months)  [Fishers exact] | NR | NR | NR |
|  |  |  |  |  | 2-24 mo |  |  | 1 | NR | NR | NR | NR | NR | NR |
|  |  |  |  |  | 1 mo | <=46% |  | 1 | NR | NR | NR | NR | NR | NR |
|  |  |  |  |  | 2-24 mo |  |  | 0 | NR | NR | NR | NR | NR | NR |
|  | Clopidogrel+aspirin | 20 uM ADP aggregation | Death |  | 1 mo | >46% platelet aggregation (HPR) |  | 0 | OR (calculate)=1.95 | 0.1-31.5 | P=1.0  (HPR vs NPR over 1-24 months)  [Fishers exact] | NR | NR | NR |
|  |  |  |  |  | 2-24 mo |  |  | 1 | NR | NR | NR | NR | NR | NR |
|  |  |  |  |  | 1 mo | <=46% |  | 1 | NR | NR | NR | NR | NR | NR |
|  |  |  |  |  | 2-24 mo |  |  | 0 | NR | NR | NR | NR | NR | NR |
| Hochholzer, 2006{Hochholzer, 2006 208 /id}  17084243  Germany  EXCELSIOR | Clopidogrel 75 mg/day | ADP LTA | Death | death | 30-day | 1st quartile <4% | Death | 0/209 | OR (calculate)=7.3 | 0.4-141.2 | P=0.119  (3rd & 4th quartile vs 1st and 2nd quartile)  [Fishers exact] | NR | NR | Cumulative incidence of major adverse cardiac events |
|  |  |  |  |  |  | 2nd quartile 4-14% |  | 0/198 |  |  |  |  |  |  |
|  |  |  |  |  |  | 3rd quartile  15-32% |  | 0/196 |  |  |  |  |  |  |
|  |  |  |  |  |  | 4th quartile  >32% |  | 3/199 (1.5%) |  |  |  |  |  |  |
| Htun, 2011{Htun, 2011 20 /id}  21273381  Germany  NR | clopidogrel LD 600 mg then 75 mg/d and aspirin 100  mg/d | LTA ADP | death | death e | 1 year | low-responder group1 (K/DOQI index III –V) | death | 17/165  (10.3) | NR | NR | 0.04 low responder vs responder) | NR | NR |  |
|  |  |  |  |  |  | responder group 1  (K/DOQI index III –V) |  | 22/396 (5.6) |  |  |  |  |  |  |
|  |  |  |  |  |  | low-responder group 2  (K/DOQI index I –II) |  | 3/161 (1.9) |  |  | 0.85 (low responder vs responder) |  |  |  |
|  |  |  |  |  |  | responder group 2  (K/DOQI index I –II) |  | 10/613 (1.6) |  |  |  |  |  |  |
| Liu, 2011{Liu, 2011 12 /id}  21613806  China  None | Clopidogrel+aspirin |  | CV death |  |  | Nonrespoders |  | 2 | OR (calculate)=4.43 | 0.4-50.7 | P=0.25  (nonresponder vs low + responder)  [Fishers exact] |  |  |  |
|  |  |  |  |  |  | Low responders |  | 1 |  |  |  |  |  |  |
|  |  |  |  |  |  | Responders |  | 0 |  |  | 0.288 across this and previous 2 rows (chi-square test) |  |  |  |
|  | Clopidogrel+aspirin | Aggregometry | CV death |  | 1 mo after stenting | Nonrespoders |  | 2 |  |  |  |  |  |  |
|  |  |  |  |  |  | Low responders |  | 1 |  |  |  |  |  |  |
|  |  |  |  |  |  | Responders |  | 0 |  |  | 0.288 across this and previous 2 rows (chi-square test) |  |  |  |
| 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 | Death | Death | 1 year | high on-treatment platelet  reactivity (RPA>14%) | Death | 7/217 (3.2%) | HR= 6 | 1.5-23.2 | P=0.003 (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%) | Death | 3/548 (0.5%) |  |  |  |  |  |  |
| Wang, 2010{Wang, 2010 37 /id}  21171668  China  None | Clopidogrel+aspirin | LTA | Cardiovascular death |  | 1 year | Clopidogrel resistance |  | 2 (6.25%) |  |  | 0.191 vs. next row (Student’s t) | 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 | Cardiovascularf death | Cardiovascularf death, | One year | Clopidogrel resistance | Cardiovascularf death | 5/65 (7.7) | NR | NR | 0.068 comparing with the following group | NO | NO |  |
|  |  |  |  |  |  | Normal response |  | 9/321  (2.8) |  |  |  |  |  |  |
|  |  |  |  |  |  | Total |  | 14/386  (3.6) |  |  |  |  |  |  |
| Gurbel 2003{Gurbel, 2003 222 /id}  12796140  USA  NR | LD 300 mg clopidogrel and maintaining 75 mg daily | ADP-LTA | Death | Death | 30 days | Clopidogrel resistance | Death | 0 | OR (calculate)=1.25 | NR | P=0.91  (resistance vs nonresistance )  [Chi square] | NO | 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 | CV death | cardiovascular death | 12 months | NPR | CV death | 0/122=0 | OR=9.8(calculated) | 0.39-245.63 | NR | NR | NR | NR |
|  |  |  |  |  |  | HPR+150 mg clopidogrel | CV death | 0/36=0 |  |  | 0.31 comparing with the low row  log-rank test |  |  |  |
|  |  |  |  |  |  | HPR +75 mg clopidogrel | CV death | 1/38=0 |  |  |  |  |  |  |
| Gaglia, 2012{Gaglia, 2011 18244 /id}  21919956  USA  NR | LD: 600 mg loading clopidogrel or 75-mg for 5 days  MD: Aspirin + clopidogrel 75 mg for 1 month in patients with BMS and 12 months in patients receiving DES | LTA 5 µmol/L ADP | death | death | 3 days | HPR with 5 μM ADP MPA >46% : n=46 | HPR | 0 | OR (calculated)=3.3 | NR | 0.6  (HPR vs NPR)  [Fishers exact test] | No | NR |  |
|  |  |  |  |  |  | NPR with 5 μM ADP MPA >46% : n=154 |  | 0 |  |  |  |  |  |  |
|  |  |  |  |  |  | HPR with 20 μM ADP  MPA >60%  n=32 | HPR | 0 | OR (calculated)=5.2 | NR | 0.4  (HPR vs NPR)  [Fishers exact test] | No | NR |  |
|  |  |  |  |  |  | NPR with 20 μM ADP  MPA >60%  n=168 |  | 0 |  |  |  |  |  |  |
| Ge, 2012{Ge, 2012 18184 /id}  21602258  China  NR | Clopidogrel 600 mg loading; maintenance clopidogrel 75 mg/d + aspirin 100 mg/d | LTA (ADP) | All-cause mortality | NR | 6 mo | Resistance (drop in reactivity <10% post-loading) | Deaths | 0/65 (0%) | NA | NA | NR | NR | NR | NR |
|  |  |  |  |  |  | Non-resistance (drop ≥10% post-loading) |  | 0/287 (0%) |  |  |  |  |  |  |