**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}20179285NetherlandsPOPULAR | maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily  | ADP LTA 5µmol/L | Death  | death,  | 1-year  | High OTPRN=445 | Death  | 11 (2.5) | OR=2.53 | 0.93-6.88 | <0.06(high vs normal)[logistic regression] | No  | NR |  |
|  |  |  |  |  |  | Normal OTPRN=604 |  | 6 (1) |  |  |  |  |  |  |
|  | maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily | ADP LTA 20 µmol/L | Death  | death,  | 1-year  | High OTPRN=392 | Death  | 6(12) | OR=0.92 | 0.34-2.50 | 0.86(high vs normal)[logistic regression] | No  | NR |  |
|  |  |  |  |  |  | Normal OTPRN=659 |  | 11 (6.2) |  |  |  |  |  |  |
| Kim, 2010{Kim, 2010 241 /id}20449634KoreaNR | 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}17291930USANR | clopidogrel75 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 | NPRN=78 | death | 0 | NR | NR | NR | NR | NR |  |
|  |  |  |  |  | Day 31-365 | HPR n=22 | death | 0 |  |  |  |  |  |  |
|  |  |  |  |  | Day 31-365 | NPRN=78 | death | 0 |  |  |  |  |  |  |
| Breet, 2011{Breet, 2011 15 /id}21478385The NetherlandsPOPular | Clopidogrel LD 300 or 600mg or maintaining 75 mg daily  | LTA5 | Death | Death | 1 year | HCPR(high on-clopidogrel platelet reactivity) or dual HPRN=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 HPRN=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}17572245ItalyNR | Clopidogre l LD 600 mg maintenance dose of 75 mg daily | LTA ADP | Cardic mortality  | Cardic mortality | 6 months  | RespondersN=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}17868803ItalyNR | 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}17005534GermanyNR | 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}19812059GermanyNR | 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}18718420ItalyRECLOSE 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}19012177USANone | 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}17084243GermanyEXCELSIOR | 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 quartile15-32%  |  | 0/196 |  |  |  |  |  |  |
|  |  |  |  |  |  | 4th quartile>32%  |  | 3/199 (1.5%) |  |  |  |  |  |  |
| Htun, 2011{Htun, 2011 20 /id}21273381GermanyNR | clopidogrel LD 600 mg then 75 mg/d and aspirin 100mg/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}21613806ChinaNone | 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}18482659GermanyEXCELSIOR (Impact of Extent of Clopidogrel- Induced Platelet Inhibition During Elective Stent Implantationon 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 plateletreactivity (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 plateletreactivity (RPA≤ 14%) | Death | 3/548 (0.5%) |  |  |  |  |  |  |
| Wang, 2010{Wang, 2010 37 /id}21171668ChinaNone | 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}19041120ChinaNR | 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}12796140USANR | 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}21902692HungaryNR | LD clopidogrel 600mg and aspirin 300mgMD 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 rowlog-rank test  |  |  |  |
|  |  |  |  |  |  | HPR +75 mg clopidogrel  | CV death  | 1/38=0 |  |  |  |  |  |  |
| Gaglia, 2012{Gaglia, 2011 18244 /id}21919956USANR | 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 ADPMPA >60% n=32 | HPR | 0 | OR (calculated)=5.2 | NR | 0.4(HPR vs NPR)[Fishers exact test] | No | NR |  |
|  |  |  |  |  |  | NPR with 20 μM ADPMPA >60% n=168 |  | 0 |  |  |  |  |  |  |
| Ge, 2012{Ge, 2012 18184 /id}21602258ChinaNR | 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%) |  |  |  |  |  |  |