**Appendix Table E18. Results from studies assessing the ability of LTA to predict bleeding 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)** |
| Kim, 2010{Kim, 2010 241 /id} 20449634 Korea NR | 300-600mg LD and 75 mg maintain dose clopidogrel | 5umol ADP-induced PRmax≥50% | TIMI bleeding | TIMI bleeding(major, minor) | 6 months | HPPR - 5umol ADP-induced PRmax≥50%  N=NR | TIMI bleeding | 6.8%  (major 4.6%, minor 2.2%) | NR | NR | 0.381  (HPPR vs no HPPR) | NR | NR |  |
|  |  |  |  |  |  | no HPPR  N=NR |  | 4.5% (major 1.9%, minor 2.6%) |  |  |  |  |  |  |
| Bliden 2007{Bliden, 2007 202 /id} 17291930 USA NR | clopidogrel  75 mg qd | ADP-induced platelet reactivity | Major bleeding | Major bleeding | Day 0-30 | HPR n=22 | Major bleeding | 1 | OR (calculated)= 10.95 | 0.4-278.6 | P= 0.15  (HPR vs NPR)  [Fisher's exact] | NR | NR |  |
|  |  |  |  |  |  | NPR  N=78 |  | 0 | NR | NR | NR | NR | NR |  |
|  |  |  |  | Major bleeding | Day 31-365 | HPR n=22 |  | 0 | OR (calculated)=3.5 | NR | P=0.54  (HPR vs NPR)  [Fisher's exact] |  |  |  |
|  |  |  |  |  |  | NPR  N=78 |  | 0 |  |  |  |  |  |  |
|  | clopidogrel  75 mg qd | ADP-induced platelet reactivity | Minor bleeding | Minor bleeding | Day 0-30 | HPR n=22 | Minor bleeding | 1 | OR (calculated)= 3.67 | 0.2-61.1 | P= 0.37  (HPR vs NPR)  [Fisher's exact] | NR | NR |  |
|  |  |  |  |  |  | NPR  N=78 |  | 1 | NR | NR | NR | NR | NR |  |
|  |  |  |  |  | Day 31-365 | HPR n=22 |  | 0 | OR (calculated)=3.5 | NR | P=0.54  (HPR vs NPR)  [Fisher's exact] |  |  |  |
|  |  |  |  |  |  | NPR  N=78 |  | 0 |  |  |  |  |  |  |
|  | clopidogrel  75 mg qd | ADP-induced platelet reactivity | bleeding events | bleeding events | Day 0-30 | HPR n=22 | bleeding events | 2 | OR (calculated): 7.7 | 0.7-89.3 | P=0.120 (HPR vs NPR at 1 year)  [Fishers exact]] | NR | NR |  |
|  |  |  |  |  |  | NPR  N=78 |  | 1 |  |  |  |  |  |  |
|  |  |  |  |  | Day 31-365 | HPR n=22 | Bleeding events | 0 | OR (calculated): 3.5 | NR | P=0.54 (HPR vs NPR at 1 year)  [Fishers exact]] |  |  |  |
|  |  |  |  |  |  | NPR  N=78 |  | 0 |  |  |  |  |  |  |
| Cuisset 2009{Cuisset, 2009 246 /id} 19736156 FranceNR | Clopidogrel 600 mg LD + Aspirin 250 mg LD | LTA | Bleeding composite | non·CABG related TIM I major and  minor bleeding | 30 days | Hyper-responder (quartile 1: ADP-induced aggregation <40%)  N=151 | Major and minor bleeding + | 10 (6.6%) | NR | NR | P=0.001  (hyper-responder versus non hyper-responder)  Chi square | NO | NR | Primary |
|  |  |  |  |  |  | Non hyperresponder (quartile 2-4: ADP-induced aggregation ≥40%)  N=429 |  | 6 (1.4%) |  |  |  |  |  |  |
| Cuisset 2006{Cuisset, 2006 237 /id} 17010792 FranceNR | Clopidogrel 300 mg LD | LTA | Bleeding | major bleeding defined as intracranial bleeding or clinically overt bleeding associated with a decrease in hemoglobin of 5 g/dL | 1 month | high post treatment platelet reactivity | bleeding | 0 | OR=3.02(calculated) | NR | NR | NR | NR |  |
|  |  |  |  |  |  | normal post treatment platelet reactivity |  | 0 |  |  |  |  |  |  |
|  | Clopidogrel 600 mg LD | LTA | Bleeding |  | 1 month | high post treatment platelet reactivity | bleeding | 0 | OR=5.53(calculated) | NR | NR | NR | NR |  |
|  |  |  |  |  |  | normal post treatment platelet reactivity |  | 0 |  |  |  |  |  |  |
| Hochholzer, 2006{Hochholzer, 2006 208 /id} 17084243 Germany EXCELSIOR | Clopidogrel 75 mg/day | ADP LTA | TIMI major bleeding | TIMI major bleeding | 30-day | 1st quartile <4%  N=209 | TIMI major bleeding | 3/209 (1.4%) | OR (calculated): 0.615 | 0.1-2.6 | P= 0.73 (3rd & 4th quartile vs 1st and second quartiles)  [Fishers exact] | NR | NR |  |
|  |  |  |  |  |  | 2nd quartile 4-14%  N=198 | 2/198 (1%) |  |  |  |  |  |  |  |
|  |  |  |  |  |  | 3rd quartile  15-32%  N=196 | 2/196(1%) |  |  |  |  |  |  |  |
|  |  |  |  |  |  | 4th quartile  >32%  N=199 | 1/199(0.5%) |  |  |  |  |  |  |  |
| Liu, 2011{Liu, 2011 12 /id} 21613806 China None | Clopidogrel+aspirin | Aggregometry | Any bleeding event | BleedScore classifications | 1 month | Nonrespoders  N=34 | Any bleeding event | 0 |  |  |  |  |  |  |
|  |  |  |  |  |  | Low responders  N=28 |  | 0 |  |  |  |  |  |  |
|  |  |  |  |  |  | Responders  N=44 |  | 6 |  |  | 0.011 (responder, nonresponders and low responders) (chi-square test) |  |  |  |
|  | Clopidogrel+aspirin | Aggregometry | Alarming bleeding event | Requiring transfusion, intracranial bleeding or any life-threatening event | 1 month | Nonrespoders  N=34 | Alarming bleeding event | 0 |  |  |  |  |  |  |
|  |  |  |  |  |  | Low responders  N=28 |  | 0 |  |  |  |  |  |  |
|  |  |  |  |  |  | Responders  N=44 |  | 0 |  |  |  |  |  |  |
|  | Clopidogrel+aspirin | Aggregometry | Internal bleeding event | Hematoma, epistaxis, blood loss from mouth or vagina, melena, eye bleed, hematuria, or hematemesis | 1 month | Nonrespoders  N=34 | Internal bleeding event | 0 |  |  |  |  |  |  |
|  |  |  |  |  |  | Low responders  N=28 |  | 0 |  |  |  |  |  |  |
|  |  |  |  |  |  | Responders  N=44 |  | 1 |  |  | 0.491 (responder, nonresponders and low responders) (chi-square test) |  |  |  |
|  | Clopidogrel+aspirin | Aggregometry | Superficial bleeding event | Easy bruising, bleeding from small cuts, petechia, or ecchymosis | 1 month | Nonrespoders  N=34 | Superficial bleeding event | 0 |  |  |  |  |  |  |
|  |  |  |  |  |  | Low responders  N=28 |  | 0 |  |  |  |  |  |  |
|  |  |  |  |  |  | Responders  N=44 |  | 5 |  |  | 0.025 (responder, nonresponders and low responders) (chi-square test) |  |  |  |
|  | Clopidogrel+aspirin | Aggregometry | Any bleeding event | BleedScore classifications | 3 month | Nonrespoders  N=34 | Any bleeding event | 1 |  |  |  |  |  |  |
|  |  |  |  |  |  | Low responders  N=28 |  | 1 |  |  |  |  |  |  |
|  |  |  |  |  |  | Responders  N=44 |  | 14 |  |  | 0.1 (responder, nonresponders and low responders) (chi-square test) |  |  |  |
|  | Clopidogrel+aspirin | Aggregometry | Alarming bleeding event | Requiring transfusion, intracranial bleeding or any life-threatening event | 3 month | Nonrespoders  N=34 | Alarming bleeding event | 0 |  |  |  |  |  |  |
|  |  |  |  |  |  | Low responders  N=28 |  | 0 |  |  |  |  |  |  |
|  |  |  |  |  |  | Responders  N=44 |  | 0 |  |  |  |  |  |  |
|  | Clopidogrel+aspirin | Aggregometry | Internal bleeding event | Hematoma, epistaxis, blood loss from mouth or vagina, melena, eye bleed, hematuria, or hematemesis | 3 month | Nonrespoders  N=34 | Internal bleeding event | 0 |  |  |  |  |  |  |
|  |  |  |  |  |  | Low responders  N=28 |  | 1 |  |  |  |  |  |  |
|  |  |  |  |  |  | Responders  N=44 |  | 3 |  |  | 0.292 (responder, nonresponders and low responders) (chi-square test) |  |  |  |
|  | Clopidogrel+aspirin | Aggregometry | Superficial bleeding event | Easy bruising, bleeding from small cuts, petechia, or ecchymosis | 3 month | Nonrespoders  N=34 | Superficial bleeding event | 01 |  |  |  |  |  |  |
|  |  |  |  |  |  | Low responders  N=28 |  | 0 |  |  |  |  |  |  |
|  |  |  |  |  |  | Responders  N=44 |  | 11 |  |  | 0.001 (responder, nonresponders and low responders) (chi-square test) |  |  |  |