Supplementary Table S1: Proportion of missing values presents in the original dataset

| **Variable** | **Included (%)** | **Missing (%)** |
| --- | --- | --- |
| Age | 89067 (100.0) | 0 (0.0) |
| Gender | 89067 (100.0) | 0 (0.0) |
| Smoking status | 80706 (90.6) | 8361 (9.4) |
| Diabetes | 85706 (96.2) | 3361 (3.8) |
| History of peripheral vascular disease | 85046 (95.5) | 4021 (4.5) |
| Hypertension | 85046 (95.5) | 4021 (4.5) |
| Hypercholesterolemia | 85046 (95.5) | 4021 (4.5) |
| History of renal disease | 80681 (90.6) | 8386 (9.4) |
| History of coronary artery bypass graft | 62921 (70.6) | 26146 (29.4) |
| History myocardial infarction | 83847 (94.1) | 5220 (5.9) |
| History of stroke | 85046 (95.5) | 4021 (4.5) |
| History of percutaneous coronary intervention | 87548 (98.3) | 1519 (1.7) |
| Left ventricular ejection fraction | 28223 (31.7) | 60844 (68.3) |
| TIMI flow | 79103 (88.8) | 9964 (11.2) |
| Access site | 85730 (96.3) | 3337 (3.7) |
| Stent | 85291 (95.8) | 3776 (4.2) |
| Vessel attempted | 88530 (99.4) | 537 (0.6) |
| Cardiogenic shock | 88553 (99.4) | 514 (0.6) |
| Intra-aortic balloon pump use | 85013 (95.4) | 4054 (4.6) |
| Ventilatory support | 82589 (92.7) | 6478 (7.3) |
| Thrombectomy | 84846 (95.3) | 4221 (4.7) |
| Bivalirudin use | 89067 (100.0) | 0 (0.0) |
| Glycoprotein IIb/IIIa inhibitors use | 85914 (96.5) | 3153 (3.5) |
| Year | 89067 (100.0) | 0 (0.0) |
| Bleeding | 87055 (97.7) | 2012 (2.3) |
| Major adverse cardiovascular event | 87051 (97.7) | 2016 (2.3) |
| 30 days mortality | 85076 (95.5) | 3991 (4.5) |
| 1 year mortality | 85060 (95.5) | 4007 (4.5) |

Supplementary Table S2: Quality of matching of propensity score matched dataset instances.

|  | **Prasugrel vs Clopidogrel**  **(332,000)** | | **Ticagrelor vs Clopidogrel**  **(245,200)** | | **Ticagrelor vs Prasugrel**  **(245,200)** | |
| --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **Cases** | **Controls** | **Cases** | **Controls** | **Cases** | **Controls** |
| Age | 61.0 (52.0 - 69.0) | 60.0 (51.0 - 70.0) | 63.0 (54.0 - 73.0) | 63.0 (53.0 - 74.0) | 63.0 (54.0 - 73.0) | 62.0 (54.0 - 70.0) |
| Gender | 128,640 (77.5%) | 128,389 (77.3%) | 90,830 (74.1%) | 91,135 (74.3%) | 90,830 (74.1%) | 93,169 (76.0%) |
| Smoking status |  |  |  |  |  |  |
| Never | 49,881 (30.0%) | 50,619 (30.5%) | 46,674 (38.1%) | 46,669 (38.1%) | 46,674 (38.1%) | 41,797 (34.1%) |
| Ex-smoker | 41,608 (25.1%) | 41,617 (25.1%) | 28,173 (23.0%) | 28,304 (23.1%) | 28,173 (23.0%) | 29,476 (24.0%) |
| Current | 74,511 (44.9%) | 73,764 (44.4%) | 47,753 (39.0%) | 47,627 (38.8%) | 47,753 (39.0%) | 51,327 (41.9%) |
| Diabetes | 22,194 (13.4%) | 21,936 (13.2%) | 18,426 (15.0%) | 18,125 (14.8%) | 18,426 (15.0%) | 17,548 (14.3%) |
| History of peripheral vascular disease | 4,124 (2.5%) | 4,194 (2.5%) | 3,366 (2.7%) | 3,309 (2.7%) | 3,366 (2.7%) | 3,152 (2.6%) |
| Hypertension | 62,496 (37.6%) | 62,800 (37.8%) | 49,750 (40.6%) | 49,795 (40.6%) | 49,750 (40.6%) | 47,949 (39.1%) |
| Hypercholesterolemia | 67,499 (40.7%) | 66,468 (40.0%) | 46,162 (37.7%) | 45,450 (37.1%) | 46,162 (37.7%) | 46,907 (38.3%) |
| History of renal disease | 758 (0.5%) | 865 (0.5%) | 441 (0.4%) | 439 (0.4%) | 441 (0.4%) | 445 (0.4%) |
| History of coronary artery bypass graft | 4,859 (2.9%) | 4,754 (2.9%) | 4,622 (3.8%) | 4,299 (3.5%) | 4,622 (3.8%) | 3,542 (2.9%) |
| History myocardial infarction | 17,872 (10.8%) | 18,166 (10.9%) | 14,857 (12.1%) | 14,577 (11.9%) | 14,857 (12.1%) | 14,059 (11.5%) |
| History of stroke | 3,174 (1.9%) | 3,580 (2.2%) | 4,238 (3.5%) | 4,174 (3.4%) | 4,238 (3.5%) | 2,882 (2.4%) |
| History of percutaneous coronary intervention | 13,906 (8.4%) | 14,066 (8.5%) | 10,551 (8.6%) | 10,261 (8.4%) | 10,551 (8.6%) | 10,631 (8.7%) |
| Left ventricular ejection fraction |  |  |  |  |  |  |
| Good (>50%) | 96,820 (58.3%) | 96,743 (58.3%) | 63,299 (51.6%) | 64,015 (52.2%) | 63,299 (51.6%) | 67,129 (54.8%) |
| Moderate (30%-50%) | 57,276 (34.5%) | 57,414 (34.6%) | 49,250 (40.2%) | 48,725 (39.7%) | 49,250 (40.2%) | 46,066 (37.6%) |
| Poor (<30%) | 11,904 (7.2%) | 11,843 (7.1%) | 10,051 (8.2%) | 9,860 (8.0%) | 10,051 (8.2%) | 9,405 (7.7%) |
| TIMI flow |  |  |  |  |  |  |
| TIMI 0 | 125,587 (75.7%) | 125,253 (75.5%) | 87,725 (71.6%) | 88,039 (71.8%) | 87,725 (71.6%) | 90,144 (73.5%) |
| TIMI 1 | 10,994 (6.6%) | 11,153 (6.7%) | 10,311 (8.4%) | 10,430 (8.5%) | 10,311 (8.4%) | 9,044 (7.4%) |
| TIMI 2 | 15,494 (9.3%) | 15,496 (9.3%) | 11,912 (9.7%) | 11,721 (9.6%) | 11,912 (9.7%) | 11,823 (9.6%) |
| TIMI 3 | 13,925 (8.4%) | 14,098 (8.5%) | 12,652 (10.3%) | 12,410 (10.1%) | 12,652 (10.3%) | 11,589 (9.5%) |
| Access site | 124,145 (74.8%) | 120,273 (72.5%) | 96,558 (78.8%) | 96,188 (78.5%) | 96,558 (78.8%) | 94,875 (77.4%) |
| Stent |  |  |  |  |  |  |
| None | 10,068 (6.1%) | 10,181 (6.1%) | 7,616 (6.2%) | 7,594 (6.2%) | 7,616 (6.2%) | 7,617 (6.2%) |
| Bare metal | 39,943 (24.1%) | 39,273 (23.7%) | 14,527 (11.8%) | 14,868 (12.1%) | 14,527 (11.8%) | 15,601 (12.7%) |
| Drug eluting | 115,989 (69.9%) | 116,546 (70.2%) | 100,457 (81.9%) | 100,138 (81.7%) | 100,457 (81.9%) | 99,382 (81.1%) |
| Vessel attempted |  |  |  |  |  |  |
| Venous or arterial graft | 2,478 (1.5%) | 2,370 (1.4%) | 1,266 (1.0%) | 1,271 (1.0%) | 1,266 (1.0%) | 1,460 (1.2%) |
| Left main stem artery | 603 (0.4%) | 639 (0.4%) | 2,075 (1.7%) | 1,767 (1.4%) | 2,075 (1.7%) | 603 (0.5%) |
| Left anterior descending artery | 64,846 (39.1%) | 64,875 (39.1%) | 47,018 (38.4%) | 47,148 (38.5%) | 47,018 (38.4%) | 48,171 (39.3%) |
| Left circumflex artery | 20,628 (12.4%) | 20,589 (12.4%) | 17,507 (14.3%) | 17,124 (14.0%) | 17,507 (14.3%) | 16,316 (13.3%) |
| Right coronary artery | 68,704 (41.4%) | 68,625 (41.3%) | 48,246 (39.4%) | 48,760 (39.8%) | 48,246 (39.4%) | 49,443 (40.3%) |
| Multiple | 8,741 (5.3%) | 8,902 (5.4%) | 6,488 (5.3%) | 6,530 (5.3%) | 6,488 (5.3%) | 6,607 (5.4%) |
| Cardiogenic shock | 9,190 (5.5%) | 9,259 (5.6%) | 7,735 (6.3%) | 7,815 (6.4%) | 7,735 (6.3%) | 7,069 (5.8%) |
| Intra-aortic balloon pump use | 5,441 (3.3%) | 5,451 (3.3%) | 4,153 (3.4%) | 4,201 (3.4%) | 4,153 (3.4%) | 3,963 (3.2%) |
| Ventilatory support | 4,103 (2.5%) | 4,192 (2.5%) | 4,134 (3.4%) | 4,043 (3.3%) | 4,134 (3.4%) | 3,556 (2.9%) |
| Thrombectomy | 83,788 (50.5%) | 84,718 (51.0%) | 64,526 (52.6%) | 62,955 (51.3%) | 64,526 (52.6%) | 63,383 (51.7%) |
| Bivalirudin use | 53,630 (32.3%) | 39,284 (23.7%) | 28,970 (23.6%) | 25,869 (21.1%) | 28,970 (23.6%) | 32,494 (26.5%) |
| Glycoprotein IIb/IIIa inhibitors use | 74,041 (44.6%) | 76,067 (45.8%) | 41,926 (34.2%) | 42,247 (34.5%) | 41,926 (34.2%) | 46,800 (38.2%) |

Supplementary Table S3: Sensitivity analysis 2 – Dataset restricted to years 2010 to 2014, only.

(a) Results of logistic regression models. Odd ratios, confidence intervals (in brackets), and p-values represent the pooled results over 10 propensity score matched dataset instances.

|  |  |  |  |
| --- | --- | --- | --- |
| Outcome | Cohort | Odd ratio (95% CI) | P-value |
| Bleeding | Prasugrel vs Clopidogrel | 0.689 (0.535-0.888) | 0.004 |
|  | Ticagrelor vs Clopidogrel | 0.587 (0.433-0.795) | <0.001 |
|  | Ticagrelor vs Prasugrel | 0.958 (0.696-1.321) | 0.795 |
| MACE | Prasugrel vs Clopidogrel | 0.882 (0.778-1.000) | 0.051 |
|  | Ticagrelor vs Clopidogrel | 0.976 (0.865-1.101) | 0.694 |
|  | Ticagrelor vs Prasugrel | 1.400 (1.233-1.589) | <0.001 |
| 30 days mortality | Prasugrel vs Clopidogrel | 0.813 (0.721-0.917) | <0.001 |
|  | Ticagrelor vs Clopidogrel | 0.900 (0.805-1.005) | 0.062 |
|  | Ticagrelor vs Prasugrel | 1.404 (1.247-1.581) | <0.001 |
| 1 year mortality | Prasugrel vs Clopidogrel | 0.814 (0.735-0.902) | <0.001 |
|  | Ticagrelor vs Clopidogrel | 0.906 (0.825-0.995) | 0.039 |
|  | Ticagrelor vs Prasugrel | 1.381 (1.254-1.520) | <0.001 |

(b) Results of Cox regression models with survival time censored at 1 year. Hazard ratios, confidence intervals (in brackets), and p-values represent the pooled results over 10 propensity score matched dataset instances.

|  |  |  |
| --- | --- | --- |
| Cohort | Hazard ratio (95% CI) | P-value |
| Prasugrel vs Clopidogrel | 0.820 (0.742-0.905) | <0.001 |
| Ticagrelor vs Clopidogrel | 0.914 (0.835-0.999) | 0.047 |
| Ticagrelor vs Prasugrel | 1.386 (1.264-1.521) | <0.001 |

Supplementary Table S4: Sensitivity analysis 3 – Dataset Including procedures undertaken in patients with multiple antiplatelets§.

(a) Results of logistic regression models. Odd ratios, confidence intervals (in brackets), and p-values represent the pooled results over 10 propensity score matched dataset instances.

|  |  |  |  |
| --- | --- | --- | --- |
| Outcome | Cohort | Odd ratio (95% CI) | P-value |
| Bleeding | Prasugrel vs Clopidogrel | 0.636 (0.481-0.842) | 0.002 |
|  | Ticagrelor vs Clopidogrel | 0.552 (0.404-0.754) | <0.001 |
|  | Ticagrelor vs Prasugrel | 0.933 (0.668-1.301) | 0.681 |
| MACE | Prasugrel vs Clopidogrel | 0.892 (0.778-1.022) | 0.099 |
|  | Ticagrelor vs Clopidogrel | 0.992 (0.880-1.119) | 0.898 |
|  | Ticagrelor vs Prasugrel | 1.418 (1.246-1.614) | <0.001 |
| 30 days mortality | Prasugrel vs Clopidogrel | 0.833 (0.733-0.947) | 0.005 |
|  | Ticagrelor vs Clopidogrel | 0.925 (0.826-1.036) | 0.178 |
|  | Ticagrelor vs Prasugrel | 1.418 (1.256-1.601) | <0.001 |
| 1 year mortality | Prasugrel vs Clopidogrel | 0.823 (0.742-0.912) | <0.001 |
|  | Ticagrelor vs Clopidogrel | 0.936 (0.853-1.026) | 0.158 |
|  | Ticagrelor vs Prasugrel | 1.402 (1.270-1.548) | <0.001 |

(b) Results of Cox regression models with survival time censored at 1 year. Hazard ratios, confidence intervals (in brackets), and p-values represent the pooled results over 10 propensity score matched dataset instances.

|  |  |  |
| --- | --- | --- |
| Cohort | Hazard ratio (95% CI) | P-value |
| Prasugrel vs Clopidogrel | 0.828 (0.750-0.915) | <0.001 |
| Ticagrelor vs Clopidogrel | 0.941 (0.862-1.028) | 0.178 |
| Ticagrelor vs Prasugrel | 1.406 (1.279-1.546) | <0.001 |

§ Patients prescribed both prasugrel and clopidogrel, and ticagrelor and clopidogrel were included in prasugrel and ticagrelor groups, respectively.

Supplementary Table S5: Baseline patient demographics, procedural details, pharmacology, and outcomes including unknown antiplatelet prescription.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Clopidogrel (58,248)** | **Prasugrel (17,714)** | **Ticagrelor (13,105)** | **Unknown (27,344)** | **P-value** |
| Age | 64.4 (±13.4) | 60.6 (±11.7) | 63.0 (±12.9) | 62.9 (±13.1) | < 0.0001 |
| Gender (Male) | 42,821 (73.5%) | 13,739 (77.6%) | 9,721 (74.2%) | 20,261 (74.1%) | < 0.0001 |
| Smoking status |  |  |  |  | < 0.0001 |
| Never | 16,934 (32.3%) | 4,797 (29.6%) | 4,545 (37.6%) | 8,835 (36.9%) |  |
| Ex-smoker | 15,465 (29.5%) | 4,021 (24.8%) | 2,742 (22.7%) | 5,821 (24.3%) |  |
| Current | 20,033 (38.2%) | 7,384 (45.6%) | 4,785 (39.6%) | 9,312 (38.9%) |  |
| Diabetes | 8,233 (14.8%) | 2,315 (13.4%) | 1,927 (15.0%) | 3,296 (12.8%) | < 0.0001 |
| History of peripheral vascular disease | 2,024 (3.6%) | 416 (2.5%) | 332 (2.7%) | 896 (3.4%) | < 0.0001 |
| Hypertension | 25,022 (44.9%) | 6,363 (37.5%) | 4,986 (40.5%) | 9,682 (37.1%) | < 0.0001 |
| Hypercholesterolemia | 23,246 (41.7%) | 6,850 (40.4%) | 4,630 (37.6%) | 9,370 (35.9%) | < 0.0001 |
| History of renal disease | 478 (0.9%) | 67 (0.4%) | 42 (0.3%) | 211 (0.8%) | < 0.0001 |
| History of coronary artery bypass graft | 1,866 (4.7%) | 356 (2.5%) | 367 (4.2%) | 1,052 (5.3%) | < 0.0001 |
| History myocardial infarction | 7,603 (14.0%) | 1,866 (10.7%) | 1,472 (12.3%) | 2,881 (12.0%) | < 0.0001 |
| History of stroke | 2,368 (4.2%) | 322 (1.9%) | 411 (3.3%) | 972 (3.7%) | < 0.0001 |
| History of percutaneous coronary intervention | 5,642 (9.9%) | 1,458 (8.3%) | 1,120 (8.7%) | 2,124 (8.2%) | < 0.0001 |
| Left ventricular ejection fraction |  |  |  |  | < 0.0001 |
| Good (>50%) | 10,098 (52.1%) | 2,764 (55.8%) | 1,978 (51.1%) | 3,400 (43.6%) |  |
| Moderate (30%-50%) | 7,117 (36.7%) | 1,763 (35.6%) | 1,532 (39.6%) | 3,493 (44.8%) |  |
| Poor (<30%) | 2,181 (11.2%) | 427 (8.6%) | 363 (9.4%) | 910 (11.7%) |  |
| TIMI flow |  |  |  |  | < 0.0001 |
| TIMI 0 | 35,718 (69.2%) | 12,239 (75.8%) | 8,140 (71.6%) | 14,182 (74.1%) |  |
| TIMI 1 | 4,660 (9.0%) | 1,057 (6.5%) | 964 (8.5%) | 1,175 (6.1%) |  |
| TIMI 2 | 5,031 (9.8%) | 1,502 (9.3%) | 1,101 (9.7%) | 1,670 (8.7%) |  |
| TIMI 3 | 6,189 (12.0%) | 1,341 (8.3%) | 1,161 (10.2%) | 2,106 (11.0%) |  |
| Access site (Radial) | 26,514 (47.1%) | 12,692 (74.9%) | 9,765 (78.3%) | 14,375 (54.7%) | < 0.0001 |
| Stent |  |  |  |  | < 0.0001 |
| None | 4,422 (8.0%) | 1,050 (6.1%) | 773 (6.1%) | 1,784 (7.2%) |  |
| Bare metal | 19,479 (35.2%) | 4,217 (24.5%) | 1,503 (11.9%) | 5,996 (24.1%) |  |
| Drug eluting | 31,492 (56.9%) | 11,974 (69.5%) | 10,381 (82.0%) | 17,111 (68.7%) |  |
| Vessel attempted |  |  |  |  | < 0.0001 |
| Venous or arterial graft | 803 (1.4%) | 259 (1.5%) | 143 (1.1%) | 512 (1.9%) |  |
| Left main stem artery | 411 (0.7%) | 67 (0.4%) | 230 (1.8%) | 380 (1.4%) |  |
| Left anterior descending artery | 22,858 (39.5%) | 6,905 (39.2%) | 4,974 (38.2%) | 10,585 (39.1%) |  |
| Left circumflex artery | 7,216 (12.5%) | 2,186 (12.4%) | 1,839 (14.1%) | 3,247 (12.0%) |  |
| Right coronary artery | 22,915 (39.6%) | 7,269 (41.2%) | 5,147 (39.5%) | 10,598 (39.1%) |  |
| Multiple | 3,671 (6.3%) | 937 (5.3%) | 700 (5.4%) | 1,767 (6.5%) |  |
| Cardiogenic shock | 4,155 (7.2%) | 988 (5.6%) | 812 (6.2%) | 2,553 (9.5%) | < 0.0001 |
| Intra-aortic balloon pump use | 2,832 (5.1%) | 567 (3.4%) | 421 (3.4%) | 1,433 (5.6%) | < 0.0001 |
| Ventilatory support | 1,891 (3.5%) | 425 (2.5%) | 392 (3.4%) | 1,726 (8.4%) | < 0.0001 |
| Thrombectomy | 25,933 (46.6%) | 8,583 (51.0%) | 6,518 (52.7%) | 13,118 (51.3%) | < 0.0001 |
| Bivalirudin use | 5,095 (8.7%) | 5,697 (32.2%) | 2,963 (22.6%) | 996 (3.6%) | < 0.0001 |
| Glycoprotein IIb/IIIa inhibitors use | 30,258 (53.7%) | 7,672 (44.5%) | 4,294 (34.8%) | 14,172 (54.5%) | < 0.0001 |
| Year |  |  |  |  | < 0.0001 |
| 2007 | 3,448 (5.9%) | 0 (0.0%) | 0 (0.0%) | 915 (3.3%) |  |
| 2008 | 5,467 (9.4%) | 0 (0.0%) | 0 (0.0%) | 1,694 (6.2%) |  |
| 2009 | 8,134 (14.0%) | 42 (0.2%) | 0 (0.0%) | 2,859 (10.5%) |  |
| 2010 | 9,491 (16.3%) | 1,649 (9.3%) | 4 (0.0%) | 3,744 (13.7%) |  |
| 2011 | 9,204 (15.8%) | 4,383 (24.7%) | 15 (0.1%) | 4,415 (16.1%) |  |
| 2012 | 8,528 (14.6%) | 5,049 (28.5%) | 1,601 (12.2%) | 5,037 (18.4%) |  |
| 2013 | 7,408 (12.7%) | 3,594 (20.3%) | 4,870 (37.2%) | 4,420 (16.2%) |  |
| 2014 | 6,568 (11.3%) | 2,997 (16.9%) | 6,615 (50.5%) | 4,260 (15.6%) |  |
| Bleeding | 843 (1.5%) | 121 (0.7%) | 76 (0.6%) | 315 (1.2%) | < 0.0001 |
| Major adverse cardiovascular event | 2,783 (4.9%) | 545 (3.2%) | 616 (4.8%) | 1,410 (5.3%) | < 0.0001 |
| 30 days mortality | 3,534 (6.4%) | 622 (3.6%) | 689 (5.5%) | 1,931 (7.5%) | < 0.0001 |
| 1 year mortality | 5,656 (10.2%) | 999 (5.9%) | 1,075 (8.5%) | 2,788 (10.8%) | < 0.0001 |