

Supplement

D. Venetsanos, E. Träff, D. Erlinge et al. **Prasugrel versus Ticagrelor in myocardial infarction patients undergoing percutaneous coronary intervention**

Figure S1. Flow chart

Appendix:

Outcome definition

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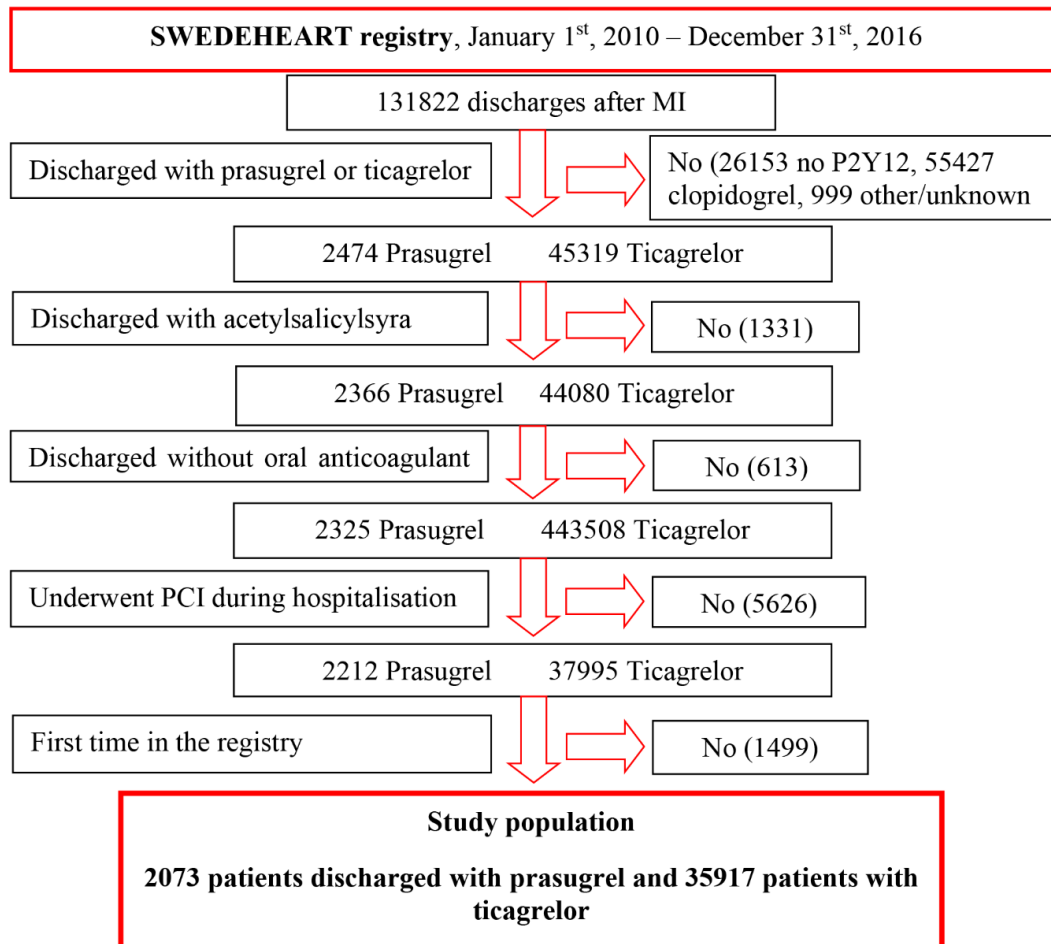
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Figure S2: Distribution of propensity score before (a) and after (b) inverse probability weighting

Figure S1. Flow chart

Appendix

Outcome definition

Major bleeding was defined as any rehospitalisation for a cerebral, gastrointestinal or urogenital bleeding or bleeding from the respiratory tract, identified by using the following International Classification of Diseases codes: I60, I61, I62, D629, D500, H356, H431, H450, H922, I850, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K625, K920, K921, K922, N421, N938, N939, N950, R041, R042, R048, R049, R210, R319, T810, N501A.

Statistical analysis

Covariates that were included in multivariable analysis and in individual propensity score calculation were selected based on investigators clinical experience. The following covariates were included: age, gender, smoking status, history of diabetes mellitus, hypertension, hyperlipidemia, previous myocardial infarction (MI), previous percutaneous coronary intervention (PCI), previous coronary artery by-pass grafting, previous stroke, previous congestive heart failure, known renal insufficiency, chronic obstructive pulmonary disease, peripheral artery disease, previous cancer, a history of bleeding, cardiopulmonary resuscitation before admission, Killip class >1, anaemia on admission, estimated glomerular filtration rate <60 ml/min/1.72m² on admission, treatment with aspirin on arrival, P2Y12 receptor inhibitors on arrival, statins on arrival, multivessel disease, PCI with stent, PCI-access site, use of continuous positive airway pressure, administration of inotropic agents, iv diuretics during the index hospitalisation, medication at discharge including beta blockers, statins, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, diuretics and antidiabetic treatment (no, po drugs or insulin) and MI type (ST segment elevation MI vs non-ST segment elevation MI).

Based on the individual PS, we calculated the stabilised inverse probability of treatment weights (IPTW). To obtain a similar number in the two treatment arms after inverse probability weighting, the weights were stabilized. Stabilization (multiplying the weight by the probability of being exposed for those exposed and the probability of being unexposed for those unexposed), results in a pseudo-population with similar percentage of patients exposed/un-exposed in each level of the covariates as the overall percentage in the study population. Stabilization does not affect the point estimates but reduces the variability of the weights.

Goodness of fit of the logistic regression, used to calculate the individual propensity score was assessed using Hosmer-Lemeshow test (0.11). The c-index was 0.73. Plots of PS after weighting for IPTW showed an

excellence balance between the two treatment groups. Finally, in a sensitivity analysis, truncation of PS score at 1st centile was performed and similar results were obtained (data not shown).

All 5 imputed data bases were used in the IPTW cox regression and multivariable cox regressions models to obtain the 5 completed data estimates of coefficients.

Table S1. Missing values

| Baseline characteristics | N missing | Clinical characteristics on arrival | N missing | Percutaneous Coronary Intervention | N missing |
|--|------------------|--|------------------|---|------------------|
| Age, years | 0 | CPR outside hospital | 425 | Access site- radial artery | 127 |
| Body weight | 472 | Thrombolysis before admission | 233 | Multivessel disease | 208 |
| Sex | 0 | Atrial Fibrillation on arrival | 313 | PCI with stent | 158 |
| Smoking | 1031 | Heart rate | 208 | Medication during PCI | |
| Previous MI | 0 | Systolic blood pressure | 208 | Aspirin | 0 |
| History of Diabetes Mellitus | 0 | Killip Class | 596 | P2Y12 receptor inhibitors | 0 |
| History of Hypertension | 130 | Laboratory data index | | Unfractionated heparin | 14 |
| History of Hyperlipidaemia | 443 | Estimated GFR | 1649 | GP IIb/IIIa receptor inhibitor | 23 |
| Previous PCI | 137 | Anaemia | 2220 | During the index hospitalisation | |
| Previous CABG | 0 | Crusade bleeding score | 2874 | CPAP | 31 |
| Previous stroke | 0 | Medication on arrival | | New onset AF | 12 |
| History of CHF | 977 | Oral Anticoagulant | 422 | Iv diuretics | 25 |
| History of Renal failure - on dialysis | 0 | Aspirin | 431 | Inotropic drug | 29 |
| History of COPD | 0 | P2Y12 receptor inhibitors | 427 | LMWH /fondaparinux | 60 |
| History of PAD | 0 | Statins | 443 | Medication at discharge | |
| History of Dementia | 0 | Beta blockers | 567 | Aspirin | 0 |
| History of Cancer | 0 | ACE-I/ARB | 503 | Beta blockers | 3 |
| Previous Bleeding | 0 | Anti-Diabetic medications | 376 | ACE-I/ARB | 0 |
| Clinical characteristics on arrival | | Diuretics | 504 | Statins | 2 |
| Infarct type | 4 | | | Anti-diabetic medications | 1 |
| Abbreviations (in order of appearance): MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery by-pass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease; CPR, cardiopulmonary resuscitation; GFR, estimated glomerular filtration rate; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Infarct type, ST segment elevation myocardial infarction or non ST segment elevation myocardial infarction; CPR, cardiopulmonary resuscitation; GFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; CPAP, continuous positive airway pressure; | | | | | |

Table S2. P2Y12 receptor inhibitors and acetylsalicylic acid dispensed prescriptions during follow-up (6 to 12 months, from discharge)

| Patients, n 37990 | Dispensed prescriptions 6-12 months after the index procedure | | | |
|--|---|--------------|-------------|-------------|
| | No or other | Ticagrelor | Prasugrel | Clopidogrel |
| Ticagrelor group | 4048 (11.3) | 28838 (80.3) | 282 (0.8) | 2749 (7.7) |
| Prasugrel group | 232 (11.2) | 59 (2.8) | 1647 (79.5) | 135 (6.5) |
| Among patients who survived the first year after discharge | | | | |
| Ticagrelor group | 3223 (9.2) | 28646 (82.2) | 281 (0.8) | 2711 (7.8) |
| Prasugrel group | 190 (9.4) | 59 (2.9) | 1641 (81.0) | 135 (6.7) |
| Acetylsalicylic acid | | | | |
| | Yes | | No | |
| Ticagrelor group | 33412 (93.0) | | 2505 (7.0) | |
| Prasugrel group | 1945 (93.8) | | 128 (6.2) | |

Table S3. Covariate balance between treatment groups, presented as mean standardised difference (MSD), before and after weighting for inverse probability of treatment weights

| | Before IPTW | | | After IPTW | | |
|--|-------------|------------|------|------------|------------|-----|
| | Prasugrel | Ticagrelor | MSD | Prasugrel | Ticagrelor | MSD |
| Age, mean | 62.2 | 66.5 | 39.5 | 65.4 | 66.2 | 7.8 |
| Female sex | 0.21 | 0.27 | 13.9 | 0.27 | 0.27 | 0.0 |
| Previous/current smokers | 0.68 | 0.62 | 11.2 | 0.62 | 0.63 | 1.1 |
| Previous MI | 0.24 | 0.18 | 13.3 | 0.21 | 0.18 | 5.3 |
| History of Diabetes Mellitus | 0.24 | 0.21 | 6.6 | 0.24 | 0.22 | 4.4 |
| History of Hypertension | 0.49 | 0.52 | 5.9 | 0.53 | 0.52 | 2.0 |
| History of Hyperlipidaemia | 0.30 | 0.25 | 10.7 | 0.27 | 0.25 | 4.7 |
| Previous PCI | 0.22 | 0.15 | 18.1 | 0.18 | 0.16 | 6.4 |
| Previous CABG | 0.05 | 0.06 | 0.3 | 0.06 | 0.06 | 0.6 |
| Previous stroke | 0.04 | 0.06 | 3.1 | 0.08 | 0.06 | 9.3 |
| History of CHF | 0.04 | 0.04 | 3.1 | 0.05 | 0.04 | 3.0 |
| History of renal failure | 0.02 | 0.02 | 0.6 | 0.02 | 0.02 | 3.0 |
| History of COPD | 0.04 | 0.05 | 5.1 | 0.05 | 0.05 | 0.8 |
| History of PAD | 0.03 | 0.03 | 0.7 | 0.03 | 0.03 | 0.5 |
| History of Cancer | 0.01 | 0.02 | 5.7 | 0.02 | 0.02 | 3.8 |
| Previous Bleeding | 0.03 | 0.04 | 3.5 | 0.04 | 0.04 | 2.8 |
| Killip Class II-IV | 0.05 | 0.05 | 0.1 | 0.05 | 0.05 | 2.1 |
| CPR outside hospital | 0.03 | 0.02 | 7.1 | 0.03 | 0.02 | 8.0 |
| Estimated GFR ≤ 60 ml/min/1.73 ² | 0.13 | 0.16 | 8.4 | 0.16 | 0.16 | 0.1 |
| Anaemia | 0.21 | 0.20 | 2.1 | 0.20 | 0.20 | 0.1 |
| Aspirin on arrival | 0.30 | 0.28 | 4.6 | 0.31 | 0.29 | 5.1 |
| P2Y12 on arrival | 0.10 | 0.04 | 24.9 | 0.04 | 0.04 | 1.5 |
| Statins on arrival | 0.30 | 0.25 | 10.5 | 0.28 | 0.26 | 4.4 |
| Multivessel disease | 0.52 | 0.49 | 5.0 | 0.52 | 0.50 | 4.0 |
| PCI with stent | 0.93 | 0.93 | 1.7 | 0.93 | 0.93 | 1.3 |
| Radial access site | 0.66 | 0.81 | 34.9 | 0.81 | 0.80 | 1.1 |
| CPAP during hospitalisation | 0.02 | 0.03 | 0.3 | 0.03 | 0.03 | 1.8 |
| Inotropic drugs | 0.05 | 0.03 | 13.1 | 0.03 | 0.03 | 2.0 |
| Beta blocker at discharge | 0.92 | 0.91 | 4.5 | 0.91 | 0.91 | 2.1 |
| ACE-I/ARB at discharge | 0.89 | 0.86 | 8.1 | 0.85 | 0.86 | 4.8 |
| Statin at discharge | 0.98 | 0.97 | 0.9 | 0.97 | 0.97 | 2.5 |
| Anti-diabetic medication at discharge | 0.20 | 0.17 | 7.3 | 0.20 | 0.18 | 4.5 |
| Diuretics at discharge | 0.18 | 0.16 | 4.3 | 0.17 | 0.16 | 2.2 |
| Infarct Type-STEMI | 0.73 | 0.46 | 56.1 | 0.50 | 0.48 | 3.9 |

Figures present proportion, if not otherwise stated. Abbreviations (in order of appearance): SD, standardised difference; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery by-pass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease; CPR, cardiopulmonary resuscitation; GFR, estimated glomerular filtration rate; ICD, implantable cardiac defibrillator; CPAP,

continuous positive airway pressure; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; STEMI, ST elevation myocardial infarction

Table S4. Propensity matched cohort

| | Ticagrelor | Prasugrel | p-value |
|--|-------------------|------------------|----------------|
| Number of patients | 2071 | 2071 | |
| Demographics | | | |
| Age, years, mean \pm SD | 62.2 (11.0) | 62.3 (10.1) | 0.29 |
| Female sex | 434 (21.0) | 435 (21.0) | 0.97 |
| Previous/current smoker | 1389 (67.1) | 1400 (67.5) | 0.72 |
| Medical History | | | |
| Previous MI | 441 (21.3) | 486 (23.5) | 0.10 |
| History of Diabetes Mellitus | 455 (22.0) | 500 (24.1) | 0.10 |
| History of Hypertension | 1023 (49.4) | 1012 (48.9) | 0.73 |
| History of Hyperlipidaemia | 589 (28.4) | 617 (29.8) | 0.34 |
| Previous PCI | 434 (21.0) | 456 (22.0) | 0.41 |
| Previous CABG | 98 (4.7) | 114 (5.5) | 0.26 |
| Previous stroke | 89 (4.3) | 90 (4.3) | 0.94 |
| History of CHF | 80 (3.9) | 93 (4.5) | 0.31 |
| History of COPD | 100 (4.8) | 88 (4.2) | 0.37 |
| History of PAD | 59 (2.8) | 71 (3.4) | 0.29 |
| History of Cancer* | 27 (1.3) | 28 (1.4) | 0.89 |
| Previous Bleeding | 66 (3.2) | 63 (3.0) | 0.79 |
| Clinical characteristics on arrival | | | |
| Killip Class II-IV | 102 (4.9) | 107 (5.2) | 0.72 |
| CPR outside hospital | 77 (3.7) | 68 (3.3) | 0.45 |
| Estimated GFR \leq 60 ml/min/1.73 ² | 250 (12.1) | 273 (13.2) | 0.28 |
| Anaemia | 419 (20.2) | 431 (20.8) | 0.64 |
| Crusade bleeding score | 20 (14- 27) | 20 (14- 27) | 0.32 |
| 1-20 | 1082 (52.2) | 1062 (51.3) | 0.54 |
| 21-30 | 658 (31.8) | 654 (31.6) | |
| 31-40 | 229 (11.1) | 232 (11.2) | |
| \geq 41 | 102 (4.9) | 123 (5.9) | |
| Medications on arrival | | | |
| Aspirin | 584 (28.2) | 628 (30.3) | 0.13 |
| P2Y12 receptor inhibitors | 176 (8.6) | 203 (9.8) | 0.17 |
| Statins | 595 (28.7) | 620 (29.9) | 0.39 |
| Percutaneous Coronary Intervention | | | |
| Multivessel disease | 1042 (50.3) | 1076 (52.0) | 0.29 |
| PCI with stent | 1939 (93.6) | 1920 (92.7) | 0.24 |
| Transradial access | 1383 (66.8) | 1361 (65.7) | 0.13 |
| During the index hospitalisation | | | |
| CPAP | 64 (3.1) | 51 (2.5) | 0.22 |
| Inotropic drug | 104 (5.0) | 104 (5.0) | 1.00 |
| Medication at discharge | | | |
| Beta blockers | 1915 (92.5) | 1906 (92.0) | 0.60 |
| ACE-I/ARB | 1836 (88.7) | 1842 (88.9) | 0.77 |
| Statins | 2013 (97.2) | 2022 (97.6) | 0.38 |
| Anti-diabetic medications | 375 (18.1) | 407 (19.7) | 0.20 |
| Diuretics | 343 (16.6) | 366 (17.7) | 0.34 |
| Infarct type | | | |
| ST-segment elevation MI | 1537 (74.2) | 1507 (72.8) | 0.29 |
| Non-ST-segment elevation MI | 534 (25.8) | 564 (27.2) | |
| Results are presented as numbers and percentages unless otherwise indicated. Abbreviations (in order of appearance): SD, standard deviation; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery by-pass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease; CPR, cardiopulmonary resuscitation; GFR, estimated glomerular filtration rate; ICD, implantable cardiac defibrillator; CPAP, continuous positive airway pressure; ACE-I, angiotensin-converting | | | |

enzyme inhibitor; ARB, angiotensin receptor blocker; *Any cancer diagnosis the last 5 years; ** Were administrated 24 hours before or during PCI

Table S5. One-year outcomes before and after multivariable Cox regression, including calendar year

| | Prasugrel | Ticagrelor | |
|---|----------------------|-------------------|--------------------|
| Patients, n | 2073 | 35917 | |
| | Events, n (%) | | HR (95% CI) |
| MACCE | | | |
| Crude | 127 (6.1) | 2196 (6.1) | 1.00 (0.84- 1.20) |
| MV analysis including calendar year | | | 1.08 (0.89- 1.32) |
| NACCE | | | |
| Crude | 174 (8.4) | 3130 (8.7) | 0.96 (0.82- 1.12) |
| MV analysis including calendar year | | | 1.07 (0.90- 1.27) |
| All-cause mortality | | | |
| Crude | 48 (2.3) | 1056 (2.9) | 0.79 (0.59- 1.05) |
| MV analysis including calendar year | | | 0.95 (0.69- 1.30) |
| Myocardial infarction | | | |
| Crude | 85 (4.1) | 1123 (3.2) | 1.32 (1.06- 1.64) |
| MV analysis including calendar year | | | 1.15 (0.90- 1.48) |
| Stroke | | | |
| Crude | 18 (0.9) | 385 (1.1) | 0.81 (0.50- 1.30) |
| MV analysis including calendar year | | | 0.84 (0.50- 1.40) |
| Major bleeding | | | |
| Crude | 51 (2.5) | 1124 (3.2) | 0.78 (0.59- 1.03) |
| MV analysis including calendar year | | | 0.98 (0.72- 1.33) |
| Major adverse cardiac and cerebrovascular events (MACCE) including all-cause death, myocardial infarction, or stroke (ischemic and haemorrhagic); Net adverse cardiac and cerebrovascular events (NACCE) including MACCE and major bleeding during follow up. Hazard ratios (HR) with 95% confidence intervals were derived from Cox regression analysis. In the unadjusted model (crude) only treatment was included as covariate. In the multivariable model (MV) 34 additional covariates and calendar year were included. | | | |

