# Electronic Supplementary Material

**Table S1.** Diagnosis codes used to identify patients with acute coronary syndrome

| Revision | Category | Diagnosis codes |
|---|---|---|
| ICD-9 CM | Acute myocardial infarction | 410, 410.01, 410.1, 410.11, 410.2, 410.21, 410.3, 410.31, 410.4, 410.41, 410.5, 410.51, 410.8, 410.81, 410.9, 410.91, 410.12, 410.22, 410.32, 410.42, 410.52, 410.82, 410.92 |
| | Other | 410.6, 410.61, 410.7, 410.71, 410.62, 410.72, 411.1, 411.81, 411.89 |
| ICD-10 CM | NSTEMI | I21.4, I22.2 |
| | STEMI | I21.0, I21.01, I21.02, I21.09, I21.1, I21.11, I21.19, I21.2, I21.21, I21.29, I21.3, I22.0, I22.1, I22.8, I22.9 |
| | Unstable angina | I20.0 |

ICD-9 CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; ICD-10 CM, *International Classification of Diseases, Tenth Revision, Clinical Modification*; *NSTEMI* non-ST-elevation myocardial infarction, *STEMI* ST-elevation myocardial infarction.

**Table S2.** Diagnosis codes used to identify hospitalizations for myocardial infarction

| Revision | CCI category | Diagnosis codes |
|---|---|---|
| ICD-9 CM | Myocardial infarction | 410.01; 410.1, 410.11 |
| | | 410.2, 410.21; 410.3, 410.31 |
| | | 410.4, 410.41; 410.5, 410.51 |
| | | 410.6, 410.61; 410.7, 410.71 |
| | | 410.8, 410.81; 410.9, 410.91 |
| ICD-10 CM | Myocardial infarction | I21.0, I21.01, I21.02, I21.09 |
| | | I21.1, I21.11, I21.19 |
| | | I21.2, I21.21, I21.29 |
| | | I21.3 |
| | | I21.4 |

*CCI* Charlson's comorbidity index, ICD-9 CM *International Classification of Diseases, Ninth Revision, Clinical Modification*, ICD-10 CM *International Classification of Diseases, Tenth Revision, Clinical Modification.*

**Table S3.** Diagnosis codes used to identify hospitalizations due to major bleeding

| Revision | CCI category | Diagnosis codes |
|---|---|---|
| ICD-9 CM | Intracranial bleeding | 430, 431, 432, 432.9 |
| | Gastrointestinal | 456, 456.2 |
| | bleeding | 530.2, 531, 531.2, 531.4, 531.6, 532, |
| | | 532.2, 532.4, 532.6, 533, 533.2, 533.4, |
| | | 533.6, 534, 534.2, 534.4, 534.6, 535, |
| | | 568.81, 569.3, 578, 578.1, 578.9 |
| | Pulmonary bleeding | 784.7, 784.8, 786.3 |
| | Urologic bleeding | 581.2, 581.3, 581.9. 599.71, 599.72, |
| | | 599.77 |
| | Other bleeding | 459 |
| | | 998 |
| ICD-10 CM | Intracranial bleeding | I60.0–I60.9, I61.0–I61.6, I61.8, I61.9, |
| | | I62.0, I62.1, I62.9 |
| | Gastrointestinal | I85.0, I98.3 |
| | bleeding | K22.1, K25.0, K25.2, K25.4, K25.6. |
| | | K26.0, K26.2, K26.4, K26.6, K27.0, |
| | | K27.2, K27.4. K27.6, K28.0, K28.2, |
| | | K28.4, K28.6, K29.0, K62.5, K66.1, |
| | | K92.0, K92.1, K92.2 |
| | Pulmonary bleeding | R040, R041, R042, R048, R049 |

| | |
|---|---|
| Urologic bleeding | N02.0–N02.9 |
| | R31.0, R31.1, R31.8 |
| Other bleeding | R58 |
| | T810 |

*CCI* Charlson's comorbidity index, ICD-9 CM *International Classification of Diseases, Ninth Revision, Clinical Modification*, ICD-10 CM *International Classification of Diseases, Tenth Revision, Clinical Modification.*

**Table S4.** Covariates used for propensity score matching

| Category | Covariate |
|---|---|
| Demographics | Age |
| | Gender |
| | Region |
| Procedures | PCI |
| | CABG |
| Diagnoses | Heart failure |
| | Myocardial infarction |
| | Chronic kidney disease |
| | Anemia |
| | Dyslipidemia |
| | Type 2 diabetes |
| | Transient ischemic attack |
| | Atrial fibrillation |
| | Peripheral artery disease |
| | Hypertension |
| | Ischemic stroke |
| | Hospitalization due to major bleeding |
| CCI | CCI score |
| Year of index event | Other |
| Type of index ACS event | Other |

*ACS* acute coronary syndrome, *CABG* coronary artery bypass grafting, *CCI* Charlson's Comorbidity Index, *PCI* percutaneous coronary intervention.

**Table S5.** Results of propensity score matching

| Covariate | Pre-matching | | Post-matching | |
|---|---|---|---|---|
| | Difference[a] | Balance (threshold: < 0.05 is balanced) | Difference[a] | Balance (threshold: < 0.05 is balanced) |
| Age | 0.3362 | *Not balanced* | 0.0134 | Balanced |
| Index date, year | | | | |
| 2012 | 0.1366 | *Not balanced* | −0.0019 | Balanced |
| 2013 | 0.0915 | *Not balanced* | −0.0041 | Balanced |
| 2014 | 0.0613 | *Not balanced* | 0.0020 | Balanced |
| 2015 | 0.0365 | Balanced | −0.0011 | Balanced |
| 2016 | 0.0040 | Balanced | −0.0006 | Balanced |
| 2017 | −0.0827 | *Not balanced* | 0.0040 | Balanced |
| 2018 | −0.1361 | *Not balanced* | −0.0042 | Balanced |
| 2019 | −0.1112 | *Not balanced* | 0.0059 | Balanced |
| Region[b] | | | | |
| Midwest | −0.0074 | Balanced | 0.0025 | Balanced |
| Northeast | 0.0140 | Balanced | −0.0006 | Balanced |
| South | −0.0358 | Balanced | −0.0033 | Balanced |
| West | 0.0289 | Balanced | 0.0012 | Balanced |
| Other | 0.0003 | Balanced | 0.0003 | Balanced |
| Gender | | | | |

| | | | | |
|---|---|---|---|---|
| Female | 0.0687 | Balanced | 0.0034 | Balanced |
| Male | −0.0688 | *Not balanced* | −0.0035 | Balanced |
| Unknown | 0.0002 | *Not balanced* | 0.0001 | Balanced |
| Comorbidity/procedures | | | | |
| HF | 0.0856 | *Not balanced* | 0.0003 | Balanced |
| MI | 0.0240 | Balanced | −0.0005 | Balanced |
| Dyslipidemia | 0.0781 | *Not balanced* | 0.0048 | Balanced |
| PAD | 0.0716 | *Not balanced* | −0.0001 | Balanced |
| CKD | 0.0817 | *Not balanced* | 0.0007 | Balanced |
| TIA | 0.0159 | Balanced | 0.0001 | Balanced |
| T2D | 0.0725 | *Not balanced* | 0.0022 | Balanced |
| Atrial fibrillation | 0.0568 | *Not balanced* | −0.0017 | Balanced |
| Hypertension | 0.1016 | *Not balanced* | 0.0094 | Balanced |
| Ischemic stroke | 0.0200 | Balanced | −0.0002 | Balanced |
| PCI | 0.0085 | Balanced | −0.0011 | Balanced |
| CABG | 0.0099 | Balanced | −0.0001 | Balanced |
| Bleeding | 0.0248 | Balanced | −0.0002 | Balanced |
| Anemia | 0.0954 | *Not balanced* | 0.0035 | Balanced |
| CCI score | 0.3032 | *Not balanced* | 0.0041 | Balanced |
| Index ACS type | | | | |
| NSTEMI | 0.1305 | *Not balanced* | 0.0087 | Balanced |
| UA | 0.0844 | *Not balanced* | −0.003 | Balanced |

| | | | | |
|---|---|---|---|---|
| STEMI | −0.2147 | *Not balanced* | −0.0058 | Balanced |
| UA + NSTEMI | −0.0005 | Balanced | 0.0001 | Balanced |

*ACS* acute coronary syndrome, *CABG* coronary artery bypass grafting, *CCI* Charlson's Comorbidity Index, *CKD* chronic kidney disease, *HF* heart failure, *MI* myocardial infarction, *NSTEMI* non-ST-elevation myocardial infarction, *PAD* peripheral artery disease, *PCI* percutaneous coronary intervention, *STEMI* ST-elevation myocardial infarction, *T2D* type 2 diabetes, *TIA* transient ischemic attack, *UA* unstable angina.

[a]Standardized mean differences for continuous variables; raw differences for categorical variables.

[b]Midwest: Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, North Dakota, Nebraska, Ohio, South Dakota, Wisconsin; Northeast: Connecticut, Massachusetts, Maine, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont; South: Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, West Virginia; West: Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, Wyoming; Other: Puerto Rico, Unknown.

**Figure S1:** Ticagrelor and clopidogrel cohorts i) pre-propensity score matching and ii) post-propensity score matching.

i)
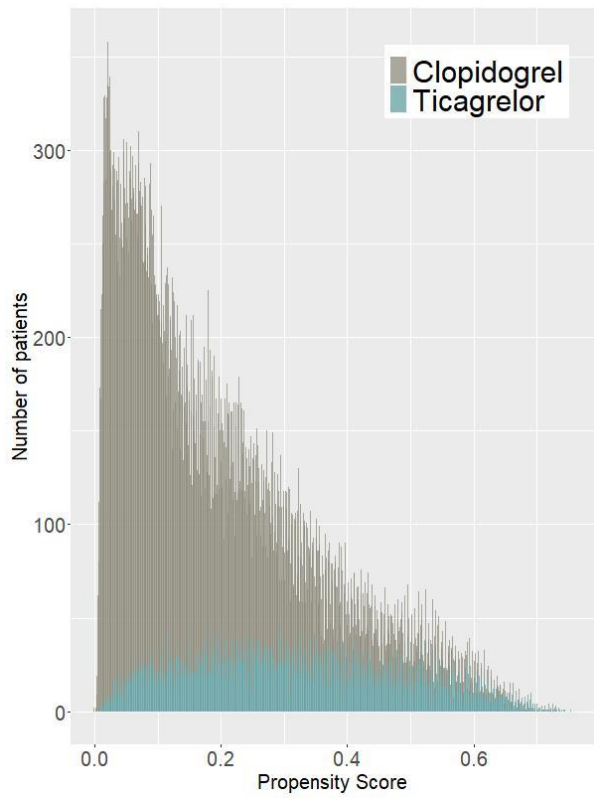
ii)
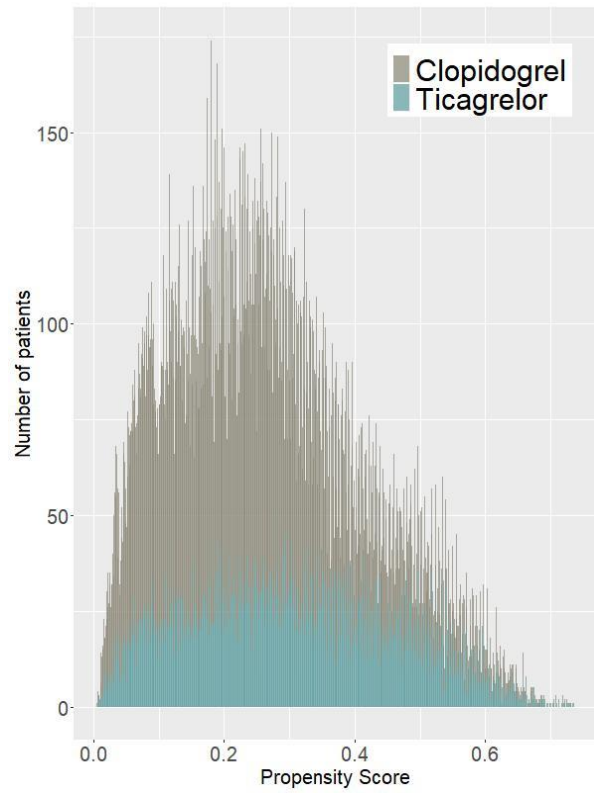
**Sensitivity analyses and propensity score matching by acute coronary syndrome type**

Exact matching was done for acute coronary syndrome (ACS) type at index and whether patients
had a prior history of myocardial infarction (MI) before the index ACS, creating 8 subclasses. Of
these, the largest was patients with non-ST-elevation MI (NSTEMI) who did not have a prior
history of MI (Table S6).

**Table S6.** Exact matching by ACS type at index

| ACS type | Prior MI[a] | Ticagrelor (n = 14,110) | Clopidogrel (n = 57,482) |
|---|---|---|---|
| STEMI | 0 | 6313 | 13,918 |
| STEMI | 1 | 429 | 1205 |
| NSTEMI | 0 | 6001 | 30,318 |
| NSTEMI | 1 | 862 | 5143 |
| UA | 0 | 427 | 6311 |
| UA | 1 | 23 | 371 |
| Other | 0 | 50 | 182 |
| Other | 1 | 5 | 34 |

[a]0 = no; 1 = yes.

*ACS* acute coronary syndrome, *MI* myocardial infarction, *NSTEMI* non-ST-elevation myocardial
infarction, *STEMI* ST-elevation myocardial infarction, *UA* unstable angina.

Optimal full matching was done for subclasses with large enough sample sizes from exact matching, using all remaining covariates. A Cox regression model weighted by the matching weights and including subclasses from the optimal matching as a cluster was used to estimate the marginal hazard ratio (HR) for ticagrelor compared with clopidogrel and its standard error. In 3 of these 5 subclasses, the HR indicated that the risk of hospitalization for MI was lower with ticagrelor compared with clopidogrel (Table S7). However, this was statistically significant only for the largest subclass, patients with NSTEMI and no prior history of MI at the time of the index ACS event. Although the risk of hospitalization for MI appeared to be higher for ticagrelor compared with clopidogrel in the subclass of patients with ST-elevation myocardial infarction who had a prior history of MI before the index ACS, this subclass was small and the difference was not statistically significant.

**Table S7.** Hospitalization for MI in ticagrelor and clopidogrel cohort subclasses following optimal full matching for ACS

| ACS type | Prior MI[a] | Ticagrelor (n = 14,110) | Clopidogrel (n = 57,482) | HR[b] | Robust SE | p-value |
|---|---|---|---|---|---|---|
| STEMI | 0 | 6313 | 13,918 | 0.80 | 0.21 | 0.30 |
| STEMI | 1 | 429 | 1205 | 1.59 | 0.63 | 0.46 |
| NSTEMI | 0 | 6001 | 30,318 | 0.70 | 0.16 | **0.03** |
| NSTEMI | 1 | 862 | 5143 | 0.62 | 0.35 | 0.18 |
| UA | 0 | 427 | 6311 | 1.00 | 0.70 | 1.00 |

Bold text indicates statistical significance.

[a]0 = no; 1 = yes.

[b]HR < 1.0 indicates lower risk with ticagrelor.

*ACS* acute coronary syndrome, *HR* hazard ratio, *MI* myocardial infarction, *NSTEMI* non-ST-elevation myocardial infarction, *SE* standard error, *STEMI* ST-elevation myocardial infarction, *UA* unstable angina.

**Figure S2.** Hospitalization for (i) myocardial infarction and (ii) major bleeding in pre-propensity score matching cohorts.
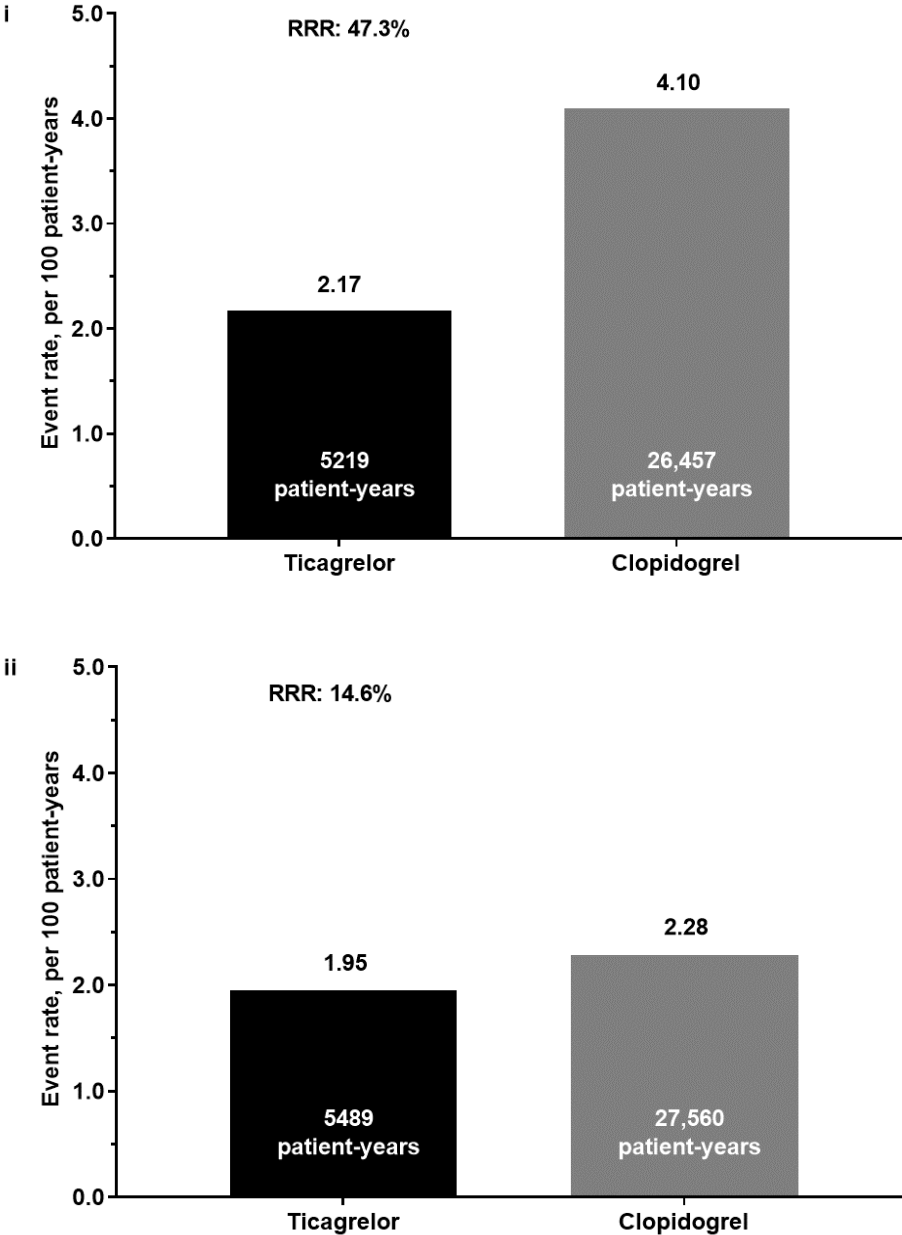
*RRR* relative risk reduction.

**Table S8.** Hospitalization for myocardial infarction in patient subgroups (post-propensity score matching)

|  | Ticagrelor | Clopidogrel |
| --- | --- | --- |
| All patients |  |  |
|     Event rate per 100 patient-years | 2.22 | 3.52 |
|     Patient-years | 4945 | 13,895 |
|     Relative rate reduction versus clopidogrel, % | 36.8* | – |
| Age, years |  |  |
|   $\geq 65$ |  |  |
|     Event rate per 100 patient-years | 2.71 | 4.15 |
|     Patient-years | 2801 | 8961 |
|     Relative rate reduction versus clopidogrel, % | 34.7† | – |
|   $< 65$ |  |  |
|     Event rate per 100 patient-years | 1.65 | 2.24 |
|     Patient-years | 2115 | 4862 |
|     Relative rate reduction versus clopidogrel, % | 26.2 | – |

PCI for index ACS event

  PCI

    Event rate per 100 patient-years      1.99                 2.95

    Patient-years      4263                 11,239

    Relative rate reduction versus clopidogrel, %      32.5‡                 –

  No PCI

    Event rate per 100 patient-years      4.64                 5.20

    Patient-years      518                 1848

    Relative rate reduction versus clopidogrel, %      10.8                 –

History of T2D diagnosis

  T2D

    Event rate per 100 patient-years      4.47                 5.75

    Patient-years      1478                 4643

    Relative rate reduction versus clopidogrel, %      22.3                 –

  No T2D

| | | |
|---|---|---|
| Event rate per 100 patient-years | 1.24 | 2.35 |
| Patient-years | 3463 | 9244 |
| Relative rate reduction versus clopidogrel, % | 47.1* | – |

History of CKD diagnosis

 CKD

| | | |
|---|---|---|
| Event rate per 100 patient-years | 5.26 | 6.65 |
| Patient-years | 475 | 1638 |
| Relative rate reduction versus clopidogrel, % | 20.9 | – |

 No CKD

| | | |
|---|---|---|
| Event rate per 100 patient-years | 1.92 | 3.07 |
| Patient-years | 4488 | 12,159 |
| Relative rate reduction versus clopidogrel, % | 37.5§ | – |

*ACS* acute coronary syndrome, *CKD* chronic kidney disease (stage 1–5), *PCI* percutaneous coronary intervention, *T2D* type 2 diabetes.

* $P < 0.0001$; † $P = 0.0005$; ‡ $P = 0.0009$; § $P=0.0001$.

**Table S9.** Hospitalization for myocardial infarction in patient subgroups (pre-propensity score matching)

|  | Ticagrelor | Clopidogrel |
|---|---|---|
| All patients |  |  |
| Event rate per 100 patient-years | 2.17 | 4.10 |
| Patient-years | 5219 | 26,457 |
| Relative rate reduction versus clopidogrel, % | 47.3 | – |
| Age, years |  |  |
| ≥ 65 |  |  |
| Event rate per 100 patient-years | 2.71 | 4.84 |
| Patient-years | 2840 | 18,373 |
| Relative rate reduction versus clopidogrel, % | 44.0 | – |
| < 65 |  |  |
| Event rate per 100 patient-years | 1.51 | 2.43 |
| Patient-years | 2377 | 8054 |
| Relative rate reduction versus clopidogrel, % | 37.8 | – |

### PCI for index ACS

#### PCI

| | | |
|---|---|---|
| Event rate per 100 patient-years | 1.90 | 3.13 |
| Patient-years | 4680 | 17,401 |
| Relative rate reduction versus clopidogrel, % | 39.2 | – |

#### No PCI

| | | |
|---|---|---|
| Event rate per 100 patient-years | 4.43 | 6.02 |
| Patient-years | 541 | 9006 |
| Relative rate reduction versus clopidogrel, % | 26.3 | – |

### History of T2D diagnosis

#### T2D

| | | |
|---|---|---|
| Event rate per 100 patient-years | 4.46 | 6.42 |
| Patient-years | 1525 | 9670 |
| Relative rate reduction versus clopidogrel, % | 30.6 | – |

#### No T2D

| | | |
|---|---|---|
| Event rate per 100 patient-years | 1.22 | 2.77 |
| Patient-years | 3684 | 16,783 |
| Relative rate reduction versus clopidogrel, % | 55.9 | – |

History of CKD diagnosis

  CKD

| | | |
|---|---|---|
| Event rate per 100 patient-years | 5.04 | 7.63 |
| Patient-years | 496 | 3839 |
| Relative rate reduction versus clopidogrel, % | 34.0 | – |

  No CKD

| | | |
|---|---|---|
| Event rate per 100 patient-years | 1.86 | 3.59 |
| Patient-years | 4734 | 22,626 |
| Relative rate reduction versus clopidogrel, % | 47.0 | – |

*ACS* acute coronary syndrome, *CKD* chronic kidney disease (stage 1–5), *PCI* percutaneous coronary intervention, *T2D* type 2 diabetes.

**Figure S3.** Hospitalization for major bleeding in patient subgroups post-propensity score matching.

*ACS* acute coronary syndrome, *CKD* chronic kidney disease (stage 1–5), *PCI* percutaneous coronary intervention, *RRR* relative risk reduction, *T2D* type 2 diabetes.
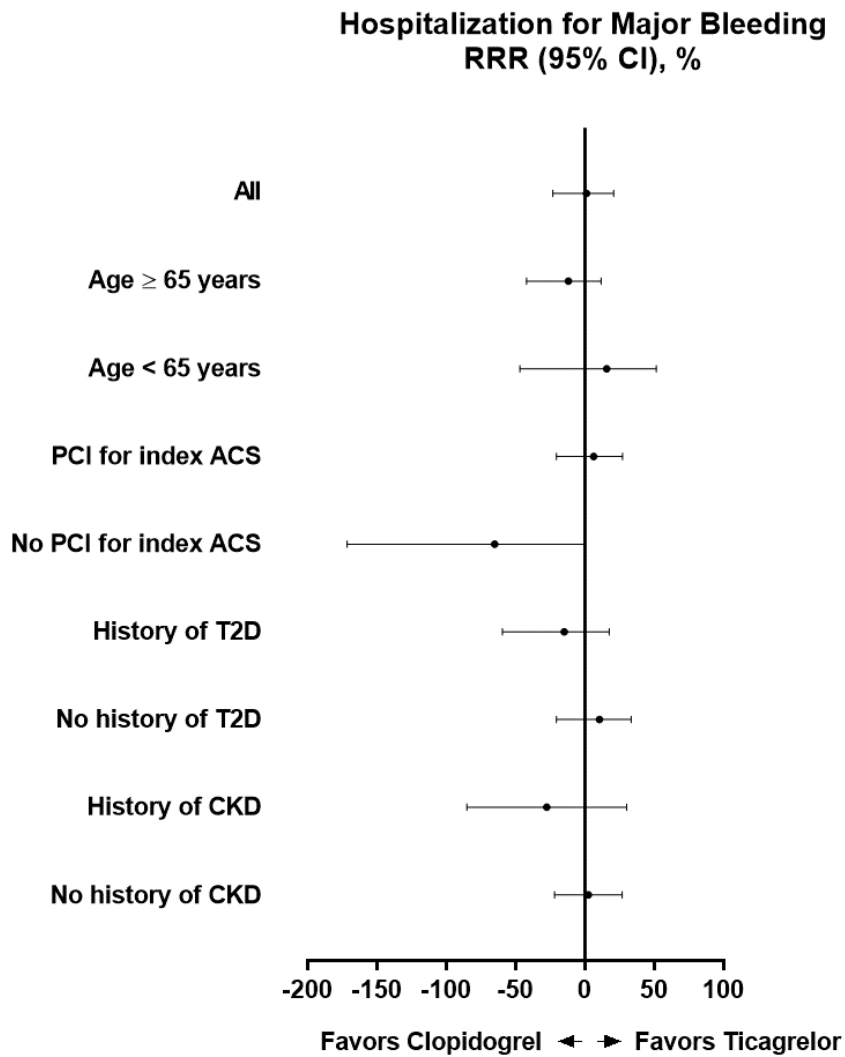
**Table S10.** Hospitalization for major bleeding in patient subgroups (post-propensity score matching)

| | Ticagrelor | Clopidogrel |
|---|---|---|
| All patients | | |
| Event rate per 100 patient-years | 2.04 | 2.06 |
| Patient-years | 5202 | 14,646 |
| Relative rate reduction versus clopidogrel, % | 1.1 | – |
| Age, years | | |
| ≥ 65 | | |
| Event rate per 100 patient-years | 3.02 | 2.70 |
| Patient-years | 2951 | 9321 |
| Relative rate reduction versus clopidogrel, % | −12.0 | – |
| < 65 | | |
| Event rate per 100 patient-years | 0.77 | 0.91 |
| Patient-years | 2220 | 5068 |
| Relative rate reduction versus clopidogrel, % | 15.7 | – |

| | | |
|---|---|---|
| **PCI for index ACS** | | |
| PCI | | |
| Event rate per 100 patient-years | 1.81 | 1.91 |
| Patient-years | 4479 | 11,662 |
| Relative rate reduction versus clopidogrel, % | 6.3 | – |
| No PCI | | |
| Event rate per 100 patient-years | 4.01 | 2.43 |
| Patient-years | 549 | 1936 |
| Relative rate reduction versus clopidogrel, % | −65.0* | – |
| **History of T2D diagnosis** | | |
| T2D | | |
| Event rate per 100 patient-years | 3.01 | 2.62 |
| Patient-years | 1564 | 4851 |
| Relative rate reduction versus clopidogrel, % | −14.8 | – |
| No T2D | | |
| Event rate per 100 patient-years | 1.60 | 1.78 |
| Patient-years | 3633 | 9603 |

| | | |
|---|---|---|
| Relative rate reduction versus clopidogrel, % | 10.3 | – |

History of CKD diagnosis

CKD

| | | |
|---|---|---|
| Event rate per 100 patient-years | 4.58 | 3.86 |
| Patient-years | 502 | 1711 |
| Relative rate reduction versus clopidogrel, % | −18.8 | – |

No CKD

| | | |
|---|---|---|
| Event rate per 100 patient-years | 1.70 | 1.78 |
| Patient-years | 4714 | 12,648 |
| Relative rate reduction versus clopidogrel, % | 4.6 | – |

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*ACS* acute coronary syndrome, *CKD* chronic kidney disease (stage 1–5), *PCI* percutaneous coronary intervention, *T2D* type 2 diabetes.

\* $P = 0.0467$.

**Table S11.** Hospitalization for major bleeding in patient subgroups (pre-propensity score matching)

|  | Ticagrelor | Clopidogrel |
| --- | --- | --- |
| All patients |  |  |
|    Event rate per 100 patient-years | 1.95 | 2.28 |
|    Patient-years | 5489 | 27,560 |
|    Relative rate reduction versus clopidogrel, % | 14.6% | – |
| Age, years |  |  |
|   ≥ 65 |  |  |
|    Event rate per 100 patient-years | 2.98 | 2.88 |
|    Patient-years | 2991 | 19,130 |
|    Relative rate reduction versus clopidogrel, % | −3.5 | – |
|   < 65 |  |  |
|    Event rate per 100 patient-years | 0.72 | 0.94 |
|    Patient-years | 2496 | 8399 |
|    Relative rate reduction versus clopidogrel, % | 23.3 | – |

PCI for index ACS

  PCI

| | | |
|---|---|---|
| Event rate per 100 patient-years | 1.73 | 2.05 |
| Patient-years | 4917 | 18,060 |
| Relative rate reduction versus clopidogrel, % | 15.6 | – |

  No PCI

| | | |
|---|---|---|
| Event rate per 100 patient-years | 3.83 | 2.74 |
| Patient-years | 575 | 9450 |
| Relative rate reduction versus clopidogrel, % | −39.7 | – |

History of T2D diagnosis

  T2D

| | | |
|---|---|---|
| Event rate per 100 patient-years | 2.97 | 2.78 |
| Patient-years | 1614 | 10,112 |
| Relative rate reduction versus clopidogrel, % | −7.0 | – |

  No T2D

| | | |
|---|---|---|
| Event rate per 100 patient-years | 1.53 | 2.00 |
| Patient-years | 3866 | 17,443 |
| Relative rate reduction versus clopidogrel, % | 23.5 | – |

History of CKD diagnosis

CKD

| | | |
|---|---|---|
| Event rate per 100 patient-years | 4.56 | 3.95 |
| Patient-years | 526 | 4021 |
| Relative rate reduction versus clopidogrel | −15.3 | – |

No CKD

| | | |
|---|---|---|
| Event rate per 100 patient-years | 1.67 | 2.00 |
| Patient-years | 4974 | 23,547 |
| Relative rate reduction versus clopidogrel, % | 16.4 | – |

*ACS* acute coronary syndrome, *CKD* chronic kidney disease (stage 1–5), *PCI* percutaneous coronary intervention, *T2D* type 2 diabetes.