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# Comparison of P<sub>2</sub>Y<sub>12</sub> receptor inhibitors in patients with ST-elevation myocardial infarction in clinical practice: a propensity score analysis of five contemporary European registries

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## Aims

Among acute coronary syndromes (ACS), ST-segment elevation myocardial infarction (STEMI) has the most severe early clinical course. Recent randomized clinical trials have demonstrated that novel antithrombotic therapies improve in-hospital outcomes in STEMI patients. We aimed to describe the effectiveness and safety of P<sub>2</sub>Y<sub>12</sub> receptor inhibitors in clinical practice in patients with STEMI based on data from contemporary European ACS registries.

## Methods and results

Five registries from the PIRAEUS initiative (AAPCI/ADPAT, ALKK-PIC, AMIS Plus, Belgium STEMI, and EYESHOT) provided data for the assessment of P<sub>2</sub>Y<sub>12</sub> receptor inhibitor-based dual antiplatelet therapy. Registries were heterogeneous in terms of setting, patient characteristics, and treatment selection. Matched pair analysis and propensity score matching were used to assess all-cause in-hospital death rates based on data from 25 250 patients (8577 patients on prasugrel, 5995 on ticagrelor, and 10 678 on clopidogrel). The odds ratio (OR) for the death of any cause when compared with clopidogrel was 0.72 [95% confidence interval (CI) 0.62–0.84, *P* < 0.001] in favour of the new P<sub>2</sub>Y<sub>12</sub> receptor inhibitors (prasugrel and ticagrelor combined). In the comparison between prasugrel and ticagrelor, there were no relevant differences (OR 0.97, 95% CI 0.77–1.23; *P* = 0.81). Event rates of cardiovascular death and stroke were also substantially lower for the new P<sub>2</sub>Y<sub>12</sub> receptor inhibitors. The differences between clopidogrel and prasugrel or ticagrelor on major bleeding were numerically in the same order as for death of any cause but were not statistically significant. No differences in ischaemic and bleeding outcomes were observed between prasugrel and ticagrelor.

## Conclusion

This analysis suggests that the prasugrel or ticagrelor compared with clopidogrel have favourable outcomes in clinical practice while not being inferior in terms of safety.

## Keywords

Effectiveness • Safety • Acute coronary syndromes • ST-segment elevation myocardial infarction • Antiplatelet agents • P<sub>2</sub>Y<sub>12</sub> receptor inhibitors • Clopidogrel • Prasugrel • Ticagrelor • Propensity score matching • Real-world evidence

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## Introduction

Contemporary European Society of Cardiology (ESC) guidelines highlight the benefit of dual antiplatelet therapy (DAPT) consisting of acetylic salicylic acid (ASA) plus one of the P<sub>2</sub>Y<sub>12</sub> receptor inhibitors, i.e. clopidogrel with a preference for prasugrel, or ticagrelor, with the aim to reduce the risk of both acute ischaemic complications and recurrent atherothrombotic events.<sup>1,2</sup> Based on their higher antithrombotic potency and proven superiority in outcome trials, prasugrel and ticagrelor are given preference over clopidogrel.<sup>1,2</sup> Recently, a direct comparison of ticagrelor and prasugrel suggested superiority of the latter compared with the former.<sup>3</sup>

Although prior studies have compared prasugrel or ticagrelor with clopidogrel in a real-world setting, a head-to-head comparison between the three available antiplatelet agents have never been performed.

We aimed to investigate whether in real-world practice, the newer P<sub>2</sub>Y<sub>12</sub> inhibitors prasugrel and ticagrelor are indeed superior to clopidogrel. We used the 'Platelet Inhibition Registry in ACS Evaluation Study' (PIRAEUS) platform which was initiated in 2014 to integrate data generated by individual European registries on acute coronary syndromes (ACS) to gain a comprehensive overview on the effectiveness and safety of the P<sub>2</sub>Y<sub>12</sub> receptor inhibitors.<sup>4</sup> The participating registries have been described in narrative and tabular form in detail in an earlier review of this group,<sup>4</sup> and the non-ST-elevation myocardial infarction (NSTEMI)<sup>5</sup> and ST-segment elevation myocardial infarction (STEMI) cohorts.<sup>6</sup>

This study presents data on STEMI patients from five European registries, with a focus on effectiveness (all-cause deaths) and safety (bleeding) for P<sub>2</sub>Y<sub>12</sub> receptor inhibitor-based DAPT specifically. In the assessment of effectiveness and safety endpoints, to account for differences in patient composition, a matched pair strategy and propensity scoring was used.

## Methods

The original PIRAEUS data set consists of 12 ACS registries and studies which are heterogenous in terms of setting, duration, documented variables, and endpoints.<sup>4</sup> The criteria to select suitable registries were as follows: European multicentre or single-centre observational studies on real-life experience in the management of ACS within the last 5 years; large unselected STEMI patient cohorts; data on percutaneous coronary intervention (PCI); data on management during initial hospitalization for ACS available; information on specific P<sub>2</sub>Y<sub>12</sub> inhibitor treatment pre-cath or in-cath lab; follow-up data on outcomes (death, cardiac events, and bleedings) available; and willingness of registry owners to share data. Five registries met the criteria: AMIS Plus, Belgium STEMI, ALKK-PCI, APCI/ADAPT, and EYESHOT. A description of these registries that provided STEMI data has been provided previously.<sup>6</sup>

All participating registries were national projects. Two were a running registry with no specified stop date for inclusion of patients (AMIS Plus and Belgium STEMI database), while the others included cohorts of patients within a defined time frame.

Registry owners were asked to provide detailed current data on STEMI patients treated with the P<sub>2</sub>Y<sub>12</sub> receptor inhibitors prasugrel, ticagrelor, or clopidogrel. While the registries collected individual patient data prospectively, for the purpose of this analysis, aggregate data in tabular format were used. Endpoints of interest comprised in-hospital events,

such as all-cause death, cardiovascular (CV) death, stroke, recurrent myocardial infarction (MI), and repeat percutaneous coronary intervention (PCI) for effectiveness, and life-threatening/major and minor bleeding. For bleeding events, the definition (e.g. BARC) was requested from the registry owners but was not always available or sometimes changed during the registry data collection. Registry owners were asked to provide percentages for the various events together with event number and patient number at the various time points.

## Statistical analysis

Patients who received either new P<sub>2</sub>Y<sub>12</sub> receptor inhibitors (prasugrel and ticagrelor combined) or clopidogrel during pre-cath or in-cath treatment were included in the analysis. Patients administered more than one kind of P<sub>2</sub>Y<sub>12</sub> receptor inhibitors during pre-cath or in-cath treatment were excluded from the event analysis.

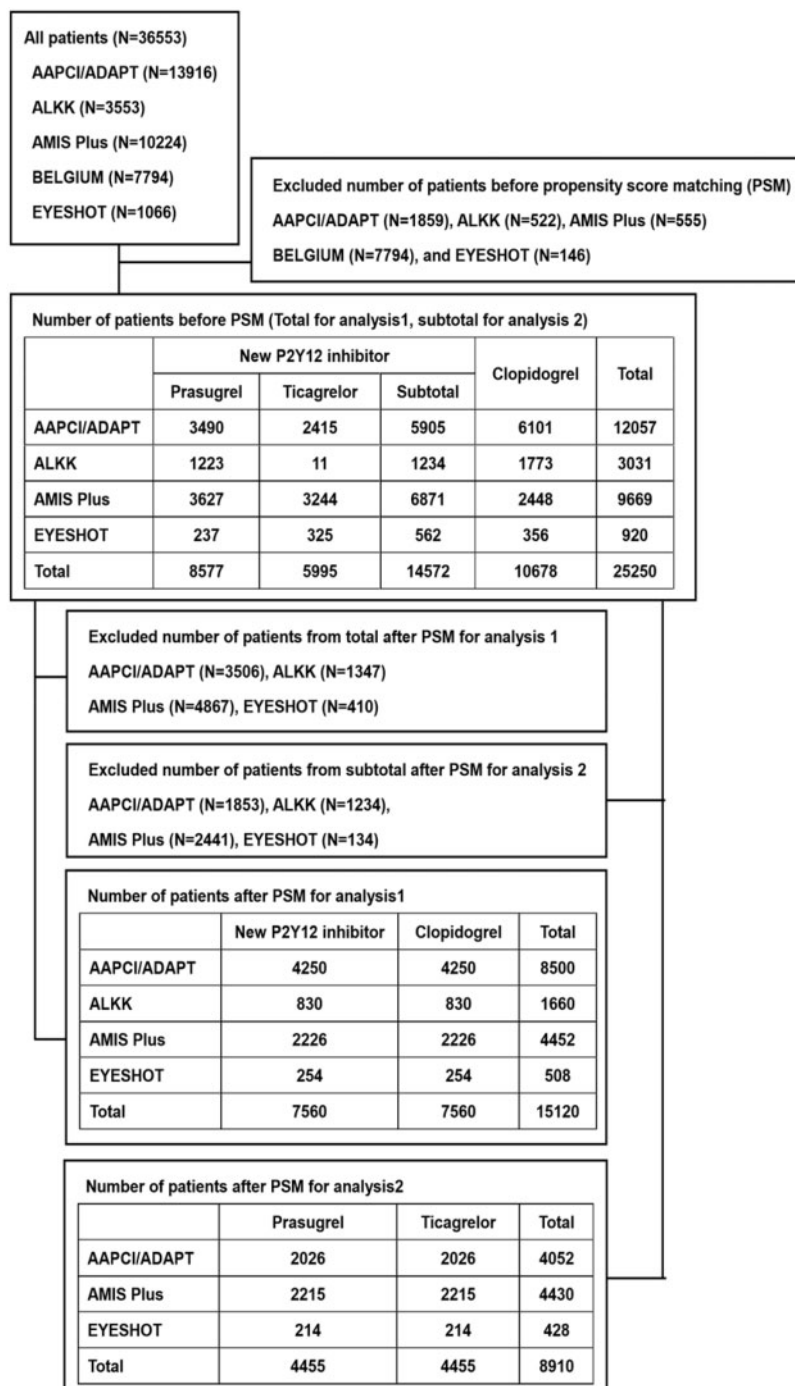
Propensity score matching<sup>7</sup> of new P<sub>2</sub>Y<sub>12</sub> receptor inhibitors and clopidogrel was based on one-to-one matching without replacement stratified by registry. The propensity score was estimated using logistic regression on a study-by-study basis including the following 24 baseline covariates: age, gender, diabetes mellitus, heart failure, atrial fibrillation, prior MI, previous stroke/transient ischaemic attack (TIA), previous coronary artery bypass grafting (CABG), arterial hypertension, peripheral arterial disease, hypercholesterolaemia, current smoking, chronic kidney disease, Killip class >2, chronic ASA, chronic P<sub>2</sub>Y<sub>12</sub> receptor inhibitors, chronic oral anticoagulation, multivessel disease, >1 stent implanted, and pre-cath or in-cath lab treatments [glycoprotein IIb/IIIa inhibitors (GPI), unfractionated heparin, low molecular weight heparin (LMWH), and bivalirudin]. The estimated propensity score was the predicted probability of treated new P<sub>2</sub>Y<sub>12</sub> receptor inhibitor from the logistic regression model. A greedy, nearest-neighbour matching algorithm was employed to match patients on the logit of the propensity score using calipers of width equal to 0.1 of the propensity score logit. The balance in baseline characteristics between matched patients was assessed by standardized differences.<sup>8</sup> Odds ratio (OR) and 95% confidence interval (CI) of new P<sub>2</sub>Y<sub>12</sub> receptor inhibitors group compared with clopidogrel group on in-hospital events was estimated using the conditional logistic regression model stratified by matched pairs (Analysis 1). In-hospital death, CV death, stroke/TIA, and any major bleeding [intracranial haemorrhage (ICH), fatal bleeding, or Thrombolysis in Myocardial Infarction (TIMI) major bleeding] were used as the outcome variables in the event analysis. Propensity score-matched analyses to compare between prasugrel and ticagrelor were done by using similar models (Analysis 2).

Means and standard deviation were calculated for continuous variables, and percentages were calculated for categorical variables based on the total number of patients excluding missing and unknown data. Statistical significance level was considered as two-sided *P*-value of 5%. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) software.

## Results

### Patient disposition

We collected data on a total of 36 553 STEMI patients. The sample size between registries varied considerably (from *n* = 1066 in EYESHOT to *n* = 13 916 in AAPCI/ADAPT). Of these, a total of 25 250 patients met the inclusion criteria for in-hospital event analysis (see Methods section) before matching patients. No patient in the BELGIUM STEMI registry met the inclusion criteria, because antiplatelet therapies during pre-cath or in-cath treatment were not



**Figure 1** Patient disposition.

recorded in the registry (only antiplatelet therapy at discharge). After matching patients, a total of 15 120 patients (Analysis 1) and 8910 (Analysis 2) were included in the in-hospital event analysis (Figure 1).

Risk factors and comorbidities by registry are shown in Table 1. In all registries, the proportion of males (range 72.0–76.0%) was higher than of females. Mean age ranged between 62.5 and 66.0 years. Comorbidities were frequent, in particular, arterial hypertension

(range 39.5–70.9%), hypercholesterolaemia (range 31.0–58.9%), and diabetes mellitus (range 16.4–22.4%). Prior MI was reported in 10.1–20.1% and current smoking in 38.5–47.9%.

ST-elevation MI characteristics and pre-treatment are shown in Table 2. The STEMI location was slightly more often in the inferior artery (range 49.8–57.4%) compared with the anterior (41.6–44.3%). Killip Class I prevailed (66.4–85.7%). Chronic pre-treatment was

**Table 1** Baseline characteristics: risk factors and comorbidities

| Registry acronym                      | AAPCI/ADAPT          | ALKK             | AMIS Plus          | BELGIUM          | EYESHOT         |
|---------------------------------------|----------------------|------------------|--------------------|------------------|-----------------|
| Patient number, n                     | 13 916               | 3553             | 10 224             | 7794             | 1066            |
| Year of enrollment, n (%)             | 13 916               | 3553             | 10 224             | 7794             | 1066            |
| Before 2009                           | 1640 (11.8)          | 104 (2.9)        | 0 (0.0)            | 0 (0.0)          | 0 (0.0)         |
| 2010                                  | 1359 (9.8)           | 1061 (29.9)      | 0 (0.0)            | 0 (0.0)          | 0 (0.0)         |
| 2011                                  | 1889 (13.6)          | 1284 (36.1)      | 1461 (14.3)        | 0 (0.0)          | 0 (0.0)         |
| 2012                                  | 1822 (13.1)          | 1104 (31.1)      | 1786 (17.5)        | 0 (0.0)          | 0 (0.0)         |
| 2013                                  | 1770 (12.7)          | 0 (0.0)          | 1966 (19.2)        | 0 (0.0)          | 844 (79.2)      |
| 2014                                  | 1392 (10.0)          | 0 (0.0)          | 1837 (18.0)        | 1133 (14.5)      | 222 (20.8)      |
| 2015                                  | 1393 (10.0)          | 0 (0.0)          | 1499 (14.7)        | 2685 (34.4)      | 0 (0.0)         |
| 2016                                  | 1137 (8.2)           | 0 (0.0)          | 1202 (11.8)        | 2482 (31.8)      | 0 (0.0)         |
| After 2017                            | 1514 (10.9)          | 0 (0.0)          | 473 (4.6)          | 1494 (19.2)      | 0 (0.0)         |
| Age (years), mean (SD)                | 62.5 (13.1)          | 62.7 (13.0)      | 64.2 (12.8)        | 63.3 (13.1)      | 66.0 (13.1)     |
| Age >75 years, n (%)                  | 2860/13 916 (20.6)   | 754/3553 (21.2)  | 2352/10 224 (23.0) | 1718/7794 (22.0) | 308/1066 (28.9) |
| Risk factors and comorbidities, n (%) |                      |                  |                    |                  |                 |
| Males                                 | 10 177/13 916 (73.1) | 2641/3553 (74.3) | 7770/10 224 (76.0) | 5891/7766 (75.9) | 767/1066 (72.0) |
| Diabetes mellitus                     | 2065/11 875 (17.4)   | 746/3330 (22.4)  | 1659/9799 (16.9)   | 1269/7717 (16.4) | 223/1041 (21.4) |
| Heart failure                         | 284/2108 (13.5)      | 387/3521 (11.0)  | 147/8880 (1.7)     | NA               | 13/1064 (1.2)   |
| Atrial fibrillation                   | 971/10 949 (8.9)     | 77/1048 (7.3)    | 343/9077 (3.8)     | NA               | NA              |
| Prior myocardial infarction           | 1294/12 766 (10.1)   | 688/3422 (20.1)  | 1220/9998 (12.2)   | 1200/7714 (15.6) | 121/1058 (11.4) |
| Previous stroke/TIA                   | 394/12 155 (3.2)     | 140/3290 (4.3)   | 386/10 027 (3.8)   | NA               | 56/1056 (5.3)   |
| Previous PCI                          | 1642/12 956 (12.7)   | 533/3457 (15.4)  | 1328/10 000 (13.3) | NA               | 107/1063 (10.1) |
| Previous CABG                         | NA                   | 125/3508 (3.6)   | 281/10 000 (2.8)   | NA               | 24/1064 (2.3)   |
| Arterial hypertension                 | 1395/3528 (39.5)     | 2232/3150 (70.9) | 5407/9750 (55.5)   | 3673/7719 (47.6) | 620/1029 (60.3) |
| Peripheral arterial disease           | 122/3528 (3.5)       | 159/3252 (4.9)   | 380/10 027 (3.8)   | 552/7710 (7.2)   | 93/1019 (9.1)   |
| Hypercholesterolaemia                 | 1093/3528 (31.0)     | 1283/2768 (46.4) | 5453/9261 (58.9)   | 3813/7160 (53.3) | 381/921 (41.4)  |
| Current smoking                       | 5461/12 467 (43.8)   | 1457/3040 (47.9) | 4124/9171 (45.0)   | 2974/7169 (41.5) | 405/1053 (38.5) |
| Chronic kidney disease                | 2050/11 834 (17.3)   | 373/3285 (11.4)  | 455/10 028 (4.5)   | 607/7158 (8.5)   | 90/1036 (8.7)   |

Percentages are based on the total number of patients excluding missing and unknown data. For BELGIUM, prior MI includes prior PCI and CABG. CKD is defined as either serum creatinine >1.5 mg/dL or eGFR <60 mL/m<sup>2</sup>. For AAPCI-ADAPT, prior PCI includes prior CABG. CABG, coronary artery bypass grafting; NA, not applicable; TIA, transient ischaemic attack.

reported for ASA in 20.0–28.7%, clopidogrel in 3.1–10.9%, prasugrel in 0.6–4.4%, and P<sub>2</sub>Y<sub>12</sub> overall in 3.8–15.4%. Chronic pre-treatment with anticoagulation was noted in 3.8–11.6%.

Information on the timing and in-hospital management are given in [Supplementary material online, Table S1](#). The timing from first medical contact to PCI was 79–101 min. Coronary angiography was performed in 94.0–100.0%.

Pre-cath and in-cath lab treatment are presented in [Supplementary material online, Table S2](#). The information on pre-cath lab treatment was available for AAPCI/ADPAT, AMIS Plus, and EYESHOT. In these registries, ASA was given in 77.0–96.6%, clopidogrel in 28.8–46.7%, prasugrel in 18.0–21.9%, and ticagrelor in 16.7–24.5%. In-cath lab treatment was available for AAPCI/ADAPT, ALKK, and EYESHOT. Acetylic salicylic acid was routinely used in ALKK (93.0%), and rarely in EYESHOT (13.0%) and AAPCI/ADAPT (0.1%). Clopidogrel use ranged between 10.8% and 60.2%, prasugrel between 8.8% and 43.5%, and ticagrelor between 2.1% and 20.6%.

[Table 3](#) displays discharge treatments, which were based on ASA (96.9–99.3%), and also included clopidogrel (10.7–48.1%), prasugrel (24.4–31.3%), and ticagrelor (20.6–64.9%).

Data on in-hospital events are presented in [Table 3](#) bottom. Data on death were available in all registries and ranged from 3.5% to 7%, data on CV death from AAPCI/ADAPT, AMIS Plus, and EYESHOT ranging from 1.9% to 3.5%. Stroke/TIA was reported in 0.3–0.8%. Information on bleeding, depending on the definition, was heterogeneous: fatal bleeding as reported in AMIS Plus and EYESHOT was 0.1% each, TIMI major bleeding in AAPCI/ADPAT and EYESHOT was 0.9% and 1.3%. Urgent revascularization in AAPCI/ADPAT and EYESHOT was 0.8% and 1.1%, respectively.

### Event analysis before matching patients

Baseline patient characteristics in all registries before matching patients were widely different between new P<sub>2</sub>Y<sub>12</sub> receptor inhibitor (prasugrel and ticagrelor combined) and clopidogrel. After matching patients, these imbalances were largely improved and the standardized differences in most of the patient characteristics in each registry were within 10% ([Supplementary material online, Tables S1-1–S1-4 and S2-1–S2-4](#)). It was not possible to match patients in ALKK-PCI for Analysis 2 due to small number of patients who received ticagrelor.

**Table 2** Information on STEMI at admission and pre-treatment

| Registry acronym  | AAPCI/ADAPT        | ALKK            | AMIS Plus        | BELGIUM         | EYESHOT         |
|---|--------------------|-----------------|------------------|-----------------|-----------------|
| Patient number, <i>n</i>                                  | 13 916             | 3553            | 10 224           | 7794            | 1066            |
| Admission   |                    |                 |                  |                 |                 |
| Rhythm at ECG, <i>n</i> (%)                               | 12 318             |                 | 9077             | .               | 1053            |
| Sinus rhythm  | 11 098 (90.1)      | NA              | 8310 (91.6)      | NA              | 980 (93.1)      |
| Atrial fibrillation                                       | 945 (7.7)          | NA              | 343 (3.8)        | NA              | 56 (5.3)        |
| Others  | 275 (2.2)          | NA              | 424 (4.7)        | NA              | 17 (1.6)        |
| STEMI location, <i>n</i> (%)                              | 13 914             | .               | 10 178           | 7747            | 1066            |
| Inferior  | 6935 (49.8)        | NA              | 5291 (52.0)      | 4449 (57.4)     | 584 (54.8)      |
| Anterior  | 6166 (44.3)        | NA              | 4288 (42.1)      | 3224 (41.6)     | 467 (43.8)      |
| Undetermined  | 813 (5.8)          | NA              | 599 (5.9)        | 74 (1.0)        | 15 (1.4)        |
| Killip class, <i>n</i> (%)                                | 10 801             | .               | 10 164           | 7681            | 1031            |
| I   | 7176 (66.4)        | NA              | 8706 (85.7)      | 6246 (81.3)     | 811 (78.7)      |
| II  | 2123 (19.7)        | NA              | 722 (7.1)        | 662 (8.6)       | 151 (14.6)      |
| III   | 616 (5.7)          | NA              | 238 (2.3)        | 214 (2.8)       | 31 (3.0)        |
| IV  | 886 (8.2)          | NA              | 498 (4.9)        | 559 (7.3)       | 38 (3.7)        |
| Killip class >2, <i>n</i> (%)                             | 1502/10 801 (13.9) | NA              | 736/10 164 (7.2) | 773/7681 (10.1) | 69/1031 (6.7)   |
| Pre-treatment, <i>n</i> (%)                               |                    |                 |                  |                 |                 |
| Chronic ASA   | 579/2893 (20.0)    | 520/2276 (22.8) | 2466/8595 (28.7) | NA              | 243/1048 (23.2) |
| Chronic clopidogrel                                       | 88/2864 (3.1)      | 389/3553 (10.9) | 359/8462 (4.2)   | NA              | 35/1055 (3.3)   |
| Chronic prasugrel   | 17/2899 (0.6)      | 156/3553 (4.4)  | 77/8423 (0.9)    | NA              | 4/1056 (0.4)    |
| Chronic ticagrelor  | 10/2815 (0.4)      | 1/1069 (0.1)    | 64/6972 (0.9)    | NA              | 8/1057 (0.8)    |
| Chronic P <sub>2</sub> Y <sub>12</sub> receptor inhibitor | 115/3026 (3.8)     | 546/3553 (15.4) | 499/8489 (5.9)   | NA              | 47/1057 (4.4)   |
| Chronic oral anticoagulation                              | 110/2862 (3.8)     | 46/1104 (4.2)   | 1015/8719 (11.6) | NA              | 33/1057 (3.1)   |
| Vital sign  |                    |                 |                  |                 |                 |
| SBP   |                    |                 |                  |                 |                 |
| <i>n</i>  | 10 626             |                 | 9864             | 4090            | 1066            |
| Mean (SD)   | 133.0 (29.2)       | NA              | 131.8 (27.6)     | 131.0 (30.7)    | 130.6 (25.2)    |
| DBP   |                    |                 |                  |                 |                 |
| <i>n</i>  | 10 386             |                 | 9851             | 4110            | 1066            |
| Mean (SD)   | 78.4 (16.5)        | NA              | 78.3 (17.0)      | 78.1 (20.7)     | 76.5 (14.8)     |
| HR  |                    |                 |                  |                 |                 |
| <i>n</i>  | 10 584             |                 | 9825             |                 | 1066            |
| Mean (SD)   | 78.5 (19.3)        | NA              | 78.5 (18.4)      | NA              | 79.1 (19.0)     |

Percentages are based on the total number of patients excluding missing and unknown data. For vital signs, extreme data with <10 or >300 were excluded. For STEMI location, lateral, inferolateral, and posterior are merged into 'inferior'. Antero-lateral is merged into 'anterior'.

Before matching patients, the overall cumulative event rates of new P<sub>2</sub>Y<sub>12</sub> receptor inhibitor, prasugrel, ticagrelor, and clopidogrel on in-hospital events were 3.2%, 2.6%, 3.9%, and 6.3% on death, 1.5%, 1.3%, 1.7%, and 4.5% on CV death, 0.4%, 0.3%, 0.6%, and 0.8% on stroke/TIA, and 0.4%, 0.4%, 0.4%, and 0.8% on any major bleedings, respectively.

### Event analysis after matching procedure

Figure 2 presents in-hospital events, by single events, differentiated by new P<sub>2</sub>Y<sub>12</sub> receptor inhibitor vs. clopidogrel as administered as pre-cath or in-cath lab treatment with matched population. As a consistent finding, the event rates appeared substantially lower with the new P<sub>2</sub>Y<sub>12</sub> receptor inhibitors (with an exception for any major bleeding with low event rates). The ORs of the new P<sub>2</sub>Y<sub>12</sub> receptor inhibitors for the death of any cause, CV death, stroke/TIA, and any major bleeding when compared with clopidogrel were 0.72 (95% CI 0.62–

0.84,  $P < 0.001$ ), 0.70 (95% CI 0.52–0.96,  $P = 0.026$ ), 0.52 (95% CI 0.33–0.80,  $P = 0.003$ ), and 0.81 (95% CI 0.53–1.24,  $P = 0.335$ ), respectively.

The standardized differences for all covariates in the matched patients were <10% after integrating registries (Supplementary material online, Tables S1-5 and S2-5).

Upon further differentiation, event rates of prasugrel and ticagrelor appeared similar across registries (Analysis 2; Figure 3). In the comparison between prasugrel and ticagrelor, there were no significant differences on any event.

### Discussion

The present analysis of contemporary European real-world registries suggests that in STEMI patients the newer P<sub>2</sub>Y<sub>12</sub> receptor inhibitors



**Table 3** Discharge treatment and events in-hospital and within 30 days after discharge in propensity-matched populations

| Registry acronym                                    | AAPCI/ADAPT          | ALKK           | AMIS Plus        | BELGIUM          | EYESHOT         |
|---|----------------------|----------------|------------------|------------------|-----------------|
| Patient number, <i>n</i>                            | 13 916               | 3553           | 10 224           | 7794             | 1066            |
| Discharge treatment, <i>n</i> (%)                   |                      |                |                  |                  |                 |
| ASA   | 13 347/13 437 (99.3) | NA             | 9629/9801 (98.2) | NA               | 993/1025 (96.9) |
| Clopidogrel   | 6102/12 680 (48.1)   | NA             | 2424/9770 (24.8) | 654/6114 (10.7)  | 350/1025 (34.1) |
| Prasugrel   | 3969/12 679 (31.3)   | NA             | 4268/9767 (43.7) | 1489/6114 (24.4) | 267/1025 (26.0) |
| Ticagrelor  | 2608/12 665 (20.6)   | NA             | 2797/8691 (32.2) | 3971/6114 (64.9) | 353/1025 (34.4) |
| Oral anticoagulation                                | 214/2714 (7.9)       | NA             | 650/9720 (6.7)   | NA               | 48/1025 (4.7)   |
| In-hospital events, <i>n</i> (%)                    |                      |                |                  |                  |                 |
| Death   | 805/13 916 (5.8)     | 124/3553 (3.5) | 416/10 224 (4.1) | 531/7613 (7.0)   | 41/1066 (3.8)   |
| Cardiovascular death                                | 111/3528 (3.1)       | NA             | 195/10 204 (1.9) | NA               | 37/1066 (3.5)   |
| Stroke/TIA  | 74/13 848 (0.5)      | 11/3553 (0.3)  | 70/10 224 (0.7)  | NA               | 9/1066 (0.8)    |
| ICH   | 31/13 916 (0.2)      | NA             | 2/358 (0.6)      | NA               | 0/1066 (0.0)    |
| Fatal bleeding                                      | NA                   | NA             | 10/9850 (0.1)    | NA               | 1/1066 (0.1)    |
| TIMI major bleeding                                 | 131/13 916 (0.9)     | NA             | NA               | NA               | 14/1066 (1.3)   |
| Any major bleeding                                  | 131/13 916 (0.9)     | NA             | 12/9850 (0.1)    | NA               | 14/1066 (1.3)   |
| TIMI minor bleeding                                 | 40/3528 (1.1)        | NA             | NA               | NA               | 24/1066 (2.3)   |
| Urgent revascularization                            | 28/3463 (0.8)        | NA             | NA               | NA               | 12/1066 (1.1)   |
| Events within 30 days after discharge, <i>n</i> (%) |                      |                |                  |                  |                 |
| Death   | NA                   | NA             | NA               | 196/3264 (6.0)   | NA              |
| Cardiovascular death                                | NA                   | NA             | NA               | NA               | NA              |
| Stroke/TIA  | NA                   | NA             | NA               | NA               | NA              |
| ICH   | NA                   | NA             | NA               | NA               | NA              |
| Fatal bleeding                                      | NA                   | NA             | NA               | NA               | NA              |
| TIMI major bleeding                                 | NA                   | NA             | NA               | NA               | NA              |
| Any major bleeding                                  | NA                   | NA             | NA               | NA               | NA              |
| TIMI minor bleeding                                 | NA                   | NA             | NA               | NA               | NA              |
| Urgent revascularization                            | NA                   | NA             | NA               | NA               | NA              |

ICH: intracranial haemorrhage.

Percentages are based on the total number of patients excluding missing and unknown data. Other events within 30 days after discharge except for death are not available in all registries. Any major bleeding includes ICH, fatal bleeding, and TIMI major bleeding.

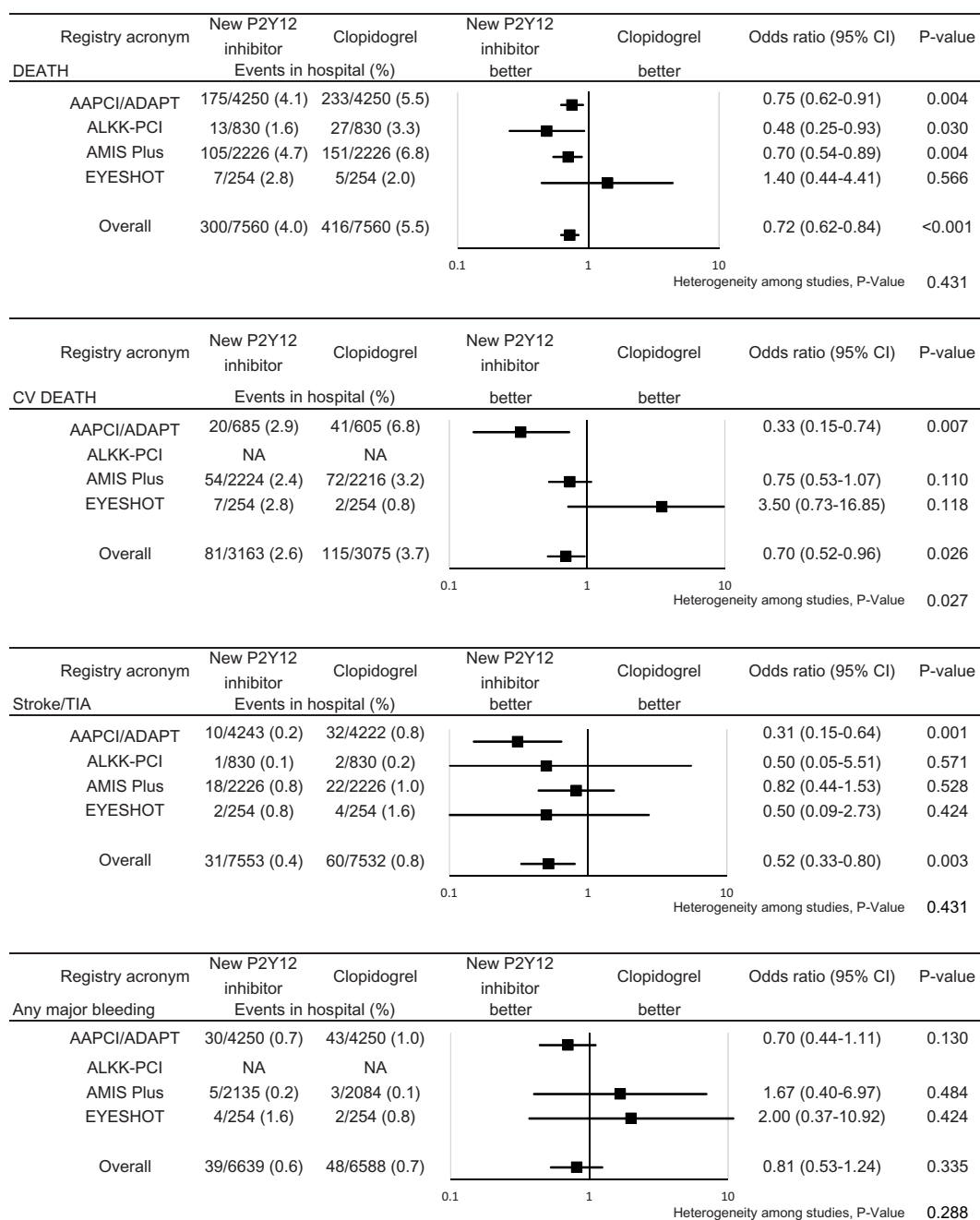
compared with clopidogrel have more favourable in-hospital outcomes, while not being inferior in terms of safety.

With respect to the setting, the majority of registries, including ALKK and APCI focused on selected (tertiary) hospitals, while others were open to all types of hospitals (AMIS Plus). Thus, the considerable differences in outcomes between the registries are likely explained by their designs. Overall across all analysed registries, however, in-hospital mortality rates associated with STEMI were quite low and homogeneous. Reasons that might account for this finding include selection bias (fewer ill patients might have been preferentially recruited) and improved ACS management over the years.<sup>9</sup> Patients in the five registries were similar in age and gender distribution. However, they differed substantially in the prevalence of comorbidities, such as arterial hypertension, diabetes mellitus, or prior MI.

Death rates, ischaemic events, and bleeding rates were overall lower than those reported in Phase III studies with P<sub>2</sub>Y<sub>12</sub> inhibitors. Regarding individual P<sub>2</sub>Y<sub>12</sub> inhibitors, patients on prasugrel, and, to a lesser degree, ticagrelor, had fewer ischaemic and bleeding events at all time points than clopidogrel-treated patients. These findings are

partly related to the fact that the newer agents were used in younger and less ill patients.

A thorough comparison of various P<sub>2</sub>Y<sub>12</sub> inhibitors can be only be made in the presence of appropriate adjustment techniques reducing indication biases that registries are prone to. In line with its labelling, the registries consistently documented that prasugrel in everyday practice conditions is used in younger patients, compared with other antiplatelet agents as recommended by the ESC Guidelines.<sup>1,2</sup> This age difference reflects the somewhat restricted labelling, as prasugrel is contraindicated in patients with prior TIA or stroke, and the drug is generally not recommended in elderly patients (≥75 years), although maintenance dose adaptation (5 mg instead of 10 mg) may be considered in such patients.<sup>10</sup> According to the product labelling, ticagrelor should be used with caution in patients with a history of asthma and/or chronic obstructive pulmonary disease (due to a relatively high incidence of dyspnoea) and also in patients with renal impairment (due to creatinine level increases).<sup>11</sup> These side effects have not been systematically assessed in the registries contributing to PIRAEUS.



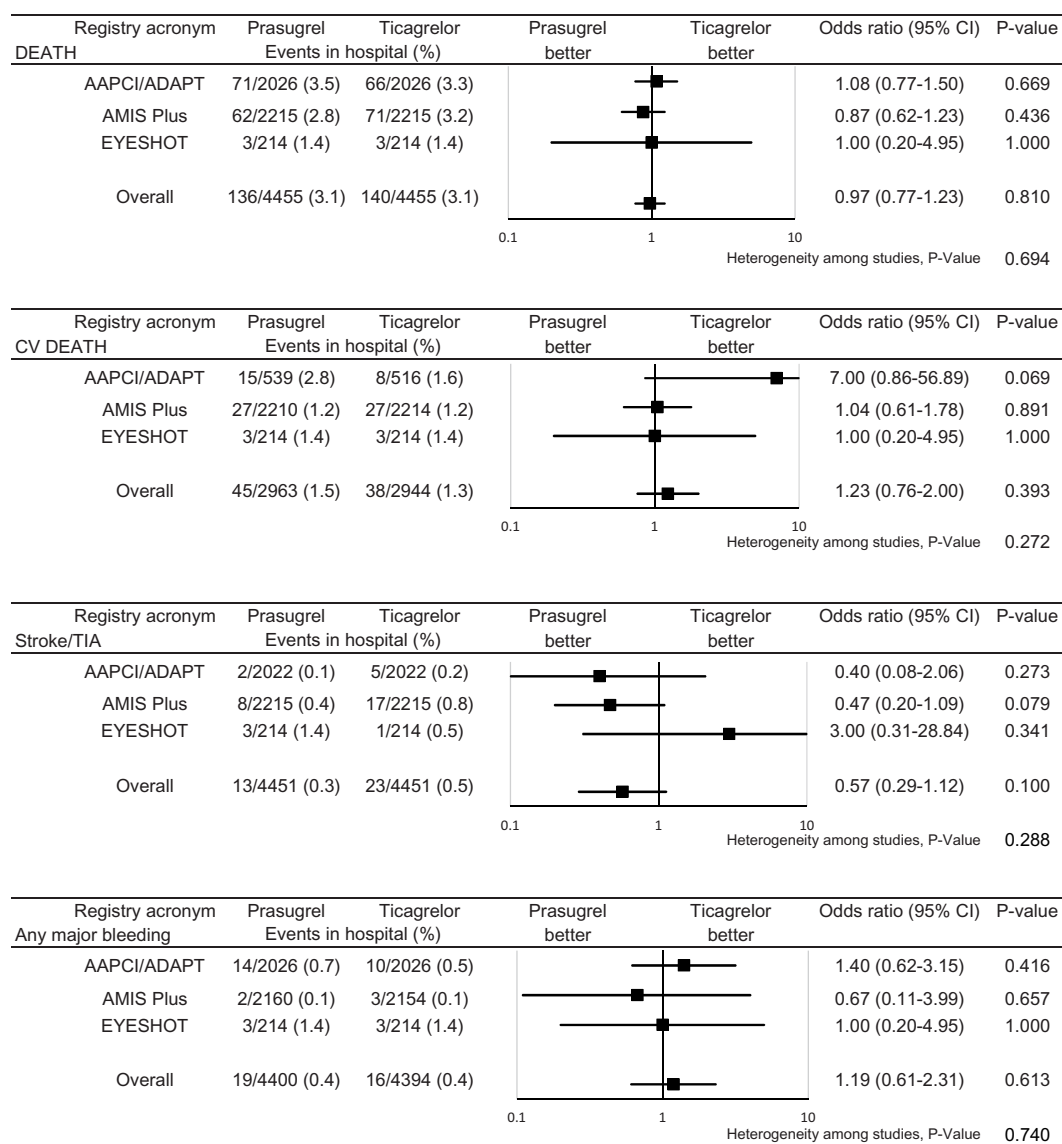
**Figure 2** Relationship between the type of P<sub>2</sub>Y<sub>12</sub> treatment and events in-hospital in propensity-matched populations (Analysis 1).

Trials comparing clopidogrel with either prasugrel or ticagrelor found a superior effectiveness of the novel antiplatelet agents,<sup>12,13</sup> even in STEMI patients.<sup>14,15</sup>

Prior studies have compared prasugrel or ticagrelor with clopidogrel also in a real-world setting, but a head-to-head comparison between the three available antiplatelet agents has never been performed. An AMIS Plus analysis using a propensity score-matched pairs analysis found significantly lower in-hospital mortality with

prasugrel (1.8%) vs. clopidogrel (3.1%).<sup>16</sup> In MULTIPRAC, a multi-national, multicentre, prospective registry enrolling 2053 STEMI patients, after adjustment for differences in baseline characteristics (including a 10-year age difference), treatment with prasugrel was associated with a significantly lower risk of CV death than treatment with clopidogrel (OR 0.248, 95% CI 0.06–0.89; data submitted).<sup>17</sup> In the SCAAR registry, the age difference was 2 years only, but the difference in 30-day all-cause mortality was substantial (prasugrel 2.5%





**Figure 3** Relationship between the type of P<sub>2</sub>Y<sub>12</sub> treatment and events in-hospital in propensity-matched populations (Analysis 2).

vs. clopidogrel 5.0%).<sup>18</sup> Accordingly, a prospective cohort study of 45 073 ACS patients enrolled into the SWEDEHEART registry confirmed the results of the PLATO trial as ticagrelor was associated with a lower risk of death, MI, or stroke compared with clopidogrel [11.7 vs. 22.3%; adjusted hazard ratio (HR) 0.85, 95% CI: 0.78–0.93], as well as death alone (5.8 vs. 12.9%; adjusted HR 0.83 95% CI: 0.75–0.92).<sup>19</sup> Re-admission for bleeding occurred more frequently with ticagrelor vs. clopidogrel (5.5 vs. 5.2%; adjusted HR 1.20, 95% CI 1.04–1.40).<sup>19</sup>

Recently, ticagrelor and prasugrel have been directly compared in the multicentre, randomized, open-label ISAR-REACT 5 trial.<sup>3</sup> Among the 4018 patients with ACS enrolled in this trial, a primary endpoint event—death from any cause, MI, or stroke at 1 year after randomization—occurred in 9.1% of patients in the ticagrelor group

and 6.8% in the prasugrel group (HR 1.36, 95% CI: 1.09–1.70;  $P=0.006$ ), without any difference in terms of major bleeding events (BARC Type 3 through 5). Among the pre-specified subgroup of patients with STEMI no difference was observed in terms of primary efficacy (10.1 vs. 7.9; HR 1.31, 95% CI 0.94–1.81) and safety endpoint across all enrolled patients, including those with STEMI.<sup>3</sup> These findings are in accordance with our real-world data showing a numerical, not significant reduction in the ischaemic event rate associated with prasugrel compared with ticagrelor, with a similar occurrence of bleeding events during the hospitalization for STEMI.

### Limitations

Not all of the previously identified suitable registries<sup>6</sup> provided data in the agreed structured format and several registries could,

therefore, not be analysed for the purpose of this article. Outcomes analyses were restricted to the short in-hospital period and does not allow for long-term assessment. The concurrent use of oral anticoagulation and other anticoagulants, such as unfractionated heparin, low-molecular-weight heparins, and fondaparinux, needs to be taken into account. Bleeding events were categorized using various definitions and were not standardized across registries. The low rate of bleeding complications is noteworthy, as real-life data are usually more likely to document increased safety hazards, compared with randomized controlled trials.

In conclusion, the present analysis of contemporary European registries suggests that in clinical practice STEMI patients the newer P<sub>2</sub>Y<sub>12</sub> receptor inhibitors compared with clopidogrel have favourable in-hospital outcomes while not being inferior in terms of safety.

## Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

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