Clopidogrel versus Aspirin after Dual Antiplatelet Therapy in Acute Myocardial Infarction Patients Undergoing Drug-Eluting Stenting

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Background and Objectives: There is a paucity of data regarding the benefit of clopidogrel monotherapy after dual antiplatelet therapy (DAPT) in patients treated with drug-eluting stents (DES). This study compared outcome between clopidogrel versus aspirin as monotherapy after DES for acute myocardial infarction (MI).

Methods: From Korea Acute Myocardial Infarction Registry-National Institute of Health database, 1,819 patients treated with DES who were switched to monotherapy with clopidogrel (n=534) or aspirin (n=1,285) after uneventful 12-month DAPT were analyzed. The primary endpoint was net adverse clinical events (NACE), defined as a composite of death...
INTRODUCTION

Current guidelines recommend at least 12-month dual antiplatelet therapy (DAPT) consisting of aspirin and a P2Y12 inhibitor in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) with drug-eluting stents (DES). The optimal duration of DAPT in such patients, however, remains a matter of debate and should be personalized considering the associated ischemic and bleeding risks.

In patients treated with DES who completed recommended duration of DAPT, indefinite single antiplatelet therapy should be administered mainly with aspirin. Aspirin inhibits platelet activation by inhibiting platelet cyclooxygenase and thromboxane production and is the most widely studied and prescribed antiplatelet agent for the secondary prevention. Clopidogrel, a thienopyridine, inhibits platelet activation by blocking the adenosine diphosphate receptor on platelets and may be used as an alternative to aspirin. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial showed that clopidogrel in patients with atherosclerotic vascular disease was more effective than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction (MI), or vascular death with comparable overall safety profile.

However, there is a paucity of data regarding the benefit of monotherapy with clopidogrel versus aspirin after DAPT in patients who underwent DES placement. In the present study, we sought to evaluate benefits of monotherapy with clopidogrel versus aspirin after DAPT in patients with acute MI treated with DES employing a large-scale, multi-center, nationwide acute MI database in Korea.

METHODS

Study population and data collection

The study population was derived from the Korea Acute Myocardial Infarction Registry-National Institutes of Health (KAMIR-NIH) database from November 2011 to December 2015. The KAMIR-NIH is a prospective, open, on-line multi-center data collection registry from 20 tertiary university hospitals capable of PCI in Korea, designed to capture real-world treatment practice and outcome of patients with acute MI.
We identified 9,001 patients with acute MI who received DAPT consisting of aspirin and a P2Y12 inhibitor after PCI with DES. Patients who received anticoagulants or other antiplatelet agents such as cilostazol were excluded. Among 8,034 patients followed-up for 12 months on DAPT (clopidogrel 64%, ticagrelor 23%, and prasugrel 13%), 699 patients who suffered major adverse cardiovascular and cerebrovascular events (MACCE), repeat revascularization, or major bleeding were excluded. Out of 7,335 patients who were event-free at 12 months, a total of 1,819 patients switched to single antiplatelet therapy with a follow-up until 24 months were divided into 2 groups according to the type of antiplatelet agent used: patients who received clopidogrel monotherapy (n=534) and patients who received aspirin monotherapy (n=1,285). Patients who received monotherapy with a potent P2Y12 inhibitor such as ticagrelor or prasugrel (n=10) were excluded. We analyzed the data using a 12-month landmark and evaluated outcomes at 24 months from the index procedure stratified by the type of single antiplatelet agent. The study flow diagram is shown in Figure 1.

PCI was performed according to the standard guidelines. Patients received loading doses of aspirin (300 mg) and a P2Y12 inhibitor (ticagrelor 180 mg, prasugrel 60 mg, or clopidogrel 300–600 mg) before PCI. The selection of vessels treated, devices used, and adjunctive drugs administered to support PCI was left to the discretion of the treating physician. After PCI, patients received maintenance doses of either ticagrelor (90 mg twice daily), prasugrel (10 mg daily), or clopidogrel (75 mg daily). Aspirin was given at a dose of 100 mg daily. The present study was conducted according to the Declaration of Helsinki. The Institutional Review Board of all participating centers approved the study protocol. The approval number was CNUH-2011-172 of Chonnam National University Hospital. Written informed consent was obtained from all participating patients.

**Clinical endpoints and definitions**

The primary endpoint of the study was net adverse clinical events (NACE), defined as a composite of death from any cause, MI, repeat PCI, stent thrombosis, ischemic stroke, or Thrombolysis in Myocardial Infarction (TIMI) major bleeding during the period from 12 to 24 months. The secondary endpoints were individual components of the primary endpoint, target vessel revascularization, definite or probable stent thrombosis, ischemic stroke, and MACCE, defined as a composite of death from any cause, MI, repeat PCI, stent thrombosis, or ischemic stroke.

MI was diagnosed when there was a rise and/or fall of cardiac biomarker values (troponin I/T or creatine kinase-MB with at least one value above the 99th percentile upper reference limit) and with at least one of the following: symptoms of myocardial ischemia, changes on the electrocardiogram including new or presumed new significant ST-segment-T wave changes, new left bundle branch block, or pathologic Q waves in 2 contiguous leads, and imaging evidence of new loss of viable myocardium or a new regional wall motion abnormality. Target vessel revascularization was defined as a repeat PCI of any segment within the entire major coronary vessel proximal and distal to a target lesion, including the target lesion itself. Stroke was defined as focal loss of neurologic function caused by an ischemic or hemorrhagic event, with residual symptoms lasting at least 24 hours or leading to death. Stent thrombosis was defined according to the Academic Research Consortium definitions. Bleeding events were classified as major and minor according to TIMI scales.
Continuous variables, expressed as mean±standard deviation or median (interquartile range), were compared using the Student t-test or the Mann-Whitney U test. Categorical variables,
reported as frequencies and percentages, were compared with the $\chi^2$ test or Fisher’s exact test, as appropriate.

In order to control for differences in baseline characteristics and potential confounding factors, an inverse probability of treatment weighting (IPTW) approach based on the propensity score was used.\textsuperscript{11,12} The propensity score was constructed using a multiple logistic regression model that estimated the probability of receiving clopidogrel monotherapy conditional on 33 covariates shown in Tables 1 and 2; age, sex, body mass index, smoking, hypertension, diabetes mellitus, dyslipidemia, prior history of MI, angina pectoris, heart failure, and stroke, family history of coronary artery disease, typical chest pain at presentation, Killip class, clinical diagnosis (ST-segment elevation MI), left ventricular ejection fraction, white blood cell count, hemoglobin, serum creatinine, radial artery access, infarct-related vessel, American College of Cardiology/American Heart Association lesion type, number of diseased vessels, pre-PCI TIMI flow grade, DES type, maximum stent diameter, total stent length, number of stents, post-PCI TIMI flow grade, use of glycoprotein IIb/IIIa inhibitor, and medications at 12 months (beta-blocker, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and statin). The Hosmer-Lemeshow goodness-of-fit test p value was 0.866, indicating good calibration and fit of the multivariable model that estimated the propensity score. Each patient was then weighted by the inverse probability of treatment received, and weighting was stabilized by multiplying the marginal

Table 1. Baseline clinical characteristics

| Characteristics                        | Overall patients               | Inverse probability of treatment-weighted analysis |
|----------------------------------------|--------------------------------|---------------------------------------------------|
|                                        | Clopidogrel (n=534)            | Aspirin (n=1,285)                                 | p value | Standardized difference | Clopidogrel (n=533) | Aspirin (n=1,286) | p value | Standardized difference |
| Age (year)                             | 62.2±11.7                      | 60.7±11.7                                        | 0.013   | 12.74                      | 60.9±11.7           | 61.1±11.7           | 0.842   | 1.08 |
| Male                                   | 395 (74.0)                     | 1,030 (80.2)                                    | 0.004   | 14.74                      | 418 (78.5)          | 1,006 (78.2)        | 0.888   | 0.74 |
| Body mass index (kg/m\(^2\))           | 24.0±3.2                       | 24.2±3.0                                        | 0.098   | 8.42                       | 24.1±3.3            | 24.1±3.0            | 0.930   | 0.49 |
| Smoking                                | 305 (57.1)                     | 840 (65.4)                                      | 0.001   | 16.99                      | 336 (63.0)          | 809 (62.9)          | 0.948   | 0.35 |
| Hypertension                           | 260 (48.7)                     | 574 (44.7)                                      | 0.117   | 8.06                       | 244 (45.7)          | 592 (46.0)          | 0.915   | 0.58 |
| Diabetes mellitus                      | 109 (20.4)                     | 282 (22.0)                                      | 0.468   | 3.75                       | 110 (20.7)          | 275 (21.4)          | 0.758   | 1.69 |
| Dyslipidemia                           | 84 (15.7)                      | 161 (12.5)                                      | 0.069   | 9.19                       | 70 (13.2)           | 171 (13.3)          | 0.965   | 0.23 |
| MI                                      | 16 (3.0)                       | 37 (2.9)                                        | 0.893   | 0.69                       | 15 (2.8)            | 38 (2.9)            | 0.887   | 0.76 |
| Angina pectoris                        | 41 (7.7)                       | 61 (4.8)                                        | 0.013   | 12.16                      | 29 (5.5)            | 74 (5.8)            | 0.838   | 1.03 |
| Heart failure                          | 4 (0.8)                        | 9 (0.7)                                         | 0.911   | 0.57                       | 10 (0.8)            | 5 (0.9)             | 0.831   | 1.22 |
| Stroke                                 |                                |                                                 | 0.269   | 0.904                      |                     |                     |                     |       |
| Ischemic stroke                        | 20 (3.8)                       | 38 (3.0)                                        | 4.38    | 17 (3.1)                   | 42 (3.2)            | 0.56                |                     |       |
| Hemorrhagic stroke                     | 5 (0.9)                        | 8 (0.6)                                         | 3.57    | 3 (0.6)                    | 8 (0.6)             | 0.27                |                     |       |
| Family history of CAD                 | 39 (7.3)                       | 84 (6.5)                                        | 0.553   | 3.02                       | 37 (7.0)            | 88 (6.9)            | 0.948   | 0.34 |
| Typical chest pain                    | 478 (89.5)                     | 1,196 (93.3)                                    | 0.011   | 12.65                      | 489 (91.8)          | 1,181 (91.9)        | 0.979   | 0.14 |
| Killip class                           | 0.528                          |                                                 | 0.100   |                           |                     |                     |                     |       |
| I                                      | 468 (87.6)                     | 1,099 (85.5)                                    | 6.20    | 459 (86.1)                 | 1,108 (86.1)        | 0.22                |                     |       |
| II                                     | 30 (5.6)                       | 88 (6.9)                                        | 5.09    | 35 (6.5)                   | 83 (6.4)            | 0.40                |                     |       |
| III                                    | 20 (3.8)                       | 46 (3.6)                                        | 0.88    | 19 (3.6)                   | 48 (3.7)            | 0.39                |                     |       |
| IV                                     | 16 (3.0)                       | 52 (4.1)                                        | 5.70    | 20 (3.8)                   | 48 (3.7)            | 0.26                |                     |       |
| ST-segment elevation MI                | 248 (46.4)                     | 684 (53.2)                                      | 0.008   | 13.60                      | 273 (51.3)          | 659 (51.2)          | 0.985   | 0.10 |
| LVEF (%)                               | 53±1.9                         | 53±4.5                                          | 0.670   | 2.17                       | 53±5.9              | 53±5.9              | 0.701   | 2.09 |
| White blood cell count (10\(^3\)/µL)   | 9.6 (7.6–12.2)                 | 9.7 (7.7–12.5)                                  | 0.003   | 10.68                      | 9.6 (7.6–12.3)      | 9.7 (7.7–12.4)      | 0.623   | 1.49 |
| Hemoglobin (g/dL)                      | 14.3 (13.0–15.5)               | 14.5 (13.3–15.6)                                | 0.041   | 17.96                      | 14.4 (13.2–15.5)    | 14.5 (13.2–15.7)    | 0.255   | 1.89 |
| Serum creatinine (mg/dL)               | 0.9 (0.7–1.1)                  | 0.9 (0.7–1.0)                                   | 0.050   | 8.86                       | 0.9 (0.7–1.1)       | 0.9 (0.7–1.0)       | 0.134   | 0.38 |
| GRACE score                            | 135.0±35.0                     | 134.1±35.1                                     | 0.612   | 133.9±36.2                 | 134.4±35.1          | 0.795              |                     |       |
| DAPT score                             | 1.53±1.16                      | 1.67±1.16                                      | 0.020   | 1.63±1.15                  | 1.63±1.18           | 0.995              |                     |       |
| PRECISE-DAPT score                     | 18.1±10.7                      | 16.3±9.5                                       | 0.001   | 17.1±10.2                  | 16.6±9.8            | 0.379              |                     |       |

Values are presented as mean±standard deviation, median (interquartile range), or number (%). CAD = coronary artery disease; DAPT = dual antiplatelet therapy; GRACE = Global Registry of Acute Coronary Events; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subseqent Dual Anti Platelet Therapy.
Baseline covariate balance between the 2 groups before and after IPTW was assessed using standardized differences. Variables were considered well balanced if the standardized difference was less than 10%. For comparison of clinical outcomes between the 2 groups, a weighted Cox proportional hazards model was used to estimate hazard ratios (HRs) and their 95% confidence intervals (CI) for each outcome using a robust sandwich-type estimator to account for the weighted nature of the sample.

All p values were 2-sided, with statistical significance set at a level of <0.05. Statistical analyses were conducted using Stata version 15.1 (StataCorp, College Station, TX, USA) and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

### Table 2. Characteristics of index procedures and medical treatment at 12 months

| Characteristics                                      | Overall patients | Inverse probability of treatment-weighted analysis |
|-------------------------------------------------------|------------------|-----------------------------------------------------|
|                                                       | Clopidogrel (n=534) | Aspirin (n=1,285) | p value | Standardized difference | Clopidogrel (n=533) | Aspirin (n=1,286) | p value | Standardized difference |
| Radial artery access                                  | 219 (41.0)       | 569 (44.3)    | 0.200   | 6.61                          | 233 (43.6)        | 555 (43.2)        | 0.872   | 0.89                          |
|                                                       | Infarct-related vessel |                   |         | 0.673                         |                   |                   | 0.999   |                                |
| Left anterior descending artery                       | 261 (48.9)       | 599 (46.6)    | 4.53    | 254 (47.6)                    | 610 (47.4)        |                   | 0.45    |                                |
| Left circumflex artery                                | 95 (17.8)        | 248 (19.3)    | 3.88    | 98 (18.4)                     | 240 (18.7)        |                   | 0.84    |                                |
| Right coronary artery                                 | 170 (31.8)       | 424 (33.0)    | 2.48    | 175 (32.8)                    | 420 (32.6)        |                   | 0.30    |                                |
| Left main coronary artery                             | 8 (1.5)          | 14 (1.1)      | 3.61    | 7 (1.2)                       | 16 (1.3)          |                   | 0.37    |                                |
| ACC/AHA lesion type                                   |                  |               | 0.241   |                              |                   |                   | 0.999   |                                |
| A                                                     | 13 (2.4)         | 15 (1.2)      | 9.53    | 9 (1.6)                       | 22 (1.7)          |                   | 0.56    |                                |
| B1                                                    | 78 (14.6)        | 191 (14.9)    | 0.72    | 78 (14.6)                     | 189 (14.7)        |                   | 0.27    |                                |
| B2                                                    | 176 (33.0)       | 442 (34.4)    | 3.04    | 182 (34.1)                    | 436 (33.9)        |                   | 0.38    |                                |
| C                                                     | 267 (50.0)       | 637 (49.6)    | 0.86    | 265 (49.7)                    | 640 (49.8)        |                   | 0.03    |                                |
| Number of diseased vessels                           | 0.191            |               | 0.004   |                              |                   |                   | 0.990   |                                |
| 1-vessel disease                                      | 307 (57.5)       | 670 (52.1)    | 10.76   | 287 (53.9)                    | 690 (53.6)        |                   | 0.52    |                                |
| 2-vessel disease                                      | 151 (28.3)       | 401 (31.2)    | 6.41    | 160 (30.3)                    | 390 (30.3)        |                   | 0.42    |                                |
| 3-vessel disease                                      | 61 (11.4)        | 185 (14.4)    | 8.87    | 71 (13.4)                     | 175 (13.6)        |                   | 0.61    |                                |
| Left-main, simple                                     | 2 (0.4)          | 3 (0.2)       | 2.56    | 2 (0.3)                       | 5 (0.4)           |                   | 1.14    |                                |
| Left-main, complex                                    | 13 (2.4)         | 26 (2.0)      | 2.78    | 12 (2.3)                      | 27 (2.1)          |                   | 1.43    |                                |
| Pre-PCI TIMI flow grade                               |                  |               | 0.002   |                              |                   |                   | 0.999   |                                |
| 0 or 1                                                | 325 (60.9)       | 733 (57.0)    | 7.76    | 309 (57.9)                    | 747 (58.1)        |                   | 0.37    |                                |
| 2                                                     | 78 (14.6)        | 145 (11.3)    | 9.90    | 68 (12.7)                     | 160 (12.5)        |                   | 0.75    |                                |
| 3                                                     | 131 (24.5)       | 407 (31.7)    | 15.93   | 157 (29.4)                    | 379 (29.5)        |                   | 0.15    |                                |
| DES type                                              |                  |               | 0.020   |                              |                   |                   | 0.976   |                                |
| Sirolimus-eluting stent                               | 20 (3.8)         | 25 (2.0)      | 10.83   | 13 (2.4)                      | 32 (2.5)          |                   | 0.36    |                                |
| Everolimus-eluting stent                              | 242 (45.3)       | 557 (43.4)    | 3.97    | 243 (45.6)                    | 568 (44.2)        |                   | 2.87    |                                |
| Zotarolimus-eluting stent                             | 135 (25.3)       | 396 (30.8)    | 12.34   | 155 (29.1)                    | 375 (29.1)        |                   | 0.09    |                                |
| Biolimus-eluting stent                                | 116 (21.7)       | 274 (21.3)    | 0.97    | 107 (20.1)                    | 274 (21.3)        |                   | 2.94    |                                |
| Other DES                                             | 21 (3.9)         | 33 (2.6)      | 7.69    | 14 (2.7)                      | 37 (2.8)          |                   | 0.84    |                                |
| Maximum stent diameter (mm)                           | 3.13±0.44        | 3.20±0.44     | 0.003   | 3.18±0.46                     | 3.18±0.44         |                   | 0.990   | 0.07                          |
| Total stent length (mm)                               | 29.2±13.4        | 28.8±13.2     | 0.630   | 29.1±13.5                     | 29.0±13.4         |                   | 0.888   | 0.78                          |
| Number of stents                                      | 1.16±0.40        | 1.15±0.38     | 0.597   | 1.16±0.40                     | 1.15±0.39         |                   | 0.888   | 0.78                          |
| Glycoprotein IIb/IIIa inhibitor                       | 66 (12.4)        | 174 (13.5)    | 3.52    | 67 (12.6)                     | 176 (13.7)        |                   | 0.553   | 3.26                          |
| Post-PCI TIMI flow grade                              |                  |               | 0.252   |                              |                   |                   | 0.873   |                                |
| 2                                                     | 17 (3.2)         | 29 (2.3)      | 5.70    | 13 (2.4)                      | 33 (2.6)          |                   | 0.82    |                                |
| 3                                                     | 517 (96.8)       | 1,256 (97.7)  | 5.70    | 520 (97.5)                    | 1,253 (97.4)      |                   | 0.82    |                                |
| Medication at 12 months                               |                  |               |         |                              |                   |                   | 0.976   |                                |
| Beta-blocker                                          | 387 (72.5)       | 1,044 (81.3)  | <0.001  | 20.90                         | 418 (78.5)        |                   | 0.980   | 0.13                          |
| ACE/ARB                                               | 380 (71.9)       | 946 (73.6)    | 0.983   | 5.50                          | 381 (71.4)        |                   | 0.669   | 2.33                          |
| Statin                                                | 513 (96.1)       | 1,236 (96.2)  | 0.904   | 0.62                          | 508 (95.3)        | 1,234 (95.9)      | 0.560   | 3.38                          |

Values are presented as mean±standard deviation or number (%).

ACC/AHA = American College of Cardiology/American Heart Association; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; DES = drug-eluting stents; PCI = percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction.
RESULTS

Baseline clinical, procedural characteristics and medical treatment
Baseline clinical characteristics of the patients are shown in Table 1. In the overall study population, patients who received clopidogrel monotherapy, compared to those receiving aspirin, were older, more often had prior history of angina pectoris, lower hemoglobin levels, and higher predicting bleeding complications in patients undergoing stent implantation and subsequent dual anti platelet therapy (PRECISE-DAPT) scores. Patients who received aspirin monotherapy were more often men and smokers, had typical chest pain at presentation, ST-segment elevation MI, and higher DAPT scores. Characteristics of index procedures and medical treatment at 12 months are presented in Table 2. Patients receiving clopidogrel were more likely to have lower pre-PCI TIMI flow grade, whereas patients treated with aspirin monotherapy more often received beta-blocker therapy at 12 months. After IPTW adjustment, there were no differences between the 2 groups in baseline clinical and procedural characteristics and medical treatment (Tables 1 and 2).

Clinical outcomes
Unadjusted and adjusted clinical outcomes during the period from month 12 to month 24 are shown in Table 3. In the IPTW-adjusted sample, patients who received clopidogrel monotherapy, as compared with those with aspirin monotherapy, had a similar incidence of NACE (0.7% and 0.7%; HR, 1.06; 95% CI, 0.31–3.60; p=0.923) (Figure 2). The clopidogrel and aspirin monotherapy groups had similar rates of death from any cause (0.1% in each group, p=0.789), MI (0.3% and 0.1%, respectively; p=0.226), repeat PCI (0.1% and 0.3%, respectively; p=0.548), stent thrombosis (0.1% and 0%, respectively; p=0.121).

The rate of TIMI major bleeding was not different between patients with clopidogrel monotherapy and those with aspirin monotherapy (0.2% in each group; HR, 1.04; 95% CI, 0.11–9.92; p=0.974). There was no significant difference between the 2 groups with respect to the rate of MACCE (0.5% in each group; HR, 1.07; 95% CI, 0.25–4.56; p=0.924).

Table 3. Unadjusted and adjusted clinical outcomes at 24 months

| Clinical outcomes                      | Overall patients       | Inverse probability of treatment-weighted analysis |
|---------------------------------------|------------------------|--------------------------------------------------|
|                                       | Clopidogrel (n=534)    | Aspirin (n=1,285)                                | Clopidogrel (n=533) | Aspirin (n=1,286) | Adjusted HR (95% CI) | p value |
| Death from any cause                  | 1 (0.2)                | 1 (0.1)                                          | 1 (0.1)             | 1 (0.1)            | 1.46 (0.09–23.4)     | 0.789   |
| MI                                    | 2 (0.4)                | 1 (0.1)                                          | 2 (0.3)             | 1 (0.1)            | 4.49 (0.40–51.0)     | 0.226   |
| Repeat PCI                            | 2 (0.4)                | 3 (0.2)                                          | 2 (0.3)             | 3 (0.2)            | 4.00 (0.40–47.2)     | 0.548   |
| Target vessel revascularization       | 0 (0.0)                | 2 (0.2)                                          | 0 (0)               | 3 (0.2)            | 0.362 (0.09–8.15)    | 0.394   |
| Non-target vessel revascularization   | 1 (0.2)                | 1 (0.1)                                          | 1 (0.1)             | 1 (0.1)            | 1.46 (0.09–23.3)     | 0.791   |
| Stent thrombosis                      | 1 (0.2)                | 0 (0.0)                                          | 1 (0.1)             | 0 (0.0)            | 0.121 (0.09–8.15)    | 0.121   |
| Ischemic stroke                       | 0 (0.0)                | 0 (0.0)                                          | 0 (0.0)             | 0 (0.0)            | -                    | -       |
| TIMI major bleeding                   | 1 (0.2)                | 3 (0.2)                                          | 1 (0.2)             | 3 (0.2)            | 1.04 (0.11–9.92)     | 0.974   |
| MACCE                                 | 3 (0.6)                | 5 (0.4)                                          | 3 (0.5)             | 6 (0.5)            | 1.07 (0.25–4.56)     | 0.924   |
| NACE                                  | 4 (0.8)                | 8 (0.6)                                          | 4 (0.7)             | 9 (0.7)            | 1.06 (0.31–3.60)     | 0.923   |

Values are presented as number (%). CI = confidence interval; HR = hazard ratio; MACCE = major adverse cardiovascular and cerebrovascular events; MI = myocardial infarction; NACE = net adverse clinical events; PCI = percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction.
DISCUSSION

The present study showed that in real-world patients with acute MI treated with DES, monotherapy with clopidogrel, as compared with aspirin, after uneventful 12-month DAPT showed similar rates of NACE. The rates of MACCE and major bleeding did not differ significantly between the 2 treatment groups.

Currently, there is a paucity of data on the benefit of monotherapy with clopidogrel versus aspirin after DAPT in patients who underwent DES implantation. Aspirin inhibits platelet activation by inhibiting platelet cyclooxygenase and thromboxane production and is the most widely studied and prescribed antiplatelet agent for the secondary prevention. Aspirin significantly reduces the risk of MI, stroke, and vascular death in patients with atherosclerotic cardiovascular disease. Clopidogrel, a thienopyridine, inhibits platelet activation by selectively and irreversibly blocking the binding of adenosine diphosphate to its receptor on platelets, and may be used as an alternative to aspirin. The CAPRIE trial was the first and largest randomized study comparing clopidogrel and aspirin in 19,185 patients with a recent stroke, MI, or peripheral artery disease. Clopidogrel had a modest superiority over aspirin in reducing the combined risk of ischemic stroke, MI, or vascular death. On subgroup analysis, however, the benefit of clopidogrel was most prominent in patients with peripheral artery disease and was not significant in those with MI, raising the possibility that clopidogrel and aspirin are equivalent in benefit in MI patients or that the benefit of clopidogrel is much greater in patients with peripheral arterial disease. There were no major differences in terms of safety. Clopidogrel was associated with lower rates of gastrointestinal hemorrhage and upper-gastrointestinal disturbances, but a higher rate of skin rash and diarrhea.

In a recent observational study, clopidogrel monotherapy, compared with aspirin monotherapy, in 3,243 patients (ACS 42%) who received 12-month DAPT after DES without adverse clinical outcomes significantly reduced the rates of cardiac death, MI, or stroke with a similar risk of bleeding. However, this study was conducted before the era of potent P2Y12 inhibitors and first-generation DES were used in the majority (57%). On the other hand, in the present study, no significant differences were found with monotherapy with clopidogrel compared to aspirin in the rates of MACCE or major bleeding with similar
NACE at 24 months in AMI patients who received uneventful 12-month DAPT after DES placement (second-generation DES 98%), suggesting that further randomized study reflecting contemporary practice with longer-term clinical follow-up may be warranted for optimal single antiplatelet therapy after recommended duration of DAPT. Meanwhile, it seems prudent to infer that aspirin remains the first-line antiplatelet agent and the role of clopidogrel in clinical practice needs to be determined by the proportional risk reduction weighed against its cost. Clopidogrel might be a reasonable alternative in patients with allergy or appreciable gastrointestinal symptoms even with low dose aspirin.  

The present study has several limitations. First, although these results come from a large cohort and adjustment was made using propensity score analysis for confounding variables, unmeasured factors may still exist. Second, covariates used in propensity score analysis are mainly derived from the data at the index hospitalization, which may not adjust the differences in characteristics of patients during the period between 12 and 24 months after the index hospitalization. Third, the sample size is relatively small, and the annual rates of clinical events appeared lower than expected from DES-treated patients who survived AMI, suggesting that the possibility of under-reporting cannot be ruled out. Fourth, detailed information as to why specific patients were switched between DAPT and single antiplatelet therapy and vice versa during the period between 12 and 24 months were not available from our registry. Fifth, the causes of bleeding events according to the antiplatelet agent used were not available in our database. Finally, the duration of follow-up may not have been sufficient to fully assess the benefits and risks of monotherapy with clopidogrel versus aspirin in the real-world population with acute MI.

In conclusion, monotherapy with clopidogrel after uneventful 12-month DAPT in real-world patients with acute MI treated with DES demonstrated efficacy and safety profiles comparable to aspirin monotherapy.

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