Real-world evidence of switching P2Y12 receptor–inhibiting therapies to prasugrel after PCI in patients with ACS: results from EFF-K registry

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Abstract

Background

Potent $P2Y_{12}$ inhibitors are recommended for up to 12 months after percutaneous coronary intervention (PCI) in patients diagnosed with acute coronary syndrome (ACS). However, the prescription pattern is diverse in real world practice, which includes various switching between antiplatelet regimens. In this study, we analyzed the prescription patterns of prasugrel, and assessed the safety and effectiveness of P2Y12 inhibitors switching patterns in a real world registry of patients subjected to PCI after ACS.

Methods

The EFF-K study included 3,077 ACS patients receiving prasugrel-based dual antiplatelet therapy. The cohort was divided into those who were administered with prasugrel as the primary antiplatelet treatment (naïve cohort) or as a substitute agent after clopidogrel or ticagrelor pre-treatment (switch cohort). The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE; a composite cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and TIMI major bleeding).

Results

A total of 3,077 patients diagnosed with ACS were included in the analysis. Among the total population, 726 patients (23.6%) were classed as the naïve cohort and 2,351 patients (76.4%) as the switch cohort. Baseline characteristics showed that the switch cohort had more comorbidities, such as hypertension, diabetes mellitus, heart failure and previous PCI. The major cause of switching to prasugrel in the switch cohort was the necessity for a more potent antiplatelet agent (56.3%). During a 12-month follow-up period, 55 patients (1.8%) experienced at least one MACCE. The incidence of MACCE did not differ between the naïve and switch cohort (1.7% vs. 1.8%, Hazard ratio 1.14, 95% Confidence interval 0.56-2.30, P=0.723). In subgroup analysis, no significant interaction was observed between the treatment strategy and the incidence of MACCE across various subgroups.

Conclusions

Dual antiplatelet therapy with prasugrel seems to be safe and effective both as a primary treatment and as a substitute for other P2Y12 inhibitors in a real world registry of Asian ACS patients receiving PCI.

Trial registration

KCT0002356, registered June 13, 2017.

Background

Acute coronary syndrome (ACS), in the form of myocardial infarction (MI) with or without ST-segment elevation and unstable angina, remains a major cause of premature death in developed countries(1). The

therapy of ACS is aimed at myocardial reperfusion, primarily through percutaneous coronary intervention (PCI)(2). While timely PCI is a life-saving procedure, it also poses some risks. Specifically, the intervention disrupts the coronary endothelium, leading to direct exposure of the subendothelium. As a consequence, intracoronary thrombosis may occur during PCI or shortly thereafter. In addition, metal stents, acting as procoagulants, can trigger thrombus formation(3).

Dual antiplatelet therapy (DAPT; aspirin plus a $P2Y_{12}$ inhibitor) lasting for up to 12 months is the treatment strategy recommended by most guidelines for the prevention of atherothrombotic events in patients diagnosed with ACS and undergoing PCI(4). The potent $P2Y_{12}$ inhibitors produce a stronger antithrombotic effect than their predecessor, clopidogrel, but also pose a higher risk of bleeding, especially when administered chronically. Prasugrel is a third-generation potent thienopyridine that irreversibly binds to the platelet $P2Y_{12}$ receptor and inhibits adenosine diphosphate-induced platelet aggregation. A pivotal study (TRITON-TIMI 38) demonstrated that DAPT with prasugrel was associated with a significantly reduced rate of ischemic events but with an increased risk of major bleeding(5). Given the intrinsic bleeding risk of antiplatelet agents and distinct effectiveness/risk profiles of various $P2Y_{12}$ inhibitors, prescription patterns tend to be complex, with switching between DAPT regimens depending on the clinical scenario(6). However, neither previous clinical trials nor guidelines elaborated on how to switch the therapies in real-world practice.

The problem mentioned above seems to be particularly important in East Asian patients, who were shown to be more prone to bleeding and less prone to thrombosis, a phenomenon referred to as the East Asian paradox(7, 8, 9, 10, 11, 12). Indeed, the evidence from some studies suggests that East Asian patients may not benefit from DAPT with potent $P2Y_{12}$ inhibitors equally to other populations, mainly due to higher bleeding event rates(9.13). However, in a recent phase IV post-marketing surveillance (PMS) study of Korean patients receiving a standard dose of prasugrel, the efficacy and safety of the agent seemed to be similar as in the pivotal trial(14).

The aim of this real-world study was to analyze the prescription patterns of prasugrel, with a particular emphasis on switching between $P2Y_{12}$ inhibitors, and to assess the safety and effectiveness of prasugrel in Korean patients subjected to PCI after ACS.

Methods

Study design and patients

The EFF-K study was a non-interventional, prospective, one-year follow-up cohort research conducted in 52 hospitals located in various regions of South Korea from March 2017 till November 2019. To avoid a selection bias, medical charts of all patients who had been on prasugrel treatment within six months after PCI were sequentially screened for the study. We included only adult patients (≥ 19 years of age) who had been on prasugrel treatment less than six months since PCI and excluded those participating in any interventional study using antiplatelet or anticoagulant agents. Only the candidate patients who

voluntarily provided their written consent were registered in the study. The investigators assessed baseline parameters in index PCI. The naïve cohort was defined as those who started receiving prasugrel in the absence of other $P2Y_{12}$ inhibitor(s) before and after PCI. Patients whose antiplatelet medication had been changed from other $P2Y_{12}$ inhibitor(s) to prasugrel within six months since index PCI were defined as the switch cohort (Fig. 1). For the switch cohort, reasons for switching to prasugrel were restricted to the following: adverse events or over-inhibition of platelet aggregation by the previous agent, drug interaction between the previous agent and other concomitant medications, the necessity of a more potent antiplatelet agent, or decreased medication compliance with a twice-daily regimen. Prasugrel regimen, duration of the treatment, and all medical procedures followed the routine clinical practices. The study protocol, including the consent form, was reviewed and approved by the IRB of each institution. The study information was registered in the public domain, the Clinical Research Information Service (https://cris.nih.go.kr/) under the registration number KCT0002356 (13/06/2017).

Study Endpoints And Data Collection

The primary endpoint of the study was a major adverse cardiac and cerebrovascular event (MACCE), defined as a composite of net clinical events, such as cardiovascular death, non-fatal MI, non-fatal stroke, or Thrombolysis in Myocardial Infarction (TIMI) major bleeding unrelated to coronary-artery bypass grafting (CABG). The list of key secondary endpoints included a composite of cardiovascular death, non-fatal MI, and non-fatal stroke as the effectiveness endpoint and a composite of TIMI major or minor bleeding unrelated to CABG as the safety endpoint. Other secondary effectiveness endpoints were individual components, such as cardiovascular death, all-cause death, non-fatal MI, non-fatal stroke, TIMI major bleeding unrelated to CABG, TIMI minor bleeding unrelated to CABG, and urgent target vessel revascularization. Also, serious adverse events and adverse events causing the withdrawal of prasugrel were analyzed as safety endpoints. A serious adverse reaction was defined as one that required hospitalization or prolongation of existing hospitalization, caused congenital malformation, resulted in persistent or significant disability or incapacity, was life-threatening, or resulted in death. Data available at 1, 3, 6, 9, and 12 months after PCI were collected via electronic case report form. Electronically captured data, as well as on-site study documents, including signed consent forms, were verified through centralized monitoring and on-site monitoring.

Statistical analysis

The target number of patients was based on the primary endpoint. Assuming the true incidence of net clinical events of 12.3% based on the TRITON-TIMI 38 study(5), a sample size of 3,213 patients was required with adjustment for 15% drop-out rate to achieve the desired precision (target width of 0.025 for confidence interval by Clopper-Pearson method) at 95% confidence level. Continuous variables are presented as mean ± standard deviation (SD) or median (range) as appropriate. Categorical variables are presented as frequency (percentage). As for the effectiveness endpoints, comparisons between cohorts or subgroups were carried out using Pearson’s chi-squared test or Fisher’s exact test depending on the data

distribution. Univariate Cox proportional hazards regression was performed to identify independent predictors of MACCE and the multivariable model was built with candidate variables being selected if of clinical interest and/or satisfying the entry criterion of $P < 0.1$ in the univariate analysis. Variables included in the model for were carefully selected to avoid overfitting and included old age (≥ 75 years old), sex, hypertension, diabetes mellitus, current smoking, presentation with STEMI, and presence of multivessel coronary disease in angiography. Results are reported as hazard ratios (HR) with 95% confidence intervals (CI). Kaplan-Meier curves were used to assess the incidence and timing of MACCE. Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA), version 22.0. For all analyses, $P < 0.05$ was considered significant. All statistical analyses were conducted using SAS® (version 9.4, SAS Institute Inc. Cary, NC, USA).

Results

Patients Characteristics

Among a total of 3,249 patients registered in the study, 3,077 were included in the analysis. The distribution of patients and the reasons for the exclusion of 172 patients are provided in Fig. 2. About one-fourth of patients (N = 726, 23.6%) were identified as the naïve cohort, and 2,351 (76.4%) patients constituted the switch cohort. Patient demographics and baseline disease information are provided in Table 1. The mean age of the patients was 60.6 ± 10.2 years; 776 (25.2%) patients were diagnosed with ST-segment elevation MI at index PCI period. Compared with the naïve cohort, the switch cohort was older, with a higher proportion of female patients. Comorbidities, such as hypertension (naïve vs. switch; 46.0% vs. 55.5%, $P < 0.001$), dyslipidemia (25.5% vs. 36.9%, $P < 0.001$), diabetes mellitus (25.1% vs. 30.8%, $P = 0.003$), heart failure (1.0% vs. 2.7, $P = 0.007$), and previous PCI (5.5% vs. 12.5, $P < 0.001$), were more common in the switch cohort. Also, the proportions of high-risk procedural factors, such as multi-vessel disease (44.7% vs. 53.5%, $P = 0.001$) and ACC/AHA type C lesions (26.4% vs. 51.3%, $P < 0.001$), were higher in the switch cohort than in the naïve cohort.

Table 1
Patient Demographics and Baseline Information

	Total (N = 3077)	Naïve cohort (N = 726)	Switch cohort (N = 2351)	P value
Age, years	60.6 ± 10.2	57.7 ± 9.6	61.56 ± 10.2	< 0.001
- < 75 years	2795 (90.8)	715 (98.5)	2080 (88.5)	
- ≥ 75 years	282 (9.2)	11 (1.5)	271 (11.5)	
Sex				< 0.001
- Female	522 (17.0)	74 (10.2)	448 (19.1)	
- Male	2555 (83.0)	652 (89.8)	1903 (80.9)	
Body weight, kg	70.0 ± 11.0	71.9 ± 10.8	69.5 ± 11.0	< 0.001
BMI, kg/m^2	25.2 ± 3.1	25.4 ± 3.1	25.2 ± 3.1	0.136
Prasugrel	1203(39.10)	103(14.19)	1100(46.79)	< 0.0001
5mg	1874(60.90)	623(85.81)	1251(53.21)	
10mg				
Clinical characteristics				
Hypertension	1636 (53.2)	334 (46.0)	1302 (55.5)	< 0.001
Dyslipidemia	1052 (34.2)	185 (25.5)	867 (36.9)	< 0.001
Diabetes mellitus	906 (29.4)	182 (25.1)	724 (30.8)	0.003
Chronic kidney disease	48 (1.6)	8 (1.1)	40 (1.7)	0.255
Heart failure	70 (2.3)	7 (1.0)	63 (2.7)	0.007
Smoking status				< 0.001
- Never-smoker	1235 (40.1)	265 (36.5)	970 (41.3)	
- Ex-smoker	606 (19.7)	131 (18.0)	475 (20.2)	

Numbers represent mean ± standard deviation for continuous variables or number of patients (percentage) for categorical variables. BMI = body mass index; CAD = coronary artery disease; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; DES = drug-eluting stent; IVUS = intravascular ultrasound-guided; STEMI = ST-segment elevation myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction

	Total (N = 3077)	Naïve cohort (N = 726)	Switch cohort (N = 2351)	P value
- Current smoker	1180 (38.4)	324 (44.6)	856 (36.4)	
Previous MI	131 (4.3)	25 (3.4)	106 (4.5)	0.214
Previous PCI	333 (10.8)	40 (5.5)	293 (12.5)	< 0.001
Previous CABG	9 (0.3)	2 (0.3)	7 (0.3)	1.000
Family history of CAD	297 (9.7)	91 (12.5)	206 (8.8)	0.003
Clinical presentation				< 0.001
- STEMI	776 (25.2)	228 (31.4)	548 (23.3)	
- NSTEMI	746 (24.2)	192 (26.5)	554 (23.6)	
- Unstable angina	1555 (50.5)	306 (42.2)	1249 (53.1)	
Angiographic characteristics				
Diseased vessels				0.001
- One vessel disease	1493 (48.5)	401 (55.2)	1092 (46.5)	
- Two vessel disease	948 (30.8)	202 (27.8)	746 (31.7)	
- Three vessel disease	635 (20.6)	123 (16.9)	512 (21.8)	
Treated lesion				0.822
- Left main coronary artery	54/3804 (1.4)	10/876 (1.1)	44/2928 (1.5)	
- Left anterior descending artery	1818/3804 (47.8)	425/876 (48.5)	1393/2928 (47.6)	
- Left circumflex artery	792/3804 (20.8)	183/876 (20.9)	609/2928 (20.8)	
- Right coronary artery	1131/3804 (29.7)	257/876 (29.3)	874/2928 (29.9)	
ACC/AHA lesion type				< 0.001
- Type A	369/3557 (10.4)	169/830 (20.4)	200/2727 (7.3)	

Numbers represent mean ± standard deviation for continuous variables or number of patients (percentage) for categorical variables. BMI = body mass index; CAD = coronary artery disease; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; DES = drug-eluting stent; IVUS = intravascular ultrasound-guided; STEMI = ST-segment elevation myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction

	Total (N = 3077)	Naïve cohort (N = 726)	Switch cohort (N = 2351)	P value
- Type B1	913/3557 (25.7)	280/830 (33.7)	633/2727 (23.2)	
- Type B2	658/3557 (18.5)	162/830 (19.5)	496/2727 (18.2)	
- Type C	1617/3557 (45.5)	219/830 (26.4)	1398/2727 (51.3)	
Procedural characteristics				
IVUS usage	1084/3075 (35.3)	245/726 (33.8)	839/2349 (35.7)	0.331
DES usage	2812/2907 (96.7)	696/726 (95.9)	2116/2181 (97.0)	0.131
Procedure success	2159/2259 (95.6)	463/482 (96.1)	1696/1777 (95.4)	0.560
Lesion success	1985/2087 (95.1)	454/473 (96.0)	1531/1614 (94.9)	0.318
Device success	2003/2101 (95.3)	457/476 (96.0)	1546/1625 (95.1)	0.429

Numbers represent mean ± standard deviation for continuous variables or number of patients (percentage) for categorical variables. BMI = body mass index; CAD = coronary artery disease; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; DES = drug-eluting stent; IVUS = intravascular ultrasound-guided; STEMI = ST-segment elevation myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction

Regarding prasugrel use in the switch cohort, the mean time elapsed since index PCI to prasugrel initiation was 15.1 ± 30.9 days; the distribution of this parameter is shown in **Additional file 1: Figure S1**. As shown in Table 2, the most common reason for conversion to prasugrel in the switch cohort was the necessity for a more potent antiplatelet agent (switching from clopidogrel to prasugrel; 56.3%) followed by decreased medication compliance with a twice-daily regimen of the previous agent (switching from ticagrelor to prasugrel; 27.7%) (Table 2). The median duration of prasugrel treatment was 306.4 ± 94.4 days.

Table 2
Reasons for Switching to Prasugrel

	Switch cohort N (%) (Total N = 2351)
Necessity for a more potent antiplatelet agent	1324 (56.3)
Decreased medication compliance with a twice-daily regimen	652 (27.7)
Adverse events of the previous agent	247 (10.5)
Drug interaction between the previous agent and other concomitant medications	91 (3.9)
Over-inhibition of platelet aggregation of the previous agent	37(1.6)

Incidence Of Major Cardiac And Cerebrovascular Events

During a 12-month follow-up period, 55 patients (1.8%) experienced at least one MACCE. The incidence of MACCE did not differ between the naïve and switch cohort (1.7% vs. 1.8%, P = 0.723). In multivariate analysis, the switch cohort was not associated with a higher risk of MACCE (HR 1.14, 95% CI 0.56–2.30, P = 0.722), while STEMI was associated with a higher risk of MACCE (HR 2.30, 95% CI 1.30–4.07, P = 0.004, Additional file 2: Table S1). A Kaplan-Meir survival analysis showed a similar result (log-rank P = 0.777, Fig. 3).

Secondary Endpoints

Table 3 presents the results for different composite endpoints and the incidence rates for each individual event. No significant differences in the effectiveness endpoint and safety endpoint were found between the naïve and switch cohort. The occurrence rates for other individual endpoints were also similar in both cohorts. In multivariate analysis, the treatment strategy (naïve and switch cohort) was not associated with a higher risk of key secondary endpoints, while STEMI was associated with a higher risk of the safety endpoint (HR 2.94, 95% CI 1.89–4.56, P < 0.001, Additional file 3: Table S2). In subgroup analysis, no significant interaction was observed between the treatment strategy and the incidence of MACCE across various subgroups (Fig. 4). Additionally, there was no difference in the adverse event rate according to the reason why prasugrel was switched from either a different agent, within the switch cohort (**Additional file 4: Table S3)**.

Table 3
Clinical Endpoints

	Total (N = 3077)	Naïve cohort (N = 726)	Switch cohort (N = 2351)	HR [95% CI]	P-Value
MACCE	55(1.8)	12 (1.7)	43 (1.8)	1.14 [0.56, 2.30]	0.723
Key Secondary Endpoints					
- Effectiveness endpoint	30(1.0)	5 (0.7)	25 (1.1)	1.64 [0.54, 4.95]	0.384
- Safety endpoint	98(3.2)	27 (3.7)	71 (3.0)	0.70 [0.43, 1.14]	0.154
Individual Events					
- All-cause death	18(0.6)	3 (0.4)	15 (0.6)	0.89 [0.23, 3.48]	0.863
- Cardiovascular death	4(0.1)	2 (0.3)	2 (0.1)	0.27 [0.03, 2.41]	0.238
- Nonfatal MI	14(0.5)	3 (0.4)	11 (0.5)	1.69 [0.35, 8.16]	0.513
- Nonfatal stroke	12(0.4)	0(0)	12(0.5)	NA [0.0, NA]	0.990
- Stent thrombosis	12(0.4)	1 (0.1)	11 (0.5)	3.46 [0.42, 28.26]	0.247
- Target vessel revascularization	17(0.6)	5 (0.7)	12 (0.5)	0.57 [0.18, 1.78]	0.334
- Bleeding					
TIMI major bleeding	29(0.9)	7 (1.0)	22 (0.9)	1.00 [0.40, 2.49]	0.997
TIMI minor bleeding	81(2.6)	22 (3.0)	59 (2.5)	0.69 [0.40, 1.19]	0.187

A multivariable cox regression analysis was performed by including the variables with a $P < 0.1$. Effectiveness endpoint denotes a composite of cardiovascular death, nonfatal MI, and nonfatal stroke; Safety endpoints denotes a composite of TIMI major or minor bleeding unrelated to CABG.

Adverse Events

During a 12-month follow-up period, 399 events reported in 345 patients (11.2%) were classified as adverse drug reactions (ADRs). The common ADRs, with a frequency of 1% or higher, included contusion (3.9%), epistaxis (1.8%), and increased tendency to bruise (1.2%). A total of 48 events reported in 44

patients (1.4%) were classified as serious ADRs. Serious ADRs with a frequency of 0.1% or higher included cardiac disorders (0.3%), vascular stent stenosis (0.2%), coronary artery stenosis (0.2%), gastric ulcer hemorrhage (0.1%), and hematochezia (0.1%). In 182 patients (5.9%), prasugrel was discontinued due to adverse events, such as contusion (1.0%), epistaxis (0.7%), and other events occurring at rates lower than 0.5%. Comparative analysis of the results for the naïve and switch cohort did not show significant differences in the rates for ADRs (10.6%, 77/726 vs. 11.4%, 268/2351, P = 0.554), serious ADRs (1.1%, 8/726 vs. 1.5%, 36/2351, P = 0.394), and AEs leading to prasugrel discontinuation (5.5%, 40/726 vs. 6.0%, 142/2351, P = 0.597).

Discussion

This real-world study included 3,077 ACS patients who received prasugrel therapy after PCI. Among the entire population, 726 patients were $P2Y_{12}$ inhibitor-naïve, and the other 2,351 were prescribed prasugrel as a substitute agent after clopidogrel or ticagrelor pre-treatment (switch cohort). The incidence of MACCE, defined as cardiovascular death, non-fatal MI, non-fatal stroke, or TIMI major bleeding unrelated to CABG, was 1.8% in the entire study population, with no significant difference found between the naïve and the switch cohort. Also, no significant differences were found between the cohorts in terms of the key secondary endpoints and adverse events (Fig. 5).

The study provided clinically relevant insight into the safety and effectiveness of prasugrel in Korean ACS patients who are potential candidates for treatment with this potent $P2Y_{12}$ inhibitor. In the pivotal trial of prasugrel (TRITON-TIMI 38), the primary efficacy endpoint (a composite of cardiovascular mortality, non-fatal MI, or non-fatal stroke) occurred in 9.9% and major bleeding in 2.4% of patients who received this agent(5). Meanwhile, in a recent Korean PMS study which included 3,283 patients with ACS who underwent successful PCI, the efficacy outcome (a composite of cardiovascular death, MI, stroke, stent thrombosis or unplanned coronary revascularization) occurred in 0.85% and major bleeding events in 0.93%(14). The event rate in our study was markedly lower than that of the pivotal trial(5), but similar as in the recent PMS study of Korean patients(14). According to the authors of the latter study, the lower incidence of the composite endpoint defined as cardiovascular death, MI, stroke, stent thrombosis and unplanned CABG might be attributed to selective characteristics of the patients, with a lesser representation of those with established risk factors of bleeding, as well as to the progress in the strut design and drug coating of stents(15).

According to the literature, the decision to switch from one antiplatelet agent to another may be driven by various factors, including clinical setting, patient characteristics, concomitant therapies, costs, social issues, development of side effects, medication adherence, and patient/physician preference(17). However, it needs to be stressed that although switching between $P2Y_{12}$ receptor-inhibiting therapies has been practiced increasingly nowadays, it has not been systematized in any published guidelines, and most evidence and recommendations in this matter originate from pharmacodynamic and registry data(6, 17, 18, 19). Our present study identified a number of reasons to switch to prasugrel. The most common cause was the necessity for a more potent antiplatelet agent (56.3%), resulting in a change from

clopidogrel to prasugrel. The second most common reason (27.7%) was an intent to increase the medication compliance through switching from a twice-daily regimen (ticagrelor) to a once-daily regimen (prasugrel). The third cause was the occurrence of adverse events after the previously administered drug (10.5%). Such a distribution of the reasons to switch reflects the strengths of prasugrel as a potent $P2Y_{12}$ inhibitor with a low adverse event rate and the once-daily regimen that promotes higher medication compliance. Regarding the clinical outcomes, they appeared to be similar in the naïve and switch cohort, even though the latter included patients with more clinical and procedural risk factors. Overall, prasugrel was well-tolerated and equally efficacious in all patients, even if not used as a primary treatment.

The results of the present study should be discussed in the context of the East Asian paradox. Based on the observation that East Asian patients are less prone to thrombotic events and more prone to bleeding, it has been suggested that their threshold of platelet reactivity is different than in Caucasians(20). While this notion was confirmed in the case of clopidogrel(11), the results for the potent $P2Y_{12}$ inhibitors in the East Asian population are inconclusive, with anti-ischemic benefits outweighing the risk of bleeding in some(14, 21, 22, 23) albeit not all studies(9, 24). As a result, many physicians in South Korea are still reluctant to apply the Western guidelines for antiplatelet agent use(10). However, the results of the present study, as well as the outcomes of the recent PMS study(14), suggest that prasugrel can be used safely in Korean ACS patients after PCI.

Study Limitations

The primary limitation of this study stems from the lack of a control group. Furthermore, no robust statistical analyses could be conducted given the small size of some subgroups. While these limitations should be considered during the interpretation of the results, also the strengths of the study related to its real-world character should be highlighted, namely, large sample size and access to information on atypical prescription patterns.

Conclusions

DAPT with prasugrel seems to be safe and effective both as a primary treatment and as a substitute for other $P2Y_{12}$ inhibitors in the routine management of Korean ACS patients after PCI.

Abbreviations

ACS
acute coronary syndrome
MI
myocardial infarction
PCI
percutaneous coronary intervention

MACCE
major adverse cardiac and cerebrovascular event
TIMI
thrombolysis in myocardial infarction
CABG
coronary-artery bypass grafting.

Declarations

Ethics approval and consent to participate

The protocol of this study was approved by the Institutional Review Board at Seoul National University Hospital (H-1702-054-832) and the ethics committee of each participating institutions. Written informed consent was obtained for all patients registered in the study. The study was conducted in accordance with the principles established by the Declaration of Helsinki(2013).

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JK: Conceptualization, Formal analysis, Investigation, Supervision, Validation, Writing - original draft, Writing - review & editing. J-KH: Writing - review & editing. KWP: Conceptualization, Investigation, Methodology, Writing - review & editing. H-MY, H-JK, B-KK, E-HC, J-YL, S-DP, Y-HL: Investigation, Writing - review & editing. H-MK: Visualization, Writing - original draft. J-HH: Visualization. H-SK: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing - review & editing. All authors read and approved the final manuscript.

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References

1. Sanchis-Gomar F, Perez-Quilis C, Leischik R, et al. Epidemiology of coronary heart disease and acute coronary syndrome. Ann Transl Med 2016;4:256. doi:10.21037/atm.2016.06.33.
2. Bhatt DL. Percutaneous Coronary Intervention in 2018. JAMA 2018;319:2127–2128.
3. D'Ascenzo F, Bollati M, Clementi F, et al. Incidence and predictors of coronary stent thrombosis: evidence from an international collaborative meta-analysis including 30 studies, 221,066 patients, and 4276 thromboses. Int J Cardiol 2013;167:575–584.
4. Collet J-P, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2020. doi:10.1093/eurheartj/ehaa575.
5. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–2015.
6. Angiolillo DJ, Rollini F, Storey RF, et al. International Expert Consensus on Switching Platelet P2Y(12) Receptor-Inhibiting Therapies. Circulation 2017;136:1955–1975.
7. Levine GN, Jeong Y-H, Goto S, et al. Expert consensus document: World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. Nat Rev Cardiol 2014;11:597–606.
8. Huo Y, Jeong Y-H, Gong Y, et al. 2018 update of expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. Sci Bull 2019;64:166–179.
9. Kang J, Han J-K, Ahn Y, et al. Third-Generation P2Y12 Inhibitors in East Asian Acute Myocardial Infarction Patients: A Nationwide Prospective Multicentre Study. Thromb Haemost 2018;118:591–600.
10. Kang J, Kim HS. The Evolving Concept of Dual Antiplatelet Therapy after Percutaneous Coronary Intervention: Focus on Unique Feature of East Asian and “Asian Paradox”. Korean Circ J 2018;48:537–551.
11. Kang J, Park KW, Palmerini T, et al. Racial Differences in Ischaemia/Bleeding Risk Trade-Off during Anti-Platelet Therapy: Individual Patient Level Landmark Meta-Analysis from Seven RCTs. Thromb Haemost 2019;119:149–162.
12. Urban P, Mehran R, Colleran R, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. Eur Heart J 2019;40:2632–2653.
13. Park D-W, Kwon O, Jang J-S, et al. Clinically Significant Bleeding With Ticagrelor Versus Clopidogrel in Korean Patients With Acute Coronary Syndromes Intended for Invasive Management: A Randomized Clinical Trial. Circulation 2019;140:1865–1877.
14. Chon M-K, Jung S-M, Lee S-Y, et al. Incidence of Cardiovascular Events and Safety Profile of Prasugrel in Korean Patients With Acute Coronary Syndrome. Circ J 2020;84:1582–1586.

15. Alraies MC, Lee SY, Lipinski MJ, et al. Effect of Bleeding Risk on Type of Stent Used in Patients Presenting With Acute Coronary Syndrome. Am J Cardiol 2017;120:1272–1278.
16. Rollini F, Franchi F, Angiolillo DJ. Switching P2Y12-receptor inhibitors in patients with coronary artery disease. Nat Rev Cardiol 2016;13:11–27.
17. Rollini F, Franchi F, Angiolillo DJ. Switching P2Y(12) Receptor Inhibiting Therapies. Interv Cardiol Clin 2017;6:67–89.
18. Gasecka A, Konwerski M, Pordzik J, et al. Switching between P2Y(12) antagonists - From bench to bedside. Vascul Pharmacol 2019;115:1–12.
19. Capranzano P, Capodanno D. Switching between P2Y(12) inhibitors: Rationale, methods, and expected consequences. Vascul Pharmacol 2019;116:4–7.
20. Jeong Y-H. "East Asian paradox": challenge for the current antiplatelet strategy of "one-guideline-fits-all races" in acute coronary syndrome. Curr Cardiol Rep 2014;16:485. doi:10.1007/s11886-014-0485-4.
21. Kim C, Shin DH, Ahn CM, et al. The Use Pattern and Clinical Impact of New Antiplatelet Agents Including Prasugrel and Ticagrelor on 30-day Outcomes after Acute Myocardial Infarction in Korea: Korean Health Insurance Review and Assessment Data. Korean Circ J 2017;47:888–897.
22. Kang H-J, Clare RM, Gao R, et al. Ticagrelor versus clopidogrel in Asian patients with acute coronary syndrome: A retrospective analysis from the Platelet Inhibition and Patient Outcomes (PLATO) Trial. Am Heart J 2015;169:899–905.
23. Saito S, Isshiki T, Kimura T, et al. Efficacy and safety of adjusted-dose prasugrel compared with clopidogrel in Japanese patients with acute coronary syndrome: the PRASFIT-ACS study. Circ J 2014;78:1684–1692.
24. Goto S, Huang C-H, Park S-J, et al. Ticagrelor vs. clopidogrel in Japanese, Korean and Taiwanese patients with acute coronary syndrome – randomized, double-blind, phase III PHILO study. Circ J 2015;79:2452–2460.

Figures

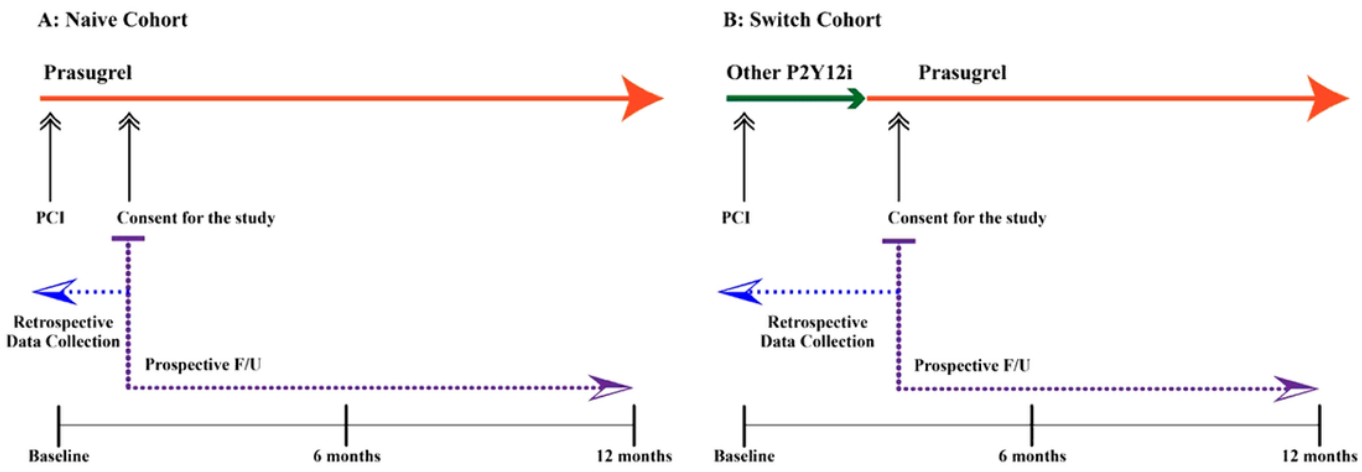

Figure 1

Study scheme

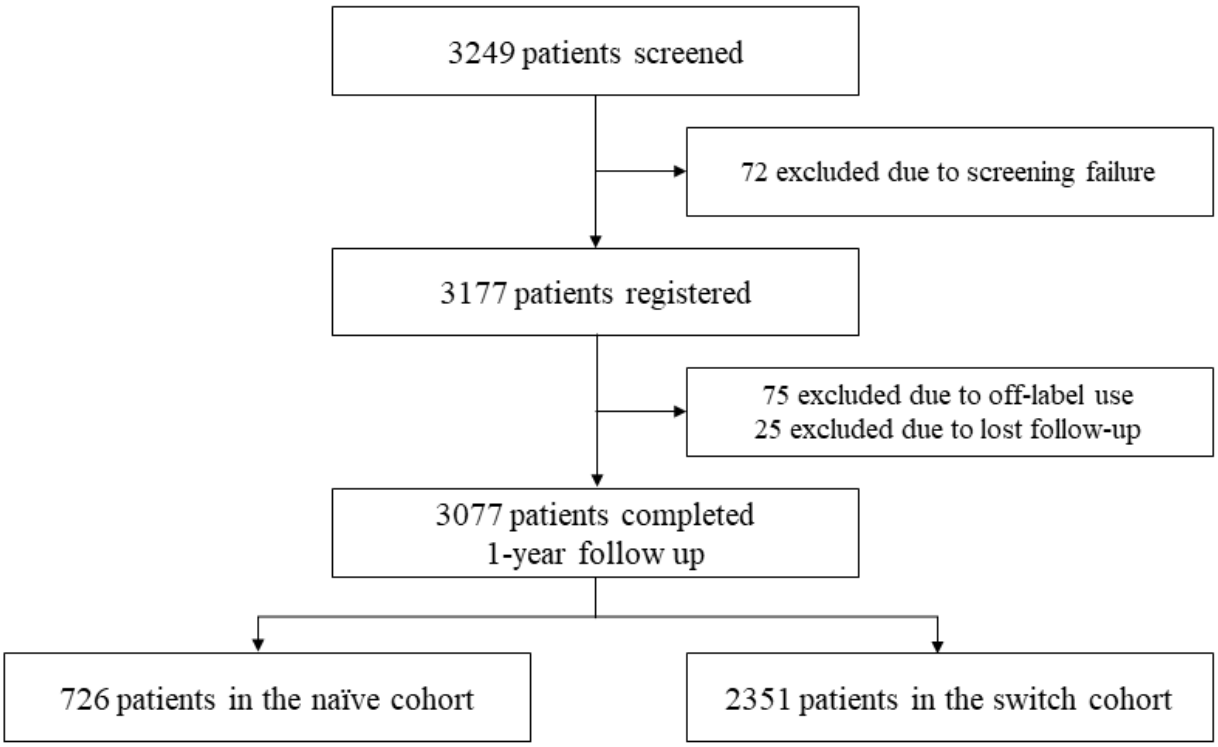

Figure 2

Patient distribution

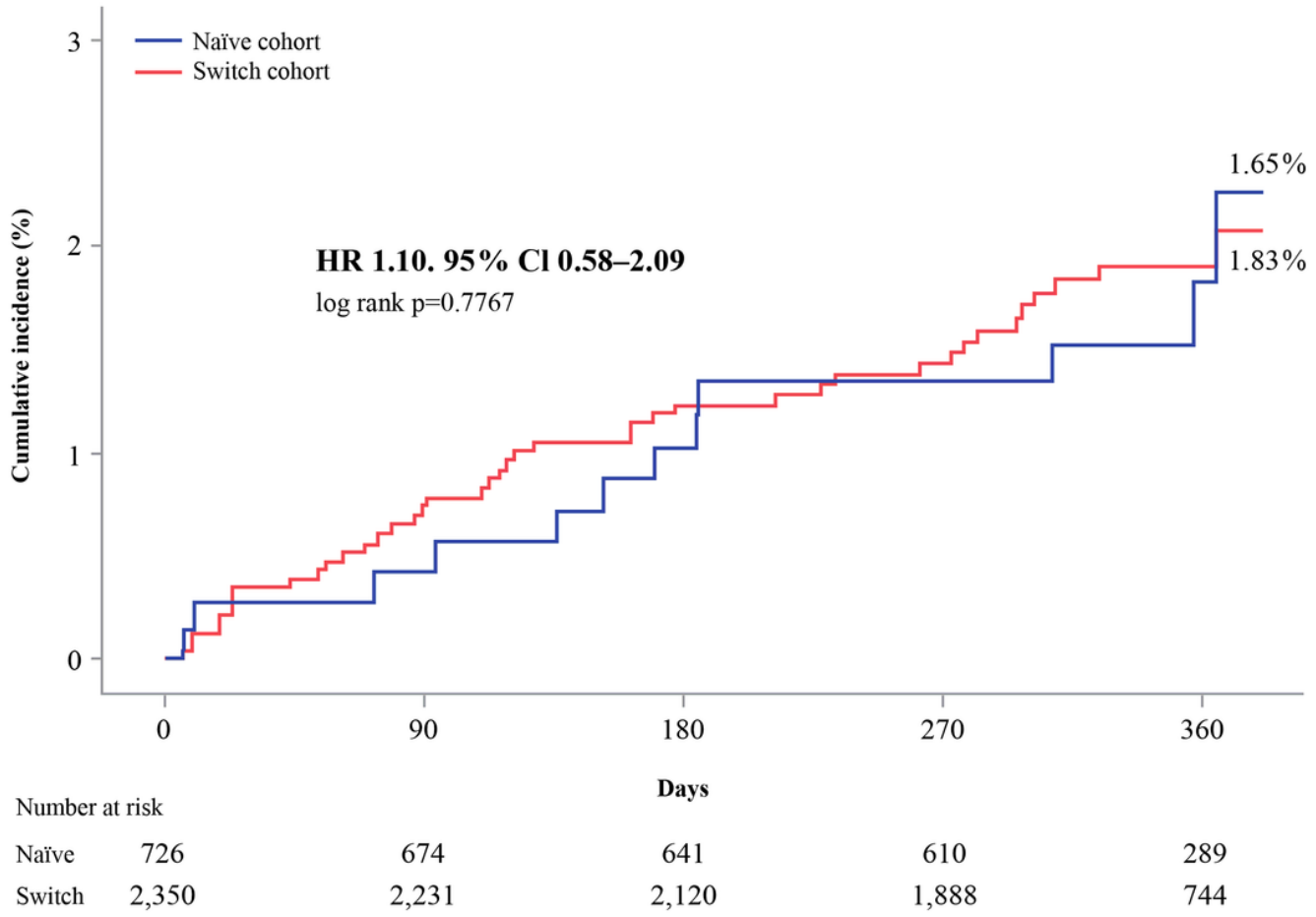

Figure 3

Kaplan-Meier curves for the incidence of MACCE

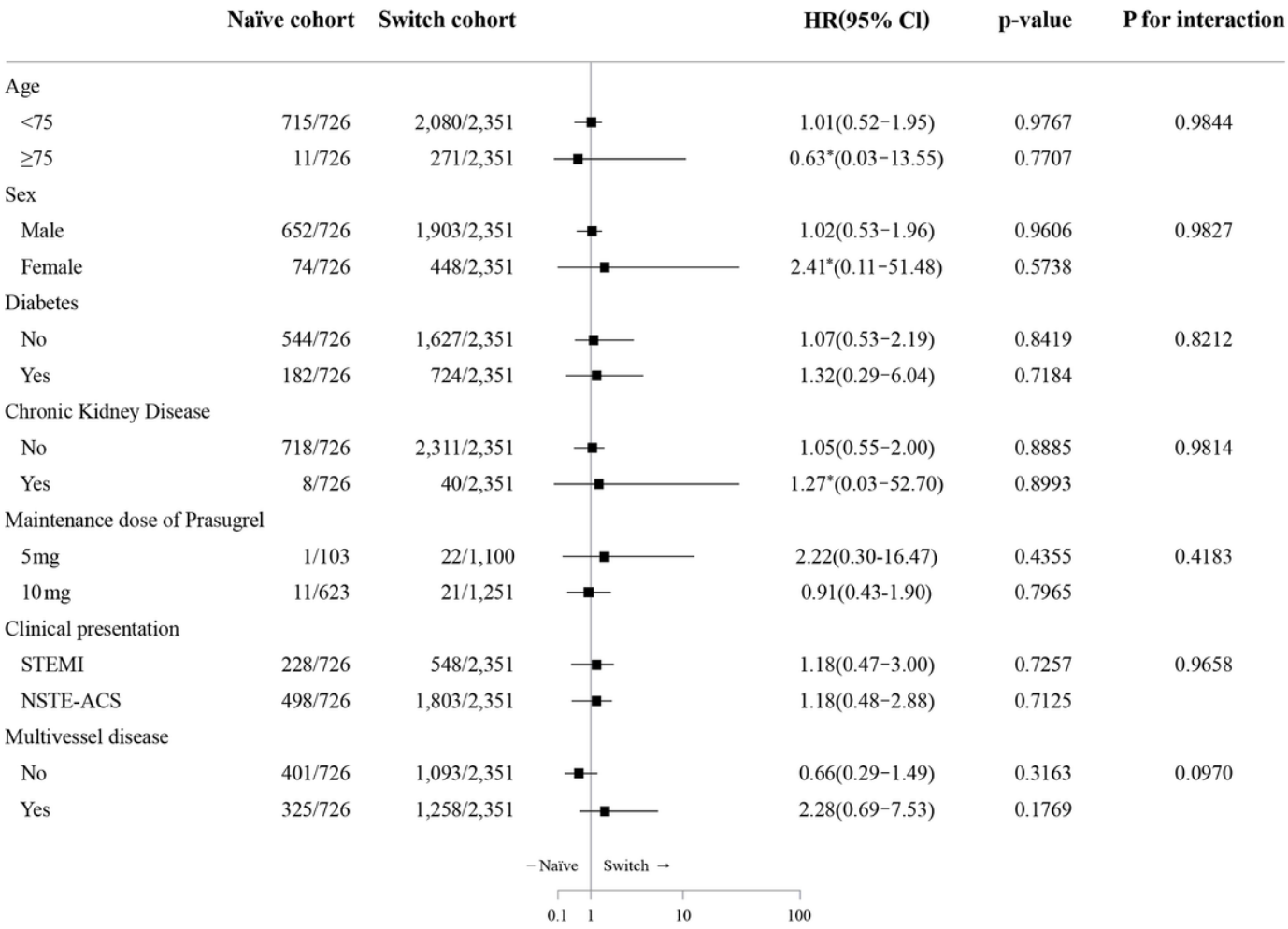

Figure 4

Subgroup analysis of the incidence of MACCE

CKD=chronic kidney disease; STEMI=ST-segment elevation myocardial infarction; NSTE-ACS=non-ST-segment elevation acute coronary syndrome.

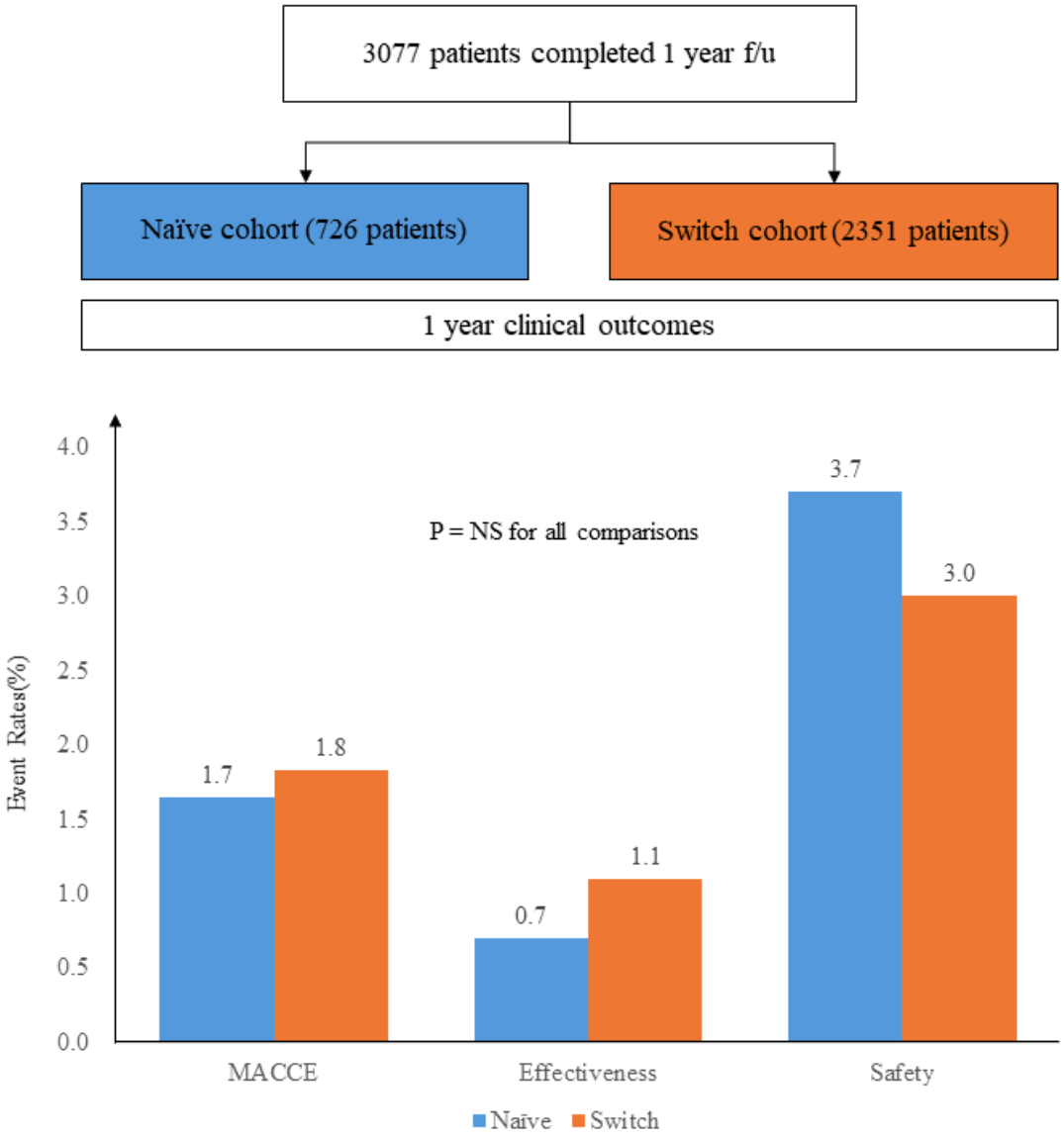

Figure 5

One year clinical outcomes

MACCE denotes a composite cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and TIMI major bleeding; Effectiveness endpoint denotes a composite of cardiovascular death, nonfatal MI,

and nonfatal stroke; Safety endpoints denotes a composite of TIMI major or minor bleeding unrelated to CABG.

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