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Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study

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Aims Newer P2Y12 blockers (prasugrel and ticagrelor) demonstrated significant ischaemic benefit over clopidogrel after acute coronary syndrome (ACS). However, both drugs are associated with an increase in bleeding complications. The objective of the present study was to evaluate the benefit of switching dual antiplatelet therapy (DAPT) from aspirin plus a newer P2Y12 blocker to aspirin plus clopidogrel 1 month after ACS.

Methods and results We performed an open-label, monocentric, and randomized trial. From March 2014 to April 2016, patients admitted with ACS requiring coronary intervention, on aspirin and a newer P2Y12 blocker and without adverse event at 1 month, were assigned to switch to aspirin and clopidogrel (switched DAPT) or continuation of their drug regimen (unchanged DAPT). The primary outcome was a composite of cardiovascular death, urgent revascularization, stroke and bleeding as defined by the Bleeding Academic Research Consortium (BARC) classification ≥2 at 1 year post ACS. Six hundred and forty six patients were randomized and 645 analysed, corresponding to 322 patients in the switched DAPT and 323 in the unchanged DAPT group. The primary endpoint occurred in 43 (13.4%) patients in the switched DAPT group and in 85 (26.3%) patients in the unchanged DAPT (HR 95%CI 0.48 (0.34–0.68), $P < 0.01$). No significant differences were reported on ischaemic endpoints, while BARC ≥ 2 bleeding occurred in 13 (4.0%) patients in the switched DAPT and in 48 (14.9%) in the unchanged DAPT group (HR 95%CI 0.30 (0.18–0.50), $P < 0.01$).

Conclusion A switched DAPT is superior to an unchanged DAPT strategy to prevent bleeding complications without increase in ischaemic events following ACS.

Keywords P2Y12 blockers • Acute coronary syndrome • Switch

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Introduction

After acute coronary syndrome (ACS), adequate platelet inhibition is crucial to minimize the risk of recurrent ischaemic events. Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) is currently recommended following ACS for 1 year.[1,2] Compared with clopidogrel, prasugrel, and ticagrelor, named initially as 'newer P2Y12 blockers', have a more pronounced inhibitory effect on platelet activation and have been associated with a lower risk of coronary thrombotic events in association with aspirin after ACS in the large TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis in myocardial infarction (TRITON-TIMI) and PLATelet inhibition and patient Outcomes (PLATO) randomized studies.[3,4] Consequently, newer P2Y12 inhibitors (i.e. prasugrel or ticagrelor) have become the standard therapy in association with aspirin for 12 months following ACS and are recommended over clopidogrel in the latest European Society of Cardiology guidelines.[1,2] The clinical benefit provided by these drugs is related to a significant reduction in recurrent ischaemic events (including acute and subacute stent thrombosis (ST), myocardial infarction (MI), and urgent revascularization). Although the ischaemic benefit was consistent throughout the first year, the greater reduction in ischaemic recurrence after ACS was observed during the initial 30 days following the treatment initiation.[3,4] In contrast, landmark analysis clearly demonstrated a significant increase in the bleeding risk with the newer P2Y12 inhibitors, occurring predominantly during the maintenance phase (after the first month).[5,6] However, for both drugs the net clinical benefit favoured the newer P2Y12 blockers throughout the entire study period.[3,4] These observations have led some authors to describe two phases after an ACS; a first ischaemic phase, with a high risk of recurrent thrombotic events, followed by a second phase where the risk of bleeding complications outweighs the ischaemic risk. The ischaemic phase would require a potent platelet inhibition, achieved with the newer P2Y12 blockers, while during the secondary phase the degree of platelet inhibition could be reduced (i.e. conversion to clopidogrel) to achieve an optimal balance between ischaemic benefit and bleeding risk. Therefore, the objective of the present study was to investigate the impact of switching from aspirin plus a newer P2Y12 blocker to a fixed dose combination (FDC) of aspirin and clopidogrel, in patients with no adverse event during the first month after ACS.

Methods

Study design and patients

The TOPIC (timing of platelet inhibition after ACS) randomized study was an open-label, single centre, randomized, controlled trial which was carried out at Timone Hospital, Marseille, France. The study is registered in ClinicalTrials.gov, number NCT02099422. All patients referred to the study centre from March 2014 to April 2016, were enrolled if they met the following criteria: admission for ACS requiring early percutaneous coronary intervention (PCI) within 72 h, treatment with aspirin and a newer P2Y12 blocker at discharge, no major adverse event one month after the ACS and age > 18 years. Exclusion criteria were history of intracranial bleeding, contraindication to use of aspirin, clopidogrel, prasugrel, or ticagrelor; major adverse event (ischaemic or bleeding event) within a month of ACS diagnosis; thrombocytopenia (platelet concentration lower than 50×10^9/L); major bleeding (according to the Bleeding Academic Research Consortium (BARC) criteria) in the last 12 months; long term anticoagulation (contraindication for newer P2Y12 blockers) and pregnancy. The indication for PCI was based on the current Guidelines from the European Society of Cardiology.[1,2] The inclusion criteria for patients with unstable angina or non-ST-elevation MI were ischaemic symptoms defined as chest pain at rest or *de novo* exercise-induced angina and either ST-segment deviation of 1 mm or more, elevated levels of a cardiac biomarker of necrosis or prior history of coronary artery disease. Patients with a negative troponin of lack of myocardial necrosis markers were classified as unstable angina. Patients with ST-elevation MI who underwent primary PCI within 12 hours after the onset of symptoms were enrolled.

Randomization

All patients received treatment with aspirin and a newer P2Y12 inhibitor for 1 month after the ACS. One month after the ACS, eligible patients were then randomly assigned in a 1:1 ratio to receive a FDC of aspirin 75 mg plus clopidogrel 75 mg (switched DAPT) or continuation of aspirin plus continuation of newer P2Y12 blocker (unchanged DAPT with same treatment than before randomization). The randomization sequence was computer generated at Timone hospital and patients' allocations were kept in sequentially numbered sealed envelopes. Group allocation was issued by the secretarial staff of the research department at Timone hospital.

Treatment

During the index admission, a 300 mg loading dose of aspirin was given to patients who were treatment naïve before the study. All patients were pre-treated with a loading dose of ticagrelor 180 mg or prasugrel 60 mg before PCI. At the discretion of the attending physician, patients were discharged on ticagrelor 90 mg bid or prasugrel 10 mg daily in addition to aspirin. At 1 month patients were randomly assigned to either continue with the standard regimen of aspirin plus newer P2Y12 blocker (unchanged DAPT) or receive a single tablet FDC of aspirin75 mg plus clopidogrel 75 mg (switched DAPT). To reduce the risk of bleeding, use of radial access, proton-pump inhibitors, and access-site-closure devices (when PCI was undertaken via femoral artery) were recommended but not mandatory. Other cardiac medications were given according to local guidelines.

Follow-up and end point assessments

The primary end point was a composite of cardiovascular death, unplanned hospitalization leading to urgent coronary revascularization, stroke, and bleeding episodes as defined by the BARC classification ≥ 2 at 1 year after ACS.[7] This combination of both ischaemic and bleeding events was defined as net clinical benefit. Each of the components was also evaluated independently, as well as the composite of all ischaemic events and all BARC bleeding episodes. Each bleeding event was classified separately according to the thrombosis in MI (TIMI) criteria (minimal, minor or major).[8] Additional predefined safety end points included ST according to the Academic Research Consortium criteria at 1 year.[9] Unplanned revascularization was defined as any unexpected coronary revascularization procedure (PCI or coronary artery bypass graft surgery (CABG)) during the follow up period. Stroke diagnosis was confirmed by a treating neurologist. Computed tomography or magnetic resonance imaging was used to distinguish ischaemic from haemorrhagic stroke. We also analysed adherence to the assigned therapy during the follow-up period using standardized questionnaire. All data were collected prospectively and were entered into a central database. Clinical follow-up was planned for 1 year after the index event or until the time of death,

whichever came first. Telephone-based interviews were also performed at 6 months for all patients by research nurse. All events were adjudicated by a locally trained research committee (composed by one of the research nurse and a physician) unaware of treatment allocations. Standardized questions were used to assess bleeding episodes, thrombotic events, and use of medications. All thrombotic and bleeding events requiring medical attention were verified by a research nurses committee blinded to the patient's study group, by analysis of medical records obtained from referring family doctors and hospitals. After being collected, data were analysed by physician at our institution dedicated to study follow-up.

Ethics

The ethics committee at our institution approved the study protocol, and we obtained written informed consent for participation in the study. We honoured the ethical principles for medical research involving human subjects as set out in the Declaration of Helsinki. The data management and statistical analysis were performed by the research and development section, Cardiology Department, Timone Hospital, Marseille, France.

Statistical analysis

The trial was powered to assess whether FDC of aspirin and clopidogrel (switched DAPT) was better than the association of aspirin and newer P2Y12 blocker (unchanged DAPT) in the prevention of the primary composite endpoint of bleeding and ischaemic events (net clinical benefit) in ACS patients treated with PCI. We assumed a 10% occurrence rate of any bleeding or ischaemic complication at 1 year in the switched DAPT group and of 18% in the unchanged DAPT group, based on data from large randomized studies that were available at the time of study design.[1,3,4,10] Based on these assumptions, we calculated that a minimum sample size of 319 patients in each group would be required to achieve an α level of 0.05 and statistical power of 0.80. All calculations were performed using the SPSS software (version 20.00) and Graphpad prism (version 7.0).

Continuous variables were reported as means and standard deviation or as medians and interquartile range (according to their distribution), and categorical variables were reported as count and percentages. Standard two-sided tests were used to compare continuous variables (Student *t* or Mann–Whitney *U* tests) or categorical variables (χ^2 or Fisher exact tests) between patient groups. We analysed the primary and secondary endpoints by means of a Cox model for survival analysis, with time to first event used for composite endpoints, and results reported as hazard ratio (HR) and 95% confidence interval (95% CI) for switched DAPT vs. unchanged DAPT. The primary analysis was assessed by modified intention to treat analysis. This study is registered with ClinicalTrials.gov, number NCT02099422.

Results

Baseline

Between March 2014 and May 2016, 646 patients were enrolled of whom 323 were randomly assigned to the switched DAPT group and 323 to the unchanged DAPT group (*Figure 1*). Follow-up at 1 year was performed for 316 (98.1%) patients in the switched DAPT group and 318 (98.5%) in the unchanged DAPT group. The median follow-up for both groups was 359 days, and the mean follow up was 355 days in the switched DAPT group vs. 356 days in the unchanged DAPT group. The characteristics of the studied cohort are summarized in *Table 1*. Baseline and procedural characteristics were similar in the two groups (*Tables 1 and 2*).

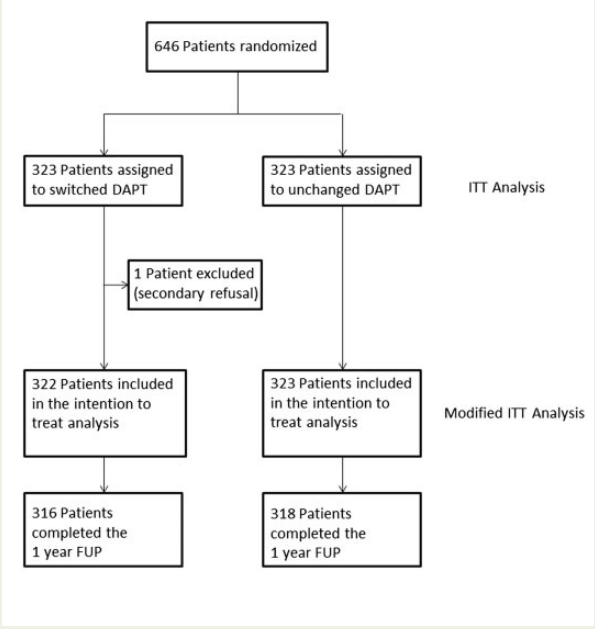

Figure 1 Flow chart. FUP, follow-up; ITT, intention to treat.

Medication adherence

At 1 year after ACS, the allocated DAPT regimen was still used by 277 (86.0%) of 322 patients in the switched DAPT group and 242 (74.9%) of 323 patients in the unchanged DAPT group ($P < 0.01$). A newer P2Y12 blocker was being used by 18 (5.6%) of 322 patients in the switched DAPT group, while 19 patients (5.9%) were treated with aspirin monotherapy and two patients (0.6%) had no antiplatelet agents. The reason for the treatment modification was an ischaemic event in 14 patients, a bleeding event in 9 patients, non-urgent surgery in 5 patients and unclear cause for 11 patients. Clopidogrel was being used by 54 (16.7%) of the 323 patients in the unchanged DAPT group, while 21 patients (6.5%) received aspirin monotherapy and 1 (0.3%) no antiplatelet. The reason for the treatment modification was a stroke in 3 patients, a bleeding event in 31 patients, non-urgent surgery in 5 patients, dyspnoea in 12 patients, need for triple therapy in 4 patients and an unclear cause for 21 patients.

Endpoints

During the 1 year follow-up, the rate of primary endpoint occurred in 43 (13.4%) patients in the switched DAPT group and in 85 (26.3%) patients in the unchanged DAPT group (HR 95%CI 0.48 (0.34–0.68), $P < 0.01$) (*Table 3*, *Figure 2*). Bleeding events defined as BARC ≥ 2 occurred in 13 (4.0%) patients in the switched DAPT group and in 48 patients (14.9%) in the unchanged DAPT group (HR 95%CI 0.30 (0.18–0.50), $P < 0.01$) (*Table 3*, *Figure 3A*). Bleeding events defined as all BARC occurred in 30 (9.3%) patients in the switched DAPT group and in 76 (23.5%) in the unchanged DAPT group (HR 95%CI 0.39 (0.27–0.57), $P < 0.01$) (*Table 3*, *Figure 3B*). Bleeding events as classified TIMI major occurred in one (0.3%) patients in the switched DAPT

Table 1 Clinical characteristics and treatment as baseline

Characteristic	All patients (n = 646)	Switched DAPT (n = 323)	Unchanged DAPT (n = 323)	P-value
Male gender (n, %)	532 (82%)	261 (81%)	271 (84%)	0.30
Age (years; m ± SD)	60.0 ± 10.2	60.6 ± 10.2	59.6 ± 10.3	0.21
BMI (kg/m^2; m ± SD)	27.2 ± 4.5	27.1 ± 4.4	27.3 ± 4.5	0.55
Medical history, (n, %)				
Hypertension	313 (48%)	151 (47%)	162 (50%)	0.39
Type II diabetes	177 (27%)	84 (26%)	93 (29%)	0.43
Dyslipidaemia	283 (44%)	136 (42%)	147 (46%)	0.38
Current smoker	286 (44%)	145 (45%)	141 (44%)	0.75
Previous CAD	197 (30%)	100 (31%)	97 (30%)	0.80
Treatment, (n, %)				
Beta blocker	445 (69%)	213 (66%)	232 (72%)	0.11
RAS-inhibitors	486 (75%)	236 (73%)	250 (77%)	0.20
Statin	614 (95%)	302 (93%)	312 (97%)	0.07
PPI	639 (99%)	316 (98%)	323 (100%)	0.01
Antiplatelet agent, (n, %)				0.53
Ticagrelor (n, %)	276 (43%)	142 (44%)	134 (42%)	
Prasugrel (n, %)	370 (57%)	181 (56%)	189 (59%)	
Presentation				0.06
STEMI (n, %)	257 (40%)	117 (36%)	140 (43%)	
UA or NSTEMI (n, %)	389 (60%)	206 (64%)	183 (57%)	
EF (%; m ± SD)	56.4 ± 7.7	57.1 ± 7.1	55.8 ± 8.2	0.04
Biological parameters				
CRP (mg/L; m ± SD)	4.5 ± 13.7	3.8 ± 6.7	5.3 ± 18.1	0.18
Platelets (G/L; m ± SD)	236.2 ± 68.6	234.0 ± 63.0	238.2 ± 73.7	0.44
Triglycerides (G/L; m ± SD)	1.4 ± 1.1	1.4 ± 1.3	1.4 ± 0.9	0.94
Cholesterol (G/L; m ± SD)	1.5 ± 0.4	1.5 ± 0.4	1.5 ± 0.4	0.41
HDL (G/L; m ± SD)	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.18
LDL (G/L; m ± SD)	0.8 ± 0.3	0.8 ± 0.3	0.8 ± 0.4	0.77
Creatinine (µmol/L)	91.3 ± 50.9	87.3 ± 28.9	95.1 ± 65.4	0.05

M, mean; SD, standard deviation; BMI, body mass index; CAD, coronary artery disease; RAS, renin-angiotensin inhibitors; PPI, proton pump inhibitors; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; UA, unstable angina; EF, ejection fraction; HDL, High density lipoprotein; LDL, low density lipoprotein; DAPT, dual antiplatelet therapy.

group and in four patients (1.2%) in the unchanged DAPT group (OR 95%CI 0.30 (0.05–1.73), P = 0.18); bleeding events defined as TIMI minor occurred in 9 (2.8%) patients in the switched DAPT group and in 26 patients (8.0%) in the unchanged DAPT group (OR 95%CI 0.37 (0.19–0.71), P < 0.01) while bleeding events defined as TIMI minimal occurred in 20 (6.2%) patients in the switched DAPT group and in 46 patients (14.2%) in the unchanged DAPT group (OR 95%CI 0.44 (0.27–0.71), P < 0.01).

Any ischaemic endpoint occurred in 30 (9.3%) patients in the switched DAPT group and in 37 (11.5%) in the unchanged DAPT group (HR 95%CI 0.80 (0.50–1.29), P = 0.36) (*Table 3*). 28 (8.7%) patients in the switched DAPT group and 30 (9.3%) in the unchanged DAPT group underwent unplanned revascularization at 1 year (HR 95%CI 0.93 (0.56–1.55), P = 0.78) (*Table 3*); one patient in the switched DAPT group and three patients in the unchanged DAPT group had a stroke event at 1 year (HR 95%CI 0.37 (0.05–2.6), P = 0.32); one patient in the switched DAPT group and four patients in the unchanged DAPT group had died from a cardiovascular cause at 1 year (HR 95%CI 0.30 (0.05–1.73), P = 0.18) (*Table 3*). The rate of ST was very low and not different between the two groups (four patients in the switched DAPT group vs. three in the unchanged DAPT group). The benefit of the switched strategy for the primary endpoint was consistent across ACS presentation, type of P2Y12 blockers and presence or not of diabetes subgroups (*Figure 4*).

Discussion

The main finding of our study is that downgrading DAPT from a newer P2Y12 blocker plus aspirin to a FDC of aspirin and clopidogrel, 1 month after an ACS, was associated with a net clinical benefit mainly driven by a significant reduction in bleeding complications, while the risk of recurrent ischaemic events was not different.

Both ticagrelor and prasugrel have proved superiority to clopidogrel for the treatment of ACS, driven by a significant reduction of recurrent ischaemic events.[3,4] However, even if this difference persisted throughout the study period, the greatest ischaemic benefit was observed during the earliest phase after ACS. In the PLATO trial,

Table 2 Baseline procedural characteristics

	All patients (n = 646)	Switched DAPT (n = 323)	Unchanged DAPT (n = 323)	P-value
Access site, *n* (%):				0.11
Femoral	28 (4%)	17 (5%)	11 (3%)	
Radial	618 (96%)	306 (95%)	312 (97%)	
Culprit lesion, *n* (%):				0.15
LMS	24 (4%)	7 (2%)	17 (5%)	
LAD	299 (46%)	155 (48%)	144 (45%)	
LCx	118 (18%)	65 (20%)	53 (16%)	
RCA	202 (31%)	95 (29%)	107 (33%)	
Venous graft	3 (1%)	1 (0%)	2 (1%)	
Number of vessel treated, *n* (%):				0.19
1	548 (85%)	266 (82%)	282 (87%)	
2	84 (13%)	48 (15%)	36 (11%)	
3	14 (2%)	9 (3%)	5 (2%)	
Stent type, *n* (%)				0.10
DES	585 (91%)	297 (92%)	288 (89%)	
BVS	21 (3%)	13 (4%)	8 (3%)	
BMS	24 (4%)	8 (3%)	16 (5%)	
None	16 (3%)	5 (2%)	11 (3%)	
Number of stent (m ± SD)	1.4 ± 0.7	1.4 ± 0.7	1.4 ± 0.7	0.39
Stent diameter, mm (m ± SD)	2.8 ± 0.6	2.8 ± 0.6	2.8 ± 0.5	0.43
Stent length, mm (m ± SD)	26.4 ± 16.4	26.9 ± 16.9	26.4 ± 15.8	0.64

If more than one stent used, the stent length denotes the sum of all stent lengths.
M, mean; SD, standard deviation; PCI, percutaneous coronary intervention; LMS, left main stem; LAD, left anterior descending coronary artery; RCA, right coronary artery; LCX, left circumflex coronary artery; DES, drug eluting stent; BMS, bare metal stent; BVS, Bioabsorbable vascular scaffold; DAPT, dual antiplatelet therapy.

Table 3 Endpoints at 1 year

	Switched DAPT	Unchanged DAPT	HR (95%IC)	P-value
Net clinical benefit	43 (13.4%)	85 (26.3%)	0.48 (0.34–0.68)	<0.01
Any ischaemic event	30 (9.3%)	37 (11.5%)	0.48 (0.34–0.68)	0.36
Cardiovascular death	1 (0.3%)	4 (1.2%)	0.30 (0.05–1.73)	0.18
Unplanned revascularization	28 (8.7%)	30 (9.3%)	0.93 (0.56–1.55)	0.78
Stroke	1 (0.3%)	3 (0.9%)	0.37 (0.05–2.60)	0.32
All bleedings	30 (9.3%)	76 (23.5%)	0.39 (0.27–0.57)	<0.01
Bleeding BARC ≥ 2	13 (4.0%)	48 (14.9%)	0.30 (0.18–0.50)	<0.01
TIMI major	1 (0.3%)	4 (1.2%)	0.30 (0.05–1.73)	0.18
TIMI minor	9 (2.8%)	26 (8.0%)	0.37 (0.19–0.71)	<0.01
TIMI minimal	20 (6.2%)	46 (14.2%)	0.44 (0.27–0.71)	<0.01

Percentages are calculated from the Kaplan–Meier curve.
BARC, Bleeding Academic Research Consortium criteria; TIMI, thrombosis in myocardial infarction; DAPT, dual antiplatelet therapy.

ticagrelor was associated with a significant 11% reduction in the ischaemic endpoint (death from vascular cause, MI, stroke) during the first month.[4] Similarly, in a landmark analysis of the TRITON-TIMI study, prasugrel led to a 25% reduction in MI during the first 30 days of treatment.[11] Conversely, both prasugrel and ticagrelor have been associated with an increased risk of bleeding complications compared with clopidogrel. In the PLATO trial, ticagrelor induced a higher rate of non-CABG related major bleeding, while in the TRITON-TIMI trial prasugrel increased the incidence of major and life-threatening bleeding complications.[3,4] In our study, the net clinical benefit associate with the switched DAPT was driven by a significant reduction in bleeding events. All bleeding events, including nuisance bleeding, BARC ≥ 2 and TIMI minor and minimal bleeding events were significantly reduced by the FDC of aspirin plus clopidogrel. However, TIMI major bleedings were infrequently noticed at 1 year but numerically higher in the unchanged DAPT group. Bleeding has become an

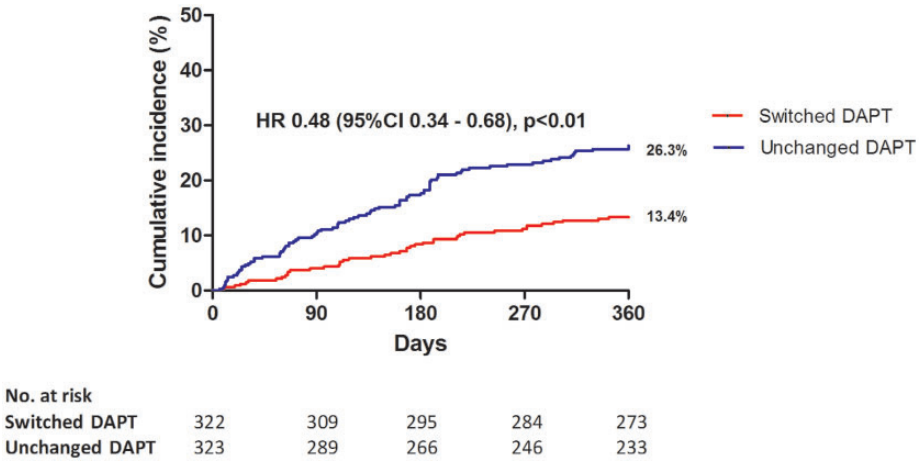

Figure 2 Incidence of the primary endpoint (net clinical benefit) at 1 year. HR, Hazard ratio.

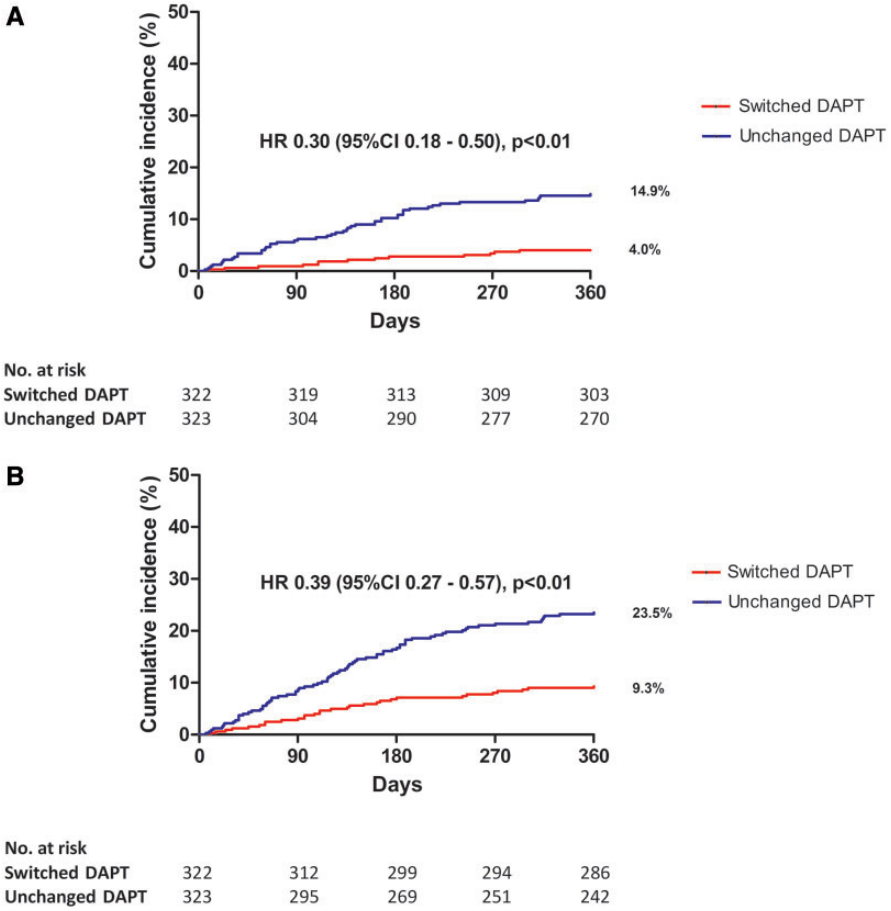

Figure 3 (*A*) Incidence of Bleeding Academic Research Consortium (BARC) ≥2 bleeding at 1 year. (*B*) Incidence of all BARC bleeding at 1 year. HR, Hazard ratio.

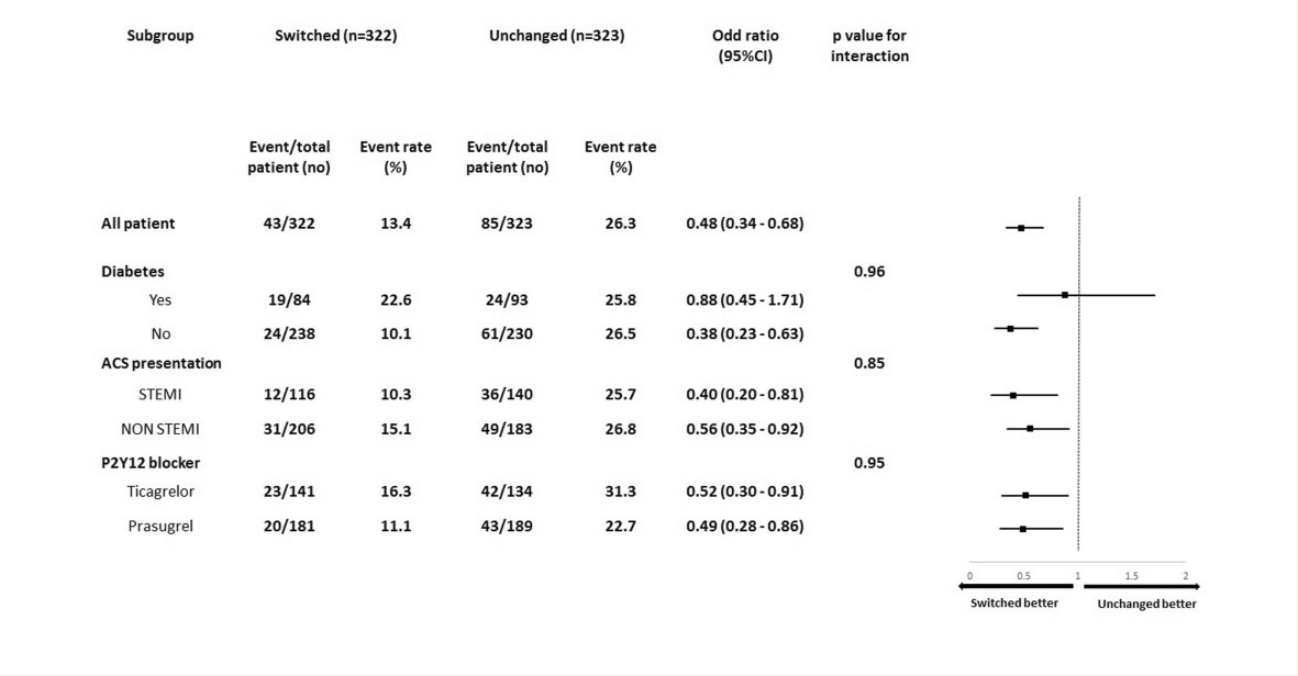

Figure 4 Subgroup analyses of the primary composite endpoint. Data are shown as the number of primary endpoint events per total number of patients in that subgroup and the event rate. Event rates were based on Kaplan Meyer estimation in time-to-first-event analyses. Hazard ratio is for the primary composite endpoint of cardiovascular death, unplanned hospitalization leading to urgent coronary revascularization, stroke and Bleeding Academic Research Consortium bleeding ≥2 at 1 year. The *P*-value for interaction represents the likelihood of interaction between the variable and the treatment.

important concern because it represents the most frequent non-cardiac complication after PCI, with an adverse prognostic impact comparable with that of ischaemic events.[12–15] Thereby, strategies aiming to reduce the incidence of bleeding complications following ACS have emerged. The decline in the use of GP2b3a antagonists and the widespread use of the radial access have led to a significant reduction of peri-procedural bleeding outcomes.[1,2] Despite the recommended use of PPI with DAPT the rate of bleeding reported following an ACS remains elevated, as shown in our cohort. Furthermore, reducing the DAPT duration to 30 days in very high bleeding risk patients treated with drug-eluting coated stents after an ACS has proved to be safer than the same duration with bare metal stents; however, one year DAPT after ACS remains the standard of care.[1,2,16] Switching from newer P2Y12 blockers to clopidogrel after 1 month is an effective strategy that allows a significant reduction of the bleeding risk with no increase in ischaemic complications.

There is a paucity of clinical data regarding the contemporary practice of switching between P2Y12 blockers after an ACS. Pharmacological studies have shown that downgrading from ticagrelor or prasugrel to clopidogrel is associated with a significant increase in platelet reactivity, which may lead to concern during the early ischaemic phase following an ACS.[17,18] However, data from registries and 'real-life' studies suggest that switching from a newer P2Y12 blocker to clopidogrel both in hospital[19] and after hospital discharge may be common, despite the fact that this strategy is currently lacking any supporting.[20] This strategy is based on the concept of dynamic and time-dependent risk evolution after ACS. Our results support switching from a potent antiplatelet inhibitor (i.e. newer P2Y12 blocker) to clopidogrel, in patients free of adverse event in the first month post ACS; thereby avoiding bleeding events without excess in ischaemic complications.

It is recognized that, after hospital discharge, there remain significant challenges in ensuring adequate compliance and adherence to ACS medications. It has been shown that up to 30% of patients discontinue at least one medication within the first month.[21] In this setting, non-observance is of particular concern because it has been associated with higher rates of all-cause mortality, cardiovascular mortality, MI, ST, and unplanned revascularization.[21] We demonstrated that a FDC of aspirin and clopidogrel, started 1 month after an ACS, led to an improvement of drug adherence, mostly attributed to the prevention of adverse events induced by the newer P2Y12 inhibitors (i.e. bleeding and dyspnoea). A recent analysis of the prevention of cardiovascular events in patients with prior heart attack using ticagrelor compared with placebo on a background of aspirin—thrombolysis in MI 54 (PEGASUS TIMI 54) trial showed that the rate of ticagrelor discontinuation affects nearly one-third of patients, is maximal during the first 90 days of treatment, and related mostly to non-serious adverse events (such as dyspnoea and non-serious bleeding).[22] By reducing the bleeding risk and avoiding classical newer P2Y12 blocker side effects (i.e. dyspnoea), the switched DAPT strategy prevents significant triggers of non-adherence to medication. Moreover, it has been shown that reducing the total number of

tablets (i.e. FDC) leads to better compliance[23] and we previously analysed this in the specific setting of ACS patients treated with fixed-combination of aspirin and clopidogrel.[24]

Limitations

The present study has some limitations. Firstly, it was an open label study, which has inherent bias. Nevertheless, all events for which medical attention was sought were adjudicated by a critical events committee unaware of treatment allocation. However, self-reported bleeding episodes and treatment discontinuation, for which patients did not consult a health-care professional, were subjective. In case of adverse event reporting or treatment modification, the letters from general practitioners and medical reports were collected and analysed. Secondarily, we used sealed envelopes for randomization with its own limits. Thirdly, the sample size of the present study limits the interpretation of differences observed in rare adverse events, such as late ST and clinical implications. However, we know that 70–80% of ST will occur within 1 month (3, 4, 9, and 25) of a coronary event and that the rate of ST has been significantly reduced by new generation drug eluting stents.[25] Fourthly, our primary endpoint used the BARC classification for bleedings inducing a high event rate. The BARC bleeding definition has been designed to avoid the use of multiples definitions in the different studies and is associated with prognosis including mortality after ACS.[7,26]

Conclusion

In conclusion, our data suggest that, in patients on aspirin plus ticagrelor or prasugrel without evidence of an adverse event in the first month following an ACS treated with PCI, switching DAPT strategy to aspirin plus clopidogrel may reduce the risk of bleeding recurrence without increased risk of ischaemic events. This finding is of major relevance to the 'real-world' management of ACS patients and offers an efficient and cost-effective alternative for ACS therapy particularly in those with a higher bleeding risk or drug compliance concerns. A future challenge will be to identify which patients would benefit from this switched DAPT strategy and which patients are best maintained on the more potent DAPT regimen for 1 year.

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