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**P2Y12 Inhibitors Monotherapy after short course of Dual Antiplatelet Therapy in Patients Undergoing Percutaneous Coronary Intervention: a meta-analysis of randomized clinical trials including 29.089 patients.**

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**BACKGROUND:** dual antiplatelet therapy (DAPT) reduces the incidence of thrombotic complications at the cost of an increase in bleedings. New antiplatelet therapies focused on minimizing bleeding and maximizing antithrombotic effects are emerging. The aim of the present study is to collect the current evidence coming from Randomized Controlled Trials (RCTs) on early aspirin interruption after Percutaneous Coronary Intervention (PCI) and current Drug Eluting Stent (DES) implantation and to perform a meta-analysis in order to evaluate the safety and efficacy of this strategy.

**METHODS:** MEDLINE/PubMed was systematically screened for RCTs comparing P2Y12 inhibitors (P2Y12i) monotherapy after a maximum of 3 months of DAPT (S-DAPT) vs DAPT for 12 months (DAPT) in patients undergoing PCI with DES. Baseline features were appraised. Major Adverse Cardiac and Cerebrovascular Events (MACCE: all causes of death, myocardial infarction and stroke) and its single composite, stent thrombosis (ST) and Bleeding Academic Research Consortium (BARC) type 3 or 5 were considered and pooled with fixed and random-effects with inverse-variance weighting.

**RESULTS:** A total of 4 RCTs including a total of 29.089 patients were identified. Overall, the majority of included patients suffered a stable coronary artery disease while ST-elevation myocardial infarction (STEMI) was the least represented clinical presentation. Complex anatomical settings like left main intervention, bifurcations and multi-lesions treatment were included although representing a minor part of the cases. At one year follow-up, MACCE rate was similar (OR 0.90; 95% CIs 0.79-1.03) as well as any of its composites (All causes of death rate: OR 0.87; 95% CIs 0.71-1.06; Myocardial Infarction: OR 1.06; 95% CIs 0.90-1.26; Stroke: OR 1.12; 95% CIs 0.82–1.53). Similarly, also ST rate was comparable in the two groups (OR 1.17; 95% CIs 0.83-1.64) while BARC 3 or 5 bleeding resulted significantly lower, adopting a S-DAPT strategy (OR 0.70; 95% CIs 0.58-0.86).

**CONCLUSION:** After a PCI with current DES, a S-DAPT strategy followed by a P2Y12i monotherapy was associated with a lower incidence of clinically relevant bleeding compared to 12 months DAPT, with no significant differences in terms of one-year cardiovascular events.

**Keywords:** DAPT, early interruption, aspirin, P2Y12i inhibitors, ACS, PCI, DES.

## **ABBREVIATIONS**

Dual antiplatelet therapy (DAPT)

Randomized Controlled Trial (RCT)

Percutaneous Coronary Intervention (PCI)

Drug Eluting Stent (DES)

Short-DAPT (S-DAPT)

Major Adverse Cardiac and Cerebrovascular Events (MACCE)

Stent Thrombosis (ST)

Bleeding Academic Research Consortium (BARC)

P2Y<sub>12</sub> inhibitor (P2Y<sub>12</sub>i)

Acute Coronary Syndrome (ACS)

Coronary Artery Disease (CAD)

Odds Ratio (OR)

Confidence Interval (CI)

ST segment-elevation myocardial infarction (STEMI)

Left Ventricular Ejection Fraction (LVEF)

## **INTRODUCTION**

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y<sub>12</sub> inhibitor (P2Y<sub>12</sub>i) is the cornerstone of therapy in patients with acute coronary syndrome (ACS) and in patients with stable coronary artery disease (CAD) treated with a percutaneous coronary intervention (PCI) <sup>1-3</sup>. DAPT reduces the incidence of thrombotic complications but at the same time increases the incidence of bleeding complications that are directly connected with an increase in mortality <sup>4,5</sup>.

The recent development of stents with a less pro-thrombotic profile and the need to reduce bleedings without a thrombotic trade-off have opened the field to studies investigating new antiplatelet strategies after PCI <sup>6</sup>.

Some pre-clinical studies have shown the key role of P2Y<sub>12</sub>i over aspirin in platelet activation pushing investigators to explore the hypothesis of withdrawing aspirin after a short period following PCI in order to better balance the risk of bleeding and the prevention of ischemic events <sup>7,8</sup>. Based on these observations, some studies focused on early interruption of aspirin after one month or three months of DAPT maintaining a single antiplatelet therapy with a P2Y<sub>12</sub>i <sup>9</sup>.

Aim of the present study is to collect the current evidence coming from randomized controlled trials (RCTs) on early aspirin interruption after PCI with current drug eluting stent (DES) implantation and to perform a meta-analysis in order to further evaluate the safety and efficacy of this strategy.

## **METHODS**

### **Data Sources**

The terms “P2Y<sub>12</sub> inhibitor”, “ticagrelor”, “prasugrel”, “clopidogrel”, “aspirin” along with “monotherapy” and “percutaneous coronary intervention” were searched across MEDLINE, EMBASE and Cochrane databases according to optimal search strategies <sup>10</sup>.

No language restrictions were imposed. The design and protocol of our systematic review and meta-analysis was previously published on PROSPERO registry (CRD42019149952).

## **Study Selection**

RCTs comparing P2Y12i monotherapy after a maximum of 3 months of DAPT vs DAPT for at least 12 months in patients undergoing PCI for stable CAD or ACS respectively with at least a one-year follow-up were included. The outcomes of interest were a) efficacy outcomes including [i] Major Adverse Cardiac and Cerebrovascular Events (MACCE) and its composite (all causes of death, myocardial infarction and stroke); [ii] Definite/probable Stent Thrombosis (ST) b) safety outcome including Bleeding Academic Research Consortium (BARC) type 3 or 5. Three investigators (EC; MB; AC) independently appraised titles, abstracts and the full texts to determine whether studies met inclusion criteria. Conflicts between reviewers were resolved through re-review and discussion.

## **Data Extraction and Quality Assessment**

Three authors (EC; MB; AC) independently abstracted data on study design, setting, antiplatelet drugs administered in experimental and control groups. Age, gender, cardiovascular risk factors and clinical presentations were also evaluated. Supplementary data files were reviewed to extract any additional data of interest.

The quality of included trials was assessed according to Cochrane, PRISMA and QUORUM statements <sup>11,12</sup>; methods to obtain sample size, selection bias (allocation and random sequence generation), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment) and attrition bias (incomplete outcome data) were assessed and graphically described. The Jadad Scale <sup>13</sup> was used to appraise methodological quality of included studies. The population included in our meta-analysis

was the sum of the populations included in the “intention to treat analysis” of each single study selected.

## Data Synthesis and Analysis

Fixed-effects models with generic inverse-variance weighting were used to compute dichotomous comparisons reporting Odds Ratio (OR) with 95% Confidence Intervals (95% CIs) for each single outcome. Random-effects models were also tested and their results reported if different from random effect. Hypothesis testing for statistical homogeneity was set at the two-tailed 0.10 level and based on the Cochran Q test, with  $I^2$  values of 25%, 50%, and 75% representing mild, moderate, and extensive statistical heterogeneity respectively. A funnel plot analysis and Egger’s test were performed to identify small study bias. RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) and Comprehensive Meta-Analysis software (Biostat Software, New York, USA) were used to perform the pooled analysis.

## RESULTS

The abstracts of 102 studies were initially included and 21 were finally appraised as full text. Thirteen further studies were excluded because S-DAPT vs DAPT were not considered; three studies were excluded because of different protocol design; one study because only the design and rationale of the trial were reported. Four RCTs were finally included <sup>14–17</sup> encompassing 29,089 patients (**Table 1**). In STOPDAPT-2 and GLOBAL LEADERS, S-DAPT regimen was up to 1 month, while TWILIGHT and SMART-CHOICE studies prolonged the S-DAPT therapy up to 3 months. Both STOPDAPT-2 and SMART-CHOICE studies enrolled around 1500 patients from Japan and Korea respectively, while GLOBAL LEADERS and TWILIGHT encompassed almost 8000 and 7000 patients respectively from Europe, Canada, South America, North America and Asia. Composite

primary endpoint differs in each study but all endpoints of interests were reported and comparable through the different trials. Inclusion and exclusion criteria were substantially the same among all studies apart from ST segment-elevation myocardial infarction (STEMI) patients that were excluded only in TWILIGHT trial.

Clinical and procedural characteristics were reported in **Table 2**. Clinical features mainly reflect a real-world population with a mean age of about 65 years old, 80% male with a normal distribution of risk factors. Patients were admitted with an ACS in half of the cases. Left Ventricular Ejection Fraction (LVEF) was not reported in GLOBAL-LEADERS and TWILIGHT while it was preserved in the other two RCTs. Overall, only one-fourth of cases were performed by femoral access. Angiographic characteristics indicate a higher number of multi-lesion interventions in SMART-CHOICE and GLOBAL-LEADERS (about one-fourth of cases) compared with 6-7% of cases in STOPDAPT-2. Left main PCI ranges from 1.2 to 5.2% while bifurcation treatment was performed on up to one-fourth of cases. Second generation DES were used in all four studies.

Antiplatelet adherence was reported in all studies: at one-year follow-up, it ranged from 79% to 95% in all groups except the DAPT arm in STOPDAPT-2 where it was 56%.

Outcomes occurrence in each individual study was summarized in **Table 3**. At pooled analysis, MACCE rate was similar (OR 0.90; 95% CIs 0.79-1.03, **figure 2**) as well as any of its composite: all causes of death (OR 0.87; 95% CIs 0.71-1.06, **figure 3**); Myocardial Infarction (OR 1.06; 95% CIs 0.90-1.26, **figure A suppl. material**) and stroke (OR 1.12; 95% CIs 0.82-1.53, **figure B suppl. material**). Similarly, also definite/probable ST rate was similar in the two groups (OR 1.17; 95% CIs 0.83-1.64, **figure 4**). Conversely, BARC 3 or 5 bleeding resulted significantly lower adopting a S-DAPT strategy (OR 0.70; 95% CIs 0.58-0.86, **figure 5**). Random-effects analysis showed similar results (**Figures E suppl. Material**). Risk of bias of included RCTs (evaluated both with JADAD scale and Cochrane) was low, especially regarding randomization and selection bias. (Appendix, web only,



**Figure C** and **Table A**). Funnel plots analysis did not show relevant publication bias. (Appendix, web only, **Figures D**). Egger's test was not significant ( $p = 0.72$ ).

## DISCUSSION

The main finding of the present meta-analysis is the absence of MACCE increase in patients interrupting aspirin in the first three months after a PCI for stable CAD or ACS compared to those continuing DAPT for twelve months. The second most important finding is the significant reduction in clinically relevant bleeding in patients in which aspirin therapy is interrupted after the first three months.

The first datum seems directly connected to the very low adverse events rate connected to second and third generation DES<sup>18,19</sup>. The low thrombogenicity of new devices could allow a less intense antiplatelet therapy shortly after their implantation and the previously demonstrated superiority of P2Y12i over aspirin in preventing platelet aggregation make the ADP signaling pathway the preferred target to block when one of the two antiplatelet therapies is interrupted. Even the CAPRIE study, in a pre-stent era, had already shown similar results<sup>20,21</sup>. The results of our meta-analysis seem to support these observations and potentially they open the field to P2Y12i monotherapy after the first 3 months of DAPT in patients treated with current DES. Notably, the pooled analysis of data highlights an overall significant difference in terms of BARC 3 or 5 bleedings between patients treated with short vs standard DAPT. Nevertheless, due to the absence of studies with similar design, testing the hypothesis of early interrupting P2Y12i and continuing aspirin, we don't know if aspirin would have led to similar results. In our opinion, previous data showing a high incidence of aspirin sub-optimal response in patients with diabetes and the potentially detrimental effects of prostacyclin inhibition connected to aspirin use on top of P2Y12i therapy make this way less practicable<sup>22-24</sup>.

In order to clarify if a strategy of early aspirin interruption is ready for “prime time”, five sub-studies of the GLOBAL LEADERS Trial were recently published, further analyzing data from this study: the GLOBAL LEADERS Adjudication Sub-Study (GLASSY) <sup>25</sup>, a Post Hoc Analysis of ACS patients <sup>26</sup>, a Post Hoc Analysis in patients with long stenting <sup>27</sup>, a Post Hoc Analysis in patients who underwent complex PCI <sup>28</sup> and finally a Post Hoc analysis of patients > 75 years old <sup>29</sup>.

In the GLASSY pre-specified sub-study, considering also potential unreported event triggers in the 20 highest recruiting sites, at 2 years the S-DAPT strategy (1-month DAPT followed by 23-month Ticagrelor alone) resulted non-inferior to conventional treatment for efficacy (all causes of death, non-fatal MI/stroke or urgent target vessel revascularization) but did not reach superiority as well as for safety (no reduction in BARC 3 or 5 bleedings). The Post Hoc Analysis by Tomaniak et al. examined 1-to-12 month clinical outcomes in the ACS population of the Trial, aiming to clarify the impact of aspirin in the context of a more potent P2Y12 antagonist; it showed a significant increase of bleeding risk for conventional post-ACS DAPT (aspirin plus Ticagrelor) compared to Ticagrelor alone, with no additional benefit in terms of reduction of ischemic events. These outcomes, somehow comparable with those of the TWILIGHT, strongly support the results of our meta-analysis. One more ongoing study is currently exploring the topic of S-DAPT with aspirin discontinuation in ACS patients, the TICO study <sup>30</sup>. The TICO randomized open-label trial evaluated whether ticagrelor monotherapy following 3-month DAPT was superior to 12-month ticagrelor-based DAPT in terms of net adverse clinical events (NACE) including efficacy and safety in ACS patients treated with ultrathin bioresorbable polymer sirolimus-eluting stents. It enrolled 3,056 subjects in Korea and showed a significant reduction of NACE in ticagrelor monotherapy group driven by a reduced risk of TIMI major bleeding without differences in ischemic events. However, this study had several limitations. Firstly, overall event rates were lower than anticipated and the trial was powered for the NACE composite outcome making

comparisons of ischemic events underpowered. Secondly, patients at high bleeding risk were excluded and the results cannot be extrapolated to this group of patients commonly treated with stenting in everyday practice<sup>31</sup>. Thus, future information on ACS all-comers patients treated with contemporary DES remains of paramount importance because in this setting the coexistence of high bleeding and high thrombotic risk is very common and the needs of optimize the treatment the greatest.

Two Post Hoc Analysis of the GLOBAL LEADERS evaluated patients undergoing complex PCI on the basis of the definition of the ESC guidelines on myocardial revascularization (containing at least one of the following characteristics: multivessel PCI,  $\geq 3$  stents implanted,  $\geq 3$  lesions treated, bifurcation PCI with  $\geq 2$  stents, or total stent length  $> 60$  mm) or long stenting<sup>27,28,32</sup>. Both the studies showed that ticagrelor monotherapy after first month DAPT could balance ischemic and bleeding risk in patients undergoing complex PCI or with stent length  $> 46$  mm. The TWILIGHT study including in the same way patients undergoing complex PCI showed similar results. In particular, the recently published TWILIGHT-COMPLEX study<sup>33</sup> reported about 2342 patients enrolled in TWILIGHT that met the criteria for complex PCI defined as: 3 vessels or 3 or more lesions treated, total stent length greater than 60 mm, bifurcation with 2 stents implanted, atherectomy device use, left main PCI, surgical bypass graft or chronic total occlusion as target lesions. Results of the analysis showed a significantly lower rates of BARC 2, 3, or 5 bleeding ( $< 0.0001$ ), and BARC 3 or 5 type bleeding in patients treated with ticagrelor alone compared to ticagrelor plus aspirin ( $P = .009$ ) without differences in any ischemic outcomes. In our opinion these results are very interesting and in the future, could allow aspirin being stopped early in patients with concomitant high ischemic and bleeding risk like elderly patients.

Finally, three major questions remain unsolved: which is the best P2Y<sub>12</sub>i in the context of S-DAPT after PCI? Is it possible to safely interrupt aspirin before one month? Which medications should be continued after twelve months?

Outcomes stratified on the basis of different P2Y12i were not available for the studies included in our meta-analysis. Ticagrelor is the most studied P2Y12i in this context at the moment but future studies, like the ASET trial could contribute to understand if also prasugrel is a good option for S-DAPT after PCI <sup>34</sup>. Moreover, the ASET trial will be the first study trying to understand if aspirin can be interrupted even before one month in stable CAD patients undergoing PCI. Dedicated study to understand which is the best antiplatelet therapy after twelve months would be welcome in order to provide an answer to this very important question.

## **LIMITATIONS**

As in any meta-analysis, our study is subject to the limitations and the design of the selected studies. Firstly, the four studies include different P2Y12i and in two cases the S-DAPT protocol contemplates a 3-months DAPT vs 1-month in the other two studies. This does not allow any conclusions to be drawn about the safety of a one-month interruption. Moreover, due to the different P2Y12i used and the absence of end points for each of them, it is not possible to say if the safety and efficacy of early aspirin interruption is a class effect or if it is present only for more potent P2Y12i.

Secondly, two of the four studies included were conducted in East Asia, introducing a potential confounder related to ethnicity. This potential bias is mitigated by the fact that most of the patients included in the analysis come from wide international studies.

Thirdly, separate results for particular subgroups such as ACS patients were not available in the considered studies as dedicated subgroup analysis was not possible in our meta-analysis. However a non-prespecified, post hoc analysis of the GLOBAL LEADERS among ACS patients explored this topic showing that, between 1 month and 12 months after PCI, aspirin was associated with increased bleeding risk and appeared not to add to the benefit of ticagrelor on ischemic events <sup>26</sup>.

Moreover, due to the baseline characteristics of the patients included in the studies considered, our results cannot be fully generalized. In particular, a very low percentage of STEMI patients were included and the TWILIGHT study even excluded them. For these reasons an S-DAPT strategy for such patients does not appear sufficiently supported by data at the moment.

Finally, in the authors' opinion, the topic addressed by the present meta-analysis is particularly complex and the intrinsic limitations of the meta-analytic methods do not allow a general conclusion to be reached for all the wide range of clinical presentation of CAD patients.

## **CONCLUSIONS**

After a PCI with current DES, an S-DAPT strategy followed by P2Y12i monotherapy in patients without STEMI, was associated with a lower incidence of clinically relevant bleeding compared to standard DAPT duration without significant differences in terms of one-year cardiovascular events. Further studies evaluating patients with different clinical characteristics of those included in the recent RCTs are required to draw definitive conclusions on safety and efficacy of early aspirin interruption followed by P2Y12i monotherapy after PCI.

## **CONFLICT OF INTEREST**

None declared.

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## **FIGURES LEGEND**

Figure 1. Review's profile.

Figure 2. Rates of MACCE (major adverse cardiac and cerebrovascular events) a composite of all-cause mortality, myocardial infarction, or stroke during one year follow-up.

Figure 3. Rates of all cause of death during one year follow-up.

Figure 4. Rates of definite or probable stent thrombosis during one year follow-up.

Figure 5. Rates of BARC 3-5 bleeding during one year follow-up.

## **SUPPLEMENTARY FIGURES**

Figure A. Rates of myocardial infarction during one year follow-up.

Figure B. Rates of stroke during one year follow-up.

Figure C. Risk of bias.

Figure D1. Funnel plot for MACCE.

Figure D2. Funnel plot for all cause of death.

Figure D3. Funnel plot for definite or probable stent thrombosis.

Figure D4. Funnel plot for BARC 3-5.

Figure D5. Funnel plot for myocardial infarction.

Figure D6. Funnel plot for stroke.

Figure E1. Random-effect model analysis. Rates of MACCE (major adverse cardiac and cerebrovascular events) a composite of all-cause mortality, myocardial infarction, or stroke during one year follow-up.

Figure E2. Random-effect model analysis. Rates of all cause of death during one year follow-up.

Figure E3. Random-effect model analysis. Rates of definite or probable stent thrombosis during one year follow-up.

Figure E4. Random-effect model analysis. Rates of BARC 3-5 bleeding during one year follow-up.

Figure E5. Random-effect model analysis. Rates of myocardial infarction during one year follow-up.

Figure E6. Random-effect model analysis. Rates of stroke during one year follow-up.