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Short term outcome following acute phase switch among $P2Y_{12}$ inhibitors in patients presenting with acute coronary syndrome treated with PCI: A systematic review and meta-analysis including 22,500 patients from 14 studies

Enrico Cerrato [a,1], Matteo Bianco [b,*,1], Akshay Bagai [c], Leonardo De Luca [d], Simone Biscaglia [e], Alessia Luciano [b], Paola Destefanis [b], Giorgio Quadri [a], Ilaria Meynet [f], Carol Gravinese [b], Alessandra Chinaglia [g], Shaun G. Goodman [c], Roberto Pozzi [b], Gianluca Campo [e], Ferdinando Varbella [a]

[a] Interventional Cardiology, San Luigi Gonzaga University Hospital, Orbassano and Infermi Hospital, Rivoli, Turin, Italy
[b] Division of Cardiology, San Luigi Gonzaga University Hospital, Orbassano, Italy
[c] St. Michael's Hospital, Division of Cardiology, Toronto, Canada
[d] S. Giovanni Evangelista Hospital-Tivoli, Division of Cardiology, Rome, Italy
[e] University of Ferrara, Division of Cardiology, Ferrara, Italy
[f] Division of Cardiology, Infermi Hospital, Rivoli,Turin, Italy
[g] Division of Cardiology, Martini Hospital, Turin, Italy

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ABSTRACT

Introduction: The efficacy and safety of switching $P2Y_{12}$ receptor antagonists in patients admitted for acute coronary syndrome (ACS) remain unclear. We assessed the short-term clinical outcomes (in-hospital and within 30 days) of switching $P2Y_{12}$ inhibitor ($P2Y_{12}I$) drugs versus maintaining the same regimen by performing a comprehensive review and meta-analysis of available data.

Methods: MEDLINE/PubMed/SCOPUS/Cochrane databases were screened for studies regarding switching of $P2Y_{12}I$ in patients with ACS that reported 30 days follow-up. Major cardiac events (MACE) and bleeding were compared between patients who were switched/not switched.

Results: 22,500 patients from 14 studies were included. Unstable angina/non-ST elevation myocardial infarction (62.0%, interquartile range, 52.8%–68.0%) was the most common clinical presentation. The total number switched was 4294 (19.1%); escalation in 3416 (79.5%) patients (from clopidogrel to prasugrel, 62.9%) and de-escalation in 18.5%. Pooled analysis revealed no significant differences in MACE for any comparison; risk of bleeding was significantly increased among switched patients overall (odds ratio [OR], 1.60; 95% confidence interval [CI] 1.22–2.10) and increased in the escalation group (OR, 1.51; 95% CI, 1.06–2.16).

Conclusions: Among patients presenting with ACS, switching from one $P2Y_{12}I$ agent to another in the acute phase seems associated with a short-term increased risk of bleeding. Accurate upfront selection and prescription of a $P2Y_{12}I$ based on ischemic and bleeding risks is paramount to avoid adverse events switching-related during hospitalization and in the first 30 days.

1. Introduction

Dual antiplatelet therapy with aspirin combined with clopidogrel, ticagrelor, or prasugrel is the mainstay in the management of acute coronary syndrome (ACS). However, in everyday clinical practice, cardiologists must address the need to change drugs by escalating from clopidogrel to a new $P2Y_{12}I$ (ie, in pre-treated patients) or de-escalating from a new $P2Y_{12}I$ to clopidogrel.

Although data from registries have been presented recently, the efficacy and safety of switching among adenosine diphosphate (ADP) receptor antagonists remain unclear [1,2]. Published reviews and meta-analyses also include patients admitted for stable coronary artery disease (CAD) and report clinical outcomes for a long follow-up interval, making it harder to define a net clinical risk or benefit. A recent international consensus document on the topic gave clear and useful insight but many gaps in evidences still remains [3]. Thus, we sought to assess the

* Corresponding author at: A.O.U San Luigi Gonzaga, Regione Gonzole 10, 10043 Orbassano, Torino, Italy.
E-mail address: matteo.bianco87@gmail.com (M. Bianco).
URL: http://www.cardiogroup.org (M. Bianco).
[1] Joint first autorship.

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Table 1
The main descriptors of the studies.

Study	Year	Journal	Desing	Region	No. of patients	Clinical presentation	Type of comparison	Follow-up	MACE definition	Bleeding definition	Switch; when and how	Reason for switching	Funding
MULTIPRAC [11]	2015	Eur Heart J Acute Cardiovasc Care	Prospective	Denmark	2053	STEMI (100%)	Switch from clopidogrel to prasugrel versus clopidogrel or prasugrel alone	In hospital	Death, CV death, repeat MI, ST, urgent re-PCI or CABG, stroke	Non-CABG and CABG related bleeding	Before discharge	Clinical decision	Daiichi-Sankyo and Eli Lilly
Lho et al. [10]	2013	Am J Cardiol	Retrospective	USA	606	UA/NSTEMI (72.2%); STEMI (27.8%)	Switch from clopidogrel to prasugrel versus prasugrel alone	In hospital	Death, Q-wave MI, urgent PCI or bypass surgery and stroke	TIMI	Before discharge	Clinical decision	None
COAPT [5]	2016	Int J Cardiol	Retrospective	Canada	2179	UA/NSTEMI (39.1%); STEMI (60.9%)	All kinds of switch	30 days	Death, reinfarction, stent thrombosis, stroke/TIA	TIMI	Before discharge	Clinical decision	Daiichi-Sankyo and Eli Lilly
Biscaglia et al. [4]	2016	Platelets	Prospective	Italy	586	UA/NSTEMI (63%); STEMI (37%)	Switch from ticagrelor to clopidogrel versus ticagrelor alone	30 days	All-cause death, CV death, MI, TIA/stroke, definite stent thrombosis, definite/probable stent thrombosis	BARC	Before discharge (24%), after discharge (76%)	Clinical decision	None
De Luca et al. [6]	2014	J Thromb Thrombolysis	Prospective	Italy	450	UA/NSTEMI (68%); STEMI (32%)	Switch from clopidogrel to prasugrel versus clopidogrel alone	30 days	Death, re-MI, urgent TVR	TIMI	Before discharge	Study protocol	None
Kerneis et al. [8]	2013	JACC: Cardiovasc Interv	Prospective	France	300	UA/NSTEMI (66.6%) STEMI (33.4%)	Switch from prasugrel to clopidogrel versus clopidogrel alone	30 days	Ischemic events, stent thrombosis, and MI	BARC	After 15 days from hospital discharge	Study protocol	Allies in Cardiovascular Trials Initiatives and Organized Networks Group
Chinaglia et al. [14]	2015	ACC Congress Abstract	Prospective	Italy	428	UA/NSTEMI (68.9%); STEMI (31.1%)	Switch from clopidogrel to prasugrel versus prasugrel alone	In hospital	All-cause death, CV death, MI, TIA/stroke, definite stent thrombosis, definite/probable stent thrombosis	TIMI	Before discharge	Clinical decision	None
SWAP [16]	2010	J Am Coll Cardiol	RCT	USA	100	UA/NSTEMI (61.9%); STEMI (38.1%)	Switch from clopidogrel to prasugrel versus clopidogrel alone	7 days	Not specified	TIMI	After discharge	Study protocol	Daiichi-Sankyo and Eli Lilly
Almendro-Delia et al. [3]	2015	J Thromb Thrombolysis	Prospective	Spain	468	UA/NSTEMI (61.9%); STEMI (38.1%)	Switch from clopidogrel to prasugrel versus clopidogrel or prasugrel alone	In hospital	Death, reinfarction, cardiogenic shock, stent thrombosis, stroke/TIA and the need for CABG during hospitalization	TIMI	Before discharge with loading dose if >6 h after loading dose of clopidogrel	Clinically driven	None
GRAPE [7]	2014	Am Heart J	Prospective	Greece	1617	UA/NSTEMI (52.8%); STEMI (47.2%)	Switch from clopidogrel to prasugrel or ticagrelor versus clopidogrel alone	30 days	Death, MI, definite or probable stent thrombosis, urgent revascularization, stroke	BARC	Before discharge	Clinical decision	Astrazeneca
TRANSLATE-ACS [15]	2012	Eur Heart J Acute Cardiovasc Care	Prospective	USA	11,999	STEMI (51.9%); NSTEMI/UA (48.1%)	All kinds of switch, upgrade and downgrade	In hospital	Death, MI, unplanned revascularization and stroke	GUSTO	3.1% pre-PCI, 0.7% during PCI, 48.2% post-PCI, 48.0% at discharge	Clinical decision	Daiichi-Sankyo and Eli Lilly
SCOPE [12]	2017	EuroIntervention	Prospective	Italy	1363	UA/NSTEMI (75.7%); STEMI (24.3%)	All kinds of switch	30 days	All-cause death, CV death, MI, TIA/stroke, definite stent thrombosis, definite/probable stent thrombosis	BARC	Before coronary angiography (2.3%), before discharge (3.3%), before 30 days (30.6%)	Clinical decision	Daiichi-Sankyo and GISE
TRIPLET [13]	2013	Circ Cardiovasc Interv	RCT	Canada	276	UA/NSTEMI (77.2%); STEMI (22.8%)	Switch from clopidogrel to prasugrel versus prasugrel alone	In hospital	Death	Not specified	Before discharge	Study protocol	Daiichi-Sankyo and Eli Lilly
Lhermusier et al. [9]	2014	J Interv Cardiol	Prospective	USA	75	ACS (100%)	Switch from clopidogrel to prasugrel versus prasugrel alone	In hospital	Death	Not specified	Before coronary angiography	Study protocol	Eli Lilly

MACE, major cardiac event; STEMI, ST elevation myocardial infarction; CV, cardiovascular; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; UA, unstable angina; NSTEMI, non-ST elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction; TIA, transient ischemic attack; BARC, Bleeding Academic Research Consortium; TVR, transcatheter valve replacement; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. RCT: randomized controlled trial.

short-term clinical outcomes (within 30 days) of patients undergoing switching among $P2Y_{12}I$ drugs versus maintaining the same regimen by performing a comprehensive review and meta-analysis of available data.

2. Methods

The recommendations from the Cochrane Collaboration and Meta-analysis of Observational Studies in Epidemiology (MOOSE) were followed for the present systematic review [4].

2.1. Search strategy and study selection

We systematically searched four electronic databases (Medline, PubMed, Scopus, and Cochrane) for pertinent articles published in English with established methods and incorporating wild cards (identified by *), until the end of December 2017, with the following terms: ((Percutaneous coronary intervention) AND (antiplatelet therapy) and ((prasugrel) OR (ticagrelor) OR (clopidogrel)) AND (switch) NOT (review [pt] OR editorial [pt] OR letter [pt]). Presentations at major Cardiology Congresses (American College of Cardiology, American Heart Association and European Society of Cardiology) were also checked through official websites. Editorials and reviews from major medical journals published within the last 3 years were also considered for further information on studies of interest and their bibliographies were evaluated for additional citations. All the citations were discussed by two independent reviewers (M.B. and E.C.) at the title and/or abstract level, with divergences resolved after discussion. If potentially pertinent, they were appraised as complete reports. Studies were included if (1) outcomes in hospital or within 30 days of patients undergoing switching or not among $P2Y_{12}I$ drugs in the first 30 days were reported; (2) bleeding or ischemic events were reported in both arms; (3) in the setting of ACS. Exclusion criteria were: (1) non-human setting; (2) duplicate reporting (in which case the article reporting the largest sample of patients was selected); (3) $P2Y_{12}I$ use not recommended in clinical practice; (4) patients treated medically or with surgical revascularization; (5) non-English language publications.

2.2. Data extraction and endpoints

Two independent reviewers (M.B. and E.C.) abstracted the following data on pre-specified forms: authors, journal, year of publication, location of the study group, type of $P2Y_{12}I$ switch, baseline clinical features, interventional features, and definition of bleeding. Data extraction was conducted by mutual agreement and all potential disagreements were solved by consensus. The incidence of major cardiovascular events (MACE) and clinically relevant bleeding were the primary endpoints. Definitions used for MACE and bleeding and the main descriptors of the studies are shown in Table 1.

2.3. Internal validity and quality appraisal

Unblinded independent reviewers (M.B. and E.C.) evaluated the quality of studies on pre-specified forms. The MOOSE items were modified to take into account the specific features of the studies [4]. Data on the study design, setting, data source, as well as the risk of analytical, selection, adjudication, detection, and attrition bias (expressed as low, moderate, or high risk of bias, as well as incomplete reporting leading to inability to ascertain the underlying risk of bias) were abstracted separately. Data quality was assessed using the Newcastle Ottawa Quality Assessment Scale (NOS) for cohort studies [5].

2.4. Data analysis and synthesis

Continuous variables are reported as the median and interquartile range. Categorical variables are expressed as n/N (%). Statistical pooling was performed according to a random-effect model with generic inverse-variance weighting, computing odds ratios (ORs) for each study with 95% confidence intervals (Cis). Fixed and random-effects models were used to compute dichotomous comparisons. In case of discrepancy, the more conservative one was used. RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) was used. 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 was performed and reported to identify small study bias.

3. Results

A total of 66 studies were identified: after abstract evaluation, 19 were appraised as full text. Two studies were excluded because they did not test a recommended dose of clopidogrel in clinical practice,

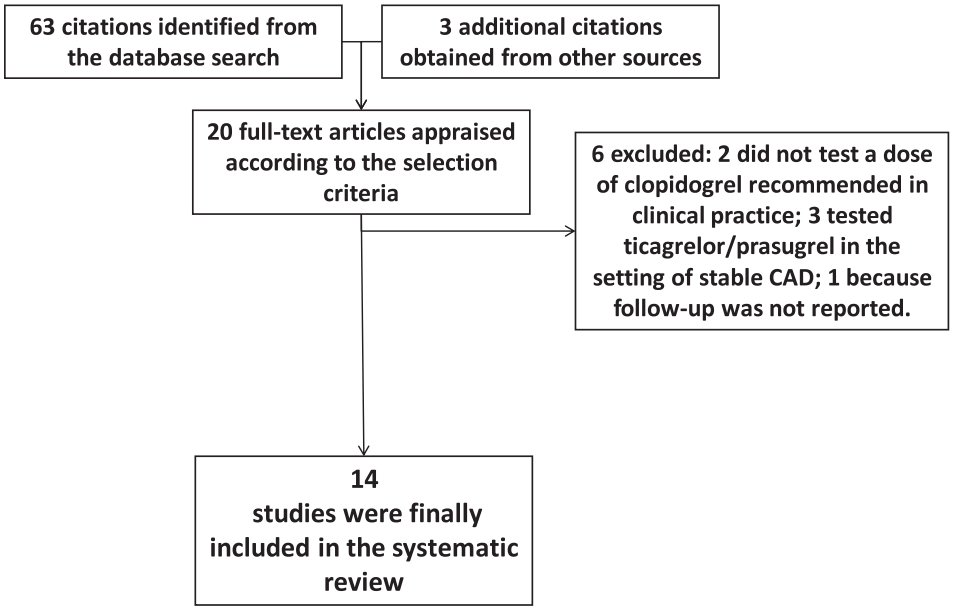

Fig. 1. Overview of the review. CAD, coronary artery disease.

3 because they tested new $P2Y_{12}I$ in patients only with stable CAD, and 1 because follow-up was not reported. Ultimately, 14 studies were included (Fig. 1) [6–19].

The methodological and quality assessment (Newcastle Ottawa Scale) reported an overall high quality of the selected studies (Supplementary Table A). Most were multicenter ($N = 11$), 2 were randomized controlled trials, and only 2 were retrospective with an acceptable risk of bias. All were conducted in high-volume percutaneous coronary intervention (PCI) centers, 9 studies came from European countries and the other 6 from the United States and Canada. Definitions of events were evaluated for each study. Eight were sponsored by pharmaceutical industries producing prasugrel or ticagrelor. The main characteristics of the studies included are summarized in Table 1.

Overall, the analysis included 22,500 patients, 18,206 in the no-switch group and 4294 (19.1%) in the switch group. Baseline characteristics are reported in Supplementary Table B. The median age of the population was 60.8 years (interquartile range [IQR], 57.6–61.6 years) with 77.6% men (IQR, 72.9%–79.7%) and a common distribution of cardiovascular risk factors. Unstable angina/non-ST elevation myocardial infarction (62.0%; IQR, 52.8%–68.0%) was the most common clinical presentation followed by ST elevation myocardial infarction (38.0%; IQR, 32.0%–54.7%). Clopidogrel was administered as a frontline $P2Y_{12}I$ in 14,863 (66.1%) patients, whereas prasugrel and ticagrelor were administered in 5314 (23.6%) and 2104 (9.3%) patients, respectively; 219 (1.0%) patients were initially treated with ticlopidine.

The most common type of switch was escalation, which occurred in 3416 (79.5%) patients, commonly from clopidogrel to prasugrel. De-escalation to clopidogrel or change between new $P2Y_{12}I$ were less common (18.5% and 2.0%, respectively; Supplementary Table B).

No significant differences were found in the pooled analysis in terms of MACE in the overall switching group (OR, 1.08; 95% CI, 0.70–1.68); the escalation-only group (OR, 1.03; 95% CI, 0.70–1.51) and the de-escalation only group (OR, 1.08; 95% CI, 0.25–4.61) were also analyzed separately (Fig. 2A–C). Conversely, risk of bleeding (OR, 1.60; 95% CI, 1.22–2.10) was significantly increased in the switched patients overall (Fig. 3A). Risk of bleeding was also increased when analyzed separately in the escalation-only group (OR, 1.51; 95% CI, 1.06–2.16) while not in the de-escalation only group (OR, 1.43; 95% CI, 0.77–2.66). No systematic bias was apparent as assessed by funnel plot inspection and Egger's test, which was not significant (Data Supplement, Online Figs. A and B).

4. Discussion

The management of $P2Y_{12}I$ therapy in the setting of ACS is an important issue for cardiologists and numerous studies have evaluated the optimal timing of administration as well as the safety and efficacy of different agents. After the introduction of prasugrel and ticagrelor in clinical practice, switching between $P2Y_{12}I$ drugs has become an important topic. Escalation from clopidogrel to ticagrelor was initially evaluated in the PLATO [20] trial without reporting a significant increase in adverse ischemic events but an increase in bleedings in the ticagrelor treated arm. In contrast, the TRITON-TIMI 38 trial [21], the validation study of prasugrel, included only patients naive to antiplatelet therapy, and for this reason, some subsequent studies evaluated the feasibility of switching from clopidogrel to prasugrel. After this initial phase, many prospective studies focused their attention on real-world practice to evaluate the safety of switching in patients, who are becoming older every day and with a larger burden of comorbidities such as atrial fibrillation and chronic kidney disease. All these studies were unfortunately limited by low sample size and a low incidence of switching to allow strong conclusions. Moreover, in the last year, two studies challenged the superiority of prasugrel and ticagrelor compared to clopidogrel suggesting that a programmed de-escalation strategy after the acute phase could improve the net clinical outcome of patients with ACS [22,23]. For this reason, a future scenario with an increase of de-escalation switching is not unlikely. Thus, we performed a systematic review and

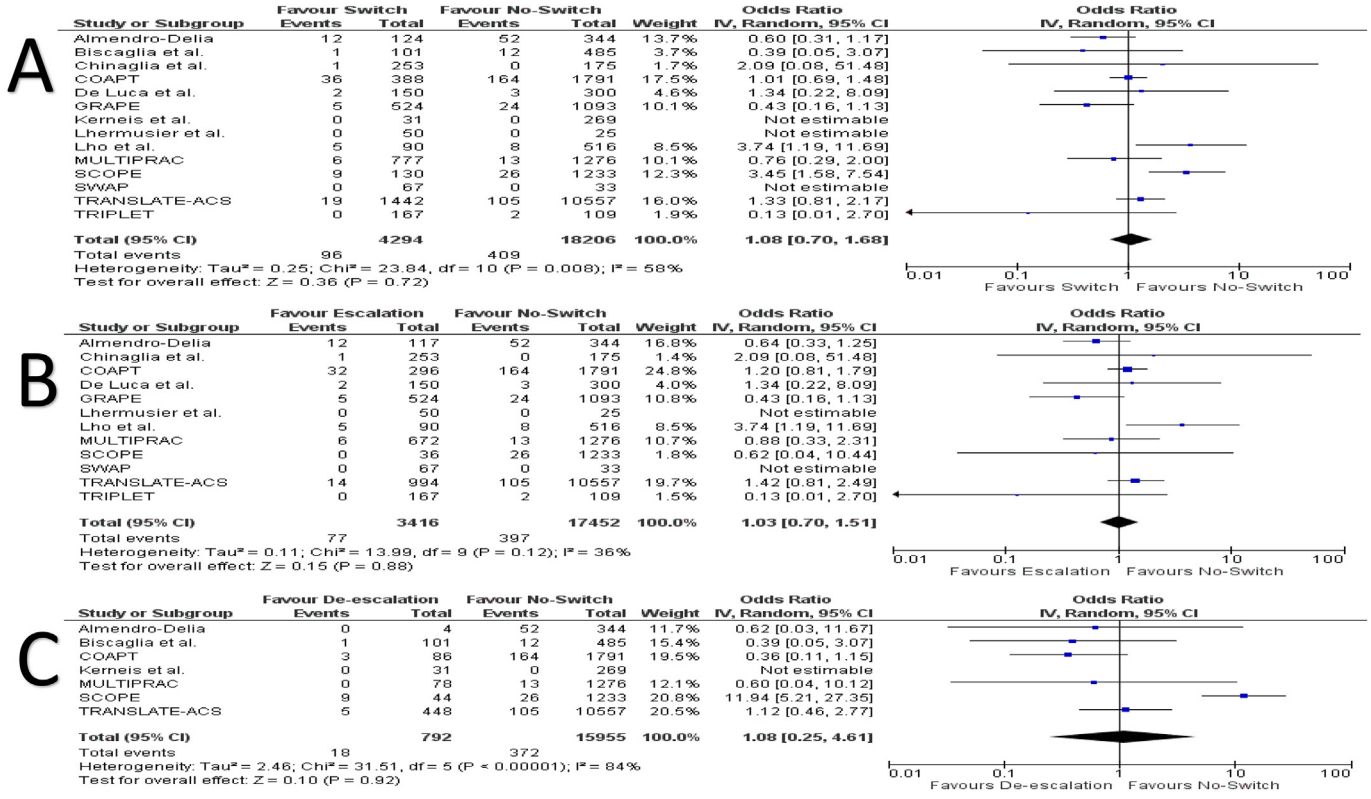

Fig. 2. (A) Meta-analysis of MACE in patients undergoing any type of switch among $P2Y_{12}$ drugs versus maintaining the same regimen. (B) Meta-analysis of MACE in patients undergoing an escalation from clopidogrel/ticlopidine to a novel $P2Y_{12}$ versus maintaining the same regimen. (C) Meta-analysis of MACE in patients undergoing a de-escalation from a novel $P2Y_{12}$ to clopidogrel versus maintaining the same regimen.

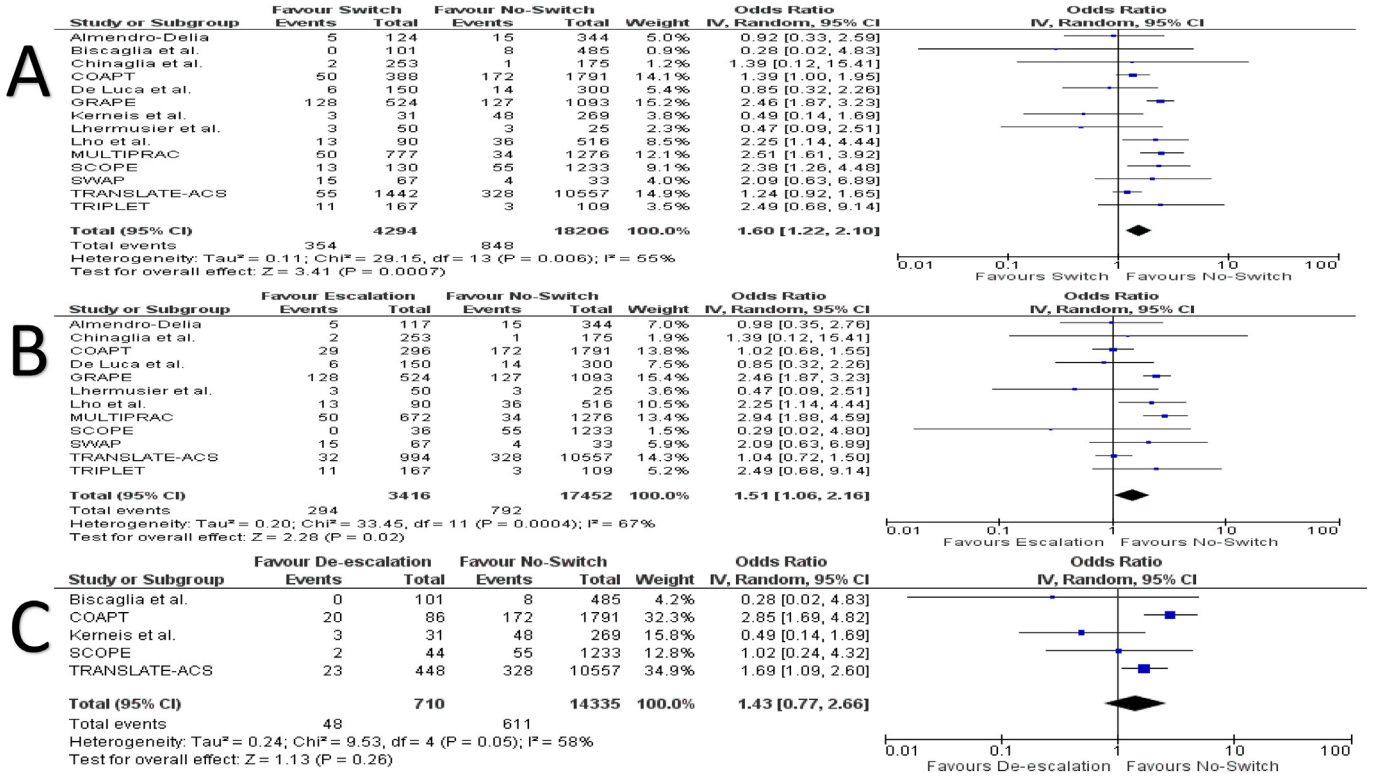

Fig. 3. (A) Meta-analysis of bleeding in patients undergoing any type of switch among $P2Y_{12}$ drugs versus maintaining the same regimen. (B) Meta-analysis of bleeding in patients undergoing an escalation from clopidogrel/ticlopidine to a novel $P2Y_{12}$ versus maintaining the same regimen. (C) Meta-analysis of bleeding in patients undergoing a de-escalation from a novel $P2Y_{12}$ to clopidogrel versus maintaining the same regimen.

meta-analysis to evaluate the problem of switching in a more comprehensive manner.

In contrast to previous reviews and meta-analyses on this topic in which non-negligible percentages of studies on patients with stable CAD were included and heterogeneous follow-up durations were reported (from in hospital up to years), we decided to focus only on short-term outcome (in hospital or within 30 days) and on ACS patients to better assess the immediate effect of switching. Overall, we were able to include a larger sample size encompassing 22,500 real-world patients with ACS from 14 studies. We observed that, within 30 days, switching from one agent to another was associated with similar MACE but seems to have a significant higher risk of bleeding compared with upfront initiation of a $P2Y_{12}$I agent without any subsequent switching.

Our findings are in line with a previous meta-analysis on this topic published by Chandrasekhar et al. [24] in 2016, which include 5 studies (11,434 patients) and reported a tendency for higher and significant bleeding when escalating the $P2Y_{12}$I agent compared with upfront initiation of a second-generation $P2Y_{12}$I agent. We expanded and confirmed this finding in a larger population, reporting an increased risk of bleeding in overall switching group as well as in the escalation-only group. Nevertheless, a trend of increased bleedings in patients who underwent a de-escalation switch is also present. Unfortunately, the overall number of patients in which a de-escalation strategy was included was small (710 patients), hence no conclusion regarding this strategy could be ultimately drawn. Current results could not safely inform clinical practice regarding treatment de-escalation in hospital or during the first month after ACS, and over-interpretation of these findings could be misleading and must be interpreted cautiously by clinicians. However, a possible explanation for these findings is that the high incidence of bleeding observed in previous studies in patients requiring a de-escalation were not due to the switching itself but to an increased risk of bleeding related to the higher risk profile of the patients (usually older, often requiring anticoagulation and with more comorbidities). In any case with the present work we cannot provide a multivariate analysis exploring independent risk of bleeding in our population.

Another recent study-level meta-analysis published by Patti et al. [25] included 15 studies exploring the safety and efficacy of escalating from clopidogrel to prasugrel. The authors concluded that there was no statistically significant increase in MACE or bleeding risk in the prasugrel switching group versus the prasugrel only group or in the prasugrel switching group versus clopidogrel only group. These findings were confirmed in a stratified subgroup analysis only in ACS studies. However, 5 of 15 selected studies included patients with stable CAD (in particular 3 studies were conducted only in the setting of stable CAD), accounting for one-fourth of the selected cohort; in addition, the follow-up varied among studies from in hospital up to 1 year. Conversely, in our analysis, we focused only on patients with ACS for acute phase outcomes, reporting an increased risk of bleeding that could be related to the more potent platelet inhibition of novel $P2Y_{12}$I agents.

Regarding the occurrence of MACE, we did not find any differences among the groups. Probably the net benefit of new $P2Y_{12}$I was mitigated, in particular in the escalation group, because we compared the non-switching group without taking account of the type of ADP receptor inhibitors administered (more than one-third of patients in the non-switching group were taking ticagrelor or prasugrel as first-line agent). Thus, the lack of improvement in ischemic outcomes is likely due to the fact that the studies were not randomized and that a significant proportion of non-switched patients were presumably on the more potent agents. Finally, any consideration about long-term superiority of escalation vs. upfront administration of a novel $P2Y_{12}$I was over the purpose of the current analysis. However, our findings did not reveal an increased rate of thrombotic events during the overlapping of different $P2Y_{12}$I, like ticagrelor or clopidogrel, even following heterogeneous switching protocols.

Overall, our findings suggest that upfront prescription of the most appropriate agent based on ischemic and bleeding risks is of utmost importance in order to deliver the greater clinical benefit soon after a hospitalization for ACS. This should be taken into account considering that the use of clopidogrel as first-line agent for ACS is still high; 65% of cases ($n = 14{,}863$) in our study, in line with all previous reports [10,15,26]. This clinical behavior arises mainly because internal hospital guidelines or emergency out-of-hospital service protocols still recommend starting dual antiplatelet therapy with aspirin plus clopidogrel, leaving the possibility of escalating to a novel agent at a later stage. In addition, this is a consequence of clinician's reluctance to start with a potent $P2Y_{12}I$ agent in fragile and older patient as demonstrated in several registries [10,26] reporting, for example, age > 75 years, malignancy, peripheral artery disease, or previous stroke as independent predictors of clopidogrel administration as first-line agent at admission. Thus, considering that, in our analysis, 19% of patients underwent a switch in hospital or in the first 30 days after an ACS, our data showing a higher risk of bleeding with switching should be taken into account. In other words, the best way to avoid switching related complication is to not switch keeping in mind that the best option is choosing the right $P2Y_{12}I$ to the right patient as upfront therapy whenever it is possible.

5. Limitations

Several caveats on the present analysis warrant further consideration. This study shares the limitations inherent to all meta-analysis based on pooling data from different studies. First, most of the selected studies had no randomized design, and we had full access to patient-level data in only some of the papers [15,17,18], limiting the possibility of adjusting for potential confounders. Furthermore, a clear statement about the time relationship between switching and MACE or bleeding events was not always reported making and consequently it cannot be ruled out if an ischemic or bleeding event is the cause or the effect of switching. Moreover, the majority of the studies were observational. Hence, an initial selection bias could not be excluded. This is of upmost importance since clinicians in routine practice base their decision for treatment escalation/de-escalation on multiple factors, which entail all the nuances of the perceived risk of MACE/Bleeding (i.e. age, prior bleeding, other high bleeding or ischemic risk features). This could ultimately confound the results of the evaluated treatment and for these reason the findings should be considered hypothesis generating. Third, heterogeneity was present regarding the endpoints for both MACE and bleeding, as well timing of switching and loading doses, allowing for misclassification and over interpretation of the risk and benefit balance with switching. However, the decision to limit the analysis to patients with ACS considering a short-term outcome may in part increase the overall reliability of our finding. Fourth, the low number of patients who underwent a de-escalation do not allow clear conclusion on the safety of this kind of switch. Anyway, due to the kind of patients that usually underwent this kind of switch the trend to an increase of bleeding found in our study seems reasonable. Moreover, due to lack of analysis, we were not able to pool together impact of switching at multivariate analysis. Data about single type of implanted stents were not available thus making impossible further sub-analysis. Anyway, the recent ESC position paper [27] on dual antiplatelet therapy highlighted the absence of correlation between kind of stent implanted, antiplatelet strategy and patient's outcome. In our opinion, the only exception to this statement could be relative to bio resorbable scaffolds in which a prolonged DAPT seems advisable independently to the need of switch [28]. Fourth, pooled analysis on patients changing from novel $P2Y_{12}I$ therapy were not performed because of the small sample size. Finally, it should also be acknowledged that escalation of $P2Y_{12}I$ inhibition was mostly represented by a transition from clopidogrel to prasugrel, whereas transition from clopidogrel to ticagrelor was underrepresented.

6. Conclusions

In patient presenting with ACS, switching from one $P2Y_{12}I$ agent to another is associated with a potential short-term increased risk of bleeding. These findings suggest that accurate upfront selection and prescription of a $P2Y_{12}I$ based on ischemic and bleeding risks of the patient is paramount to obtain a net clinical benefit and avoiding unnecessary switching during hospitalization.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2018.11.008.

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Disclosures

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