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SYSTEMATIC REVIEW

Very Short Versus Longer Dual Antiplatelet Treatment After Coronary Interventions: A Systematic Review and Meta-analysis

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Abstract

Background Very short (≤ 3 months) duration of dual antiplatelet therapy (VSDAPT) has recently been proposed after percutaneous coronary intervention (PCI) with drug-eluting stent (DES).

Objectives The aim of this systematic review and meta-analysis was to compare very short versus > 3 months' duration of dual antiplatelet treatment (DAPT) in patients undergoing PCI with DES, focusing on ischemic and bleeding events.

Methods Three major databases (Medline, Cochrane Central Register of Controlled Trials, and Scopus) were screened for eligible randomized controlled trials (RCTs). The primary endpoint of our meta-analysis was the incidence of net adverse clinical events (NACE), as defined per trial, while secondary endpoints were major adverse cardiovascular events (MACE), all-cause and cardiovascular mortality, myocardial infarction, stroke, stent thrombosis, repeat revascularization, and major bleeding.

Results We included eight RCTs with a total of 41,204 patients; 20,592 patients were allocated to VSDAPT and the remaining 20,612 patients were randomized to a longer DAPT period. The abbreviated regimen significantly reduced NACE (odds ratio [OR] 0.83, 95% confidence interval [Cl] 0.74–0.95) and major bleeding (OR 0.71, 95% Cl 0.61–0.82), without affecting mortality or ischemic events (stroke, myocardial infarction, revascularization, and stent thrombosis).

Conclusions VSDAPT significantly decreased the odds of NACEs and major bleeding by 17% and 29%, respectively, without increasing ischemic events. Thus, VSDAPT could be well tolerated and feasible after PCI with DES.

Clinical Trials Registration Open Science Framework (10.17605/OSF.IO/4H2JB)

Graphical Abstract

Very short-term DAPT significantly reduces NACE and major bleedings, without affecting mortality and ischemic events (MACE, MI, stroke, stent thrombosis and revascularization). *CI* confidence intervals, *DAPT* dual antiplatelet therapy, *DES*

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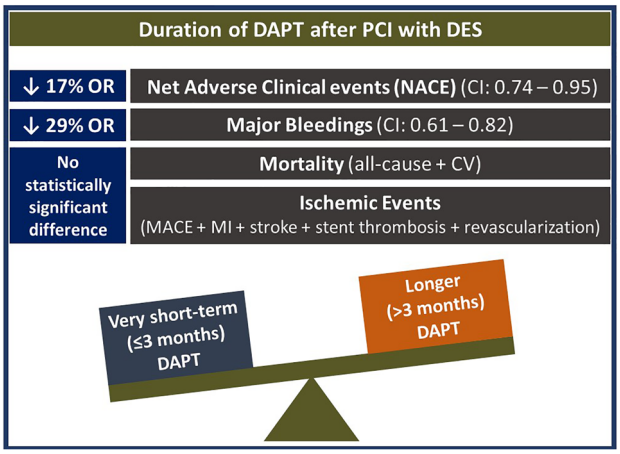
drug-eluting stents, *MACE* major adverse cardiovascular events, *MI* myocardial infarction, *NACE* net adverse clinical events, *OR* odds ratio, *PCI* percutaneous coronary interventions.



1 Introduction

Dual antiplatelet treatment (DAPT) is the standard of care after percutaneous coronary interventions (PCI), but it increases the risk of bleeding and may lead to adverse or even fatal events [1]. DAPT duration and P2Y12 inhibitor selection can significantly influence the balance between ischemia and hemorrhage. Whereas ischemic events and stent thrombosis occur mainly during the early post-PCI period, bleeding events may ensue with a longer duration of antiplatelet therapy [2].

Current guidelines recommend DAPT following PCI with drug-eluting stents (DESs) for 6 and 12 months for patients with chronic (CCS) and acute coronary syndromes (ACS), respectively; this period could be decreased to 1–3 months for high bleeding risk patients. Nevertheless, the duration of DAPT could be prolonged according to the anatomical, technical, or clinical characteristics of a patient, based on what we call individualized management [2–5]. Improvements in DES design and use of intravascular imaging and physiology for stent optimization have decreased the risk of ischemic events, including stent thrombosis [6, 7]. Against this background, several studies investigated whether a very short-term DAPT (VSDAPT) strategy could be safe and feasible after newer-generation DES implantation, with conflicting results; some studies suggested benefit with short DAPT while other studies raised concerns for increased risk of thrombotic complications [8].

The aim of this systematic review and meta-analysis was to compare the safety and efficacy of a short (≤ 3 months) versus > 3-month duration of DAPT after PCI.

2 Methods

Our systematic review and meta-analysis was conducted in compliance with the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [9]. The rationale and design of our project was registered in the Open Science Framework (https://doi.org/10.17605/OSF.IO/4H2JB). Institutional Review Board approval was not required as this was a study-level meta-analysis of previously published data.

2.1 Eligibility Criteria and Endpoints

Studies were included in the present systematic review and meta-analysis if they met all of the following criteria; (1) randomized controlled trials (RCT) including human subjects; (2) DAPT duration ≤ 90 days in the intervention arm; (3) DAPT duration of at least 91 days in the comparator arm; (4) PCI with DES in all included patients who presented with ACS or CCS; and (5) published after 1 January 2015. We set a time frame so as to include studies with only newer-generation stents and for our findings to be more compatible with current clinical practice.

The prespecified primary endpoint of our study was the incidence of net adverse clinical events (NACEs), a composite outcome of all-cause mortality, major cardiovascular events, and major bleeding. Secondary endpoints included major adverse cardiovascular events (MACE), a composite outcome of death, myocardial infarction, stroke, and stent thrombosis. Other secondary endpoints were myocardial infarction, stroke, stent thrombosis, repeat revascularization,

and major bleeding. NACE and MACE were used as defined in each included trial. Regarding major bleeding, we preferred the Bleeding Academic Research Consortium (BARC) criteria over Thrombolysis in Myocardial Infarction (TIMI) or Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients, an International Randomized Evaluation (STEEPLE) criteria for the definition of major bleeding, for better consistency between the studies. More information about the definitions for each endpoint are summarized in electronic supplementary material (ESM) Table 1.

2.2 Information Sources

We searched the current literature by conducting an electronic bibliographic database screening in three databases—Medline, Cochrane Central Register of Controlled Trials, and Scopus. All searches were undertaken on 16 January 2022. Moreover, we manually searched the reference lists of the retrieved studies to identify any other eligible trials.

2.3 Search Strategy

The electronic search included the following terms: 'dual antiplatelet treatment', 'DAPT', 'percutaneous coronary intervention', 'PCI', 'drug eluting stents', and 'DES'. The comprehensive search strategy was tailored for each database, as presented in ESM Table 1. No language restrictions were imposed.

2.4 Selection Process

All studies identified in the systematic search of the electronic databases were imported into Endnote and duplicates were removed. Supportive reports from the same study were combined. The titles, abstracts, and keywords of all articles were screened by two independent reviewers (AA, AT) and irrelevant articles were removed. The full-text articles were then evaluated by two reviewers (AA, DC). Any disagreements were resolved through discussion and consultation with the remaining authors.

2.5 Data Collection Process

A standardized data extraction form was developed to extract the study characteristics and outcomes. This form was tested in three randomly selected studies by all study authors. After completing the form, two of the authors independently extracted the data from each study (AA, DC). A third study member (GT) validated the extracted data, resolved any disagreements, and entered the data into Review Manager 5 software (Review Manager 2014).

2.6 Data Items

We extracted data from the included studies as follows: (1) the report: authors, year and source of publication; (2) the study: sample size, randomization, inclusion and exclusion criteria; (3) the participants: demographic characteristics, comorbidities, pharmacotherapy; (4) the procedure: periprocedural characteristics, stent type, indication for intervention; (5) DAPT type and duration; and (6) outcomes during the 1-year follow-up period.

2.7 Study Risk-of-Bias Assessment

We assessed risk of bias in the included studies using the revised Cochrane 'Risk of Bias' tool for randomized trials (RoB 2.0) [10]. Two authors (AA, AT) applied the previous tools in each included study. Any discrepancies in judgements of risk of bias were resolved through consultation and discussion to reach consensus between the two investigators, with a third author (GT) acting as an arbiter, when appropriate. To assess the potential publication bias, we constructed funnel plots in which the sample size was plotted against odds ratios (ORs) for each endpoint.

2.8 Statistical Analysis

All analyses were performed at the study level. ORs with 95% confidence intervals (CIs) were used for the estimation of the effect of the different DAPT regimens. Each study that did not provide adequate data about a specific outcome was excluded from the relevant analysis regarding this endpoint. All analyses were conducted in an intention-to-treat manner. The pooled OR was estimated by applying a fixed-effect model (Mantel–Haenszel) [11]. Between-study heterogeneity was evaluated by applying the statistical inconsistency test ($I^2 = 100\% \times (Q-df)/Q$, where 'Q' = Chi-square (Cochran's heterogeneity statistic) and df = degrees of freedom), and where $I^2 \leq 25\%$ signifies low heterogeneity, $I^2 \leq 50\%$ is moderate heterogeneity, and $I^2 > 50\%$ is considered high heterogeneity [12]. *P*-values < 0.05 were considered significant. Sensitivity analysis was performed by removing one study at a time and repeating the statistical analysis. Review Manager software version 5.4 (Cochrane Collaboration) was used for the analyses. Moreover, we performed trial sequential analysis (TSA) in order to examine the accrual of adequate patient sample size and minimize the risk of statistical errors. The information size required for a valid meta-analysis may be assumed to be at least as large as the sample size of a single well-powered RCT designed to confirm or refute the null hypothesis [13]. To investigate the potential interaction of ACS and the treatment effect of VSDAPT, we performed meta-regression (mixed-effects model) of the log OR against the prevalence (percentage

Table 1 Study characteristics

No	Trial	Year	Duration	Follow-up	Time of randomization	Very-short DAPT			Standard DAPT regimen		Indication for PCI	Stent used
						Regimen	Duration	Continuation with:	Regimen	Duration		
1	GLOBAL LEADERS[14]	2018	2013–2015	2 years	At index PCI	ASA 75–100 mg qd + TICA 90 mg bid	1 month	TICA 90 mg bid	ASA 75–100 mg qd + TICA 90 bid/CLOP 75 mg qd	12 months	ACS/CCS	Biolimus A9-eluting stent
2	SMART-CHOICE[15]	2019	2014–2017	1 year	At 3 months	ASA 100 mg qd + CLOP 75 mg qd or PRAS 10 mg qd or TICA 90 mg bid	3 months	CLOP 75 mg qd or PRAS 10 mg qd, or TICA 90 mg bid	ASA 100 mg qd + CLOP 75 mg qd or PRAS 10 mg qd or TICA 90 mg bid	12 months	ACS/CCS	Cobalt-chromium everolimus-eluting stents (Xience Prime®, Xience Expedition®, or Xience Alpine®; Abbott Vascular), platinum chromium everolimus-eluting stents (Promus Element®, Promus Premier®, or SYNERGY®; Boston Scientific), or sirolimus-eluting stents with biodegradable polymer (Orsiro®; Biotronik)
3	STOPDAPT-2[16]	2019	2015–2017	1 year	At 1 month	ASA 81–100 mg qd + CLOP 75 mg qd or PRAS 3.75 qd	1 month	CLOP 75 mg qd	ASA 81–100 mg qd + CLOP 75 mg qd	12 months	ACS/CCS	Cobalt-chromium everolimus-eluting stent
4	TWILIGHT[17]	2019	2015–2017	1 year	At 3 months	EC-ASA (81–100 mg qd) + TICA 90 mg bid	3 months	TICA 90 mg bid	EC-ASA (81–100 mg qd) + TICA 90 mg bid	12 months	ACS/CCS	Locally approved DES
5	REDUCE[18]	2019	2014–2016	2 years	At index PCI	ASA + PRAS, TICA (preferred over CLOP)	3 months	PRAS, TICA (preferred over CLOP)	ASA + PRAS, TICA (preferred over CLOP)	12 months	ACS	COMBO stent
6	TICO[19]	2020	2015–2018	1 year	At index PCI	ASA 100 mg qd + TICA 90 mg bid	3 months	TICA 90 mg bid	ASA 100 mg qd + TICA 90 mg bid	12 months	ACS	Ultrathin bioresorbable polymer sirolimus-eluting stents (Orsiro®; Biotronik AG)
7	One-Month DAPT[20]	2021	2015–2019	1 year	At index PCI	ASA 100 mg qd + CLOP 75 mg qd	1 month	ASA 100 mg qd	ASA 100 mg qd + CLOP 75 mg qd	6–12 months	ACS/CCS	Polymer-free drug-coated stent or biodegradable-polymer drug-eluting stent
8	MASTER-DAPT[21]	2021	2017–2019	1 year	At 1 month	ASA + CLOP or TICA or PRAS	1 month	NA	ASA + CLOP or TICA or PRAS	3–12 months	ACS/CCS	Bioresorbable polymer-coated stent

ACS acute coronary syndrome, *ASA* acetylsalicylic acid, *bid* twice daily, *CCS* chronic coronary syndrome, *CLOP* clopidogrel, *DAPT* dual antiplatelet therapy, *DES* drug-eluting stent, *EC* enteric-coated, *PCI* percutaneous coronary intervention, *PRAS* prasugrel, *qd* once daily, *TICA* ticagrelor

ratio) of ACS in the enrolled study population using R (R Foundation for Statistical Computing, Vienna, Austria).

3 Results

3.1 Search Results

Our systematic search in the three databases identified 8681 records. After removal of duplicates, 6086 records remained for title and abstract review, of which 53 underwent full-text screening. Overall, eight RCTs were eligible for inclusion in our systematic review and meta-analysis [14–21]. Our systematic search of the literature is depicted in the PRISMA flowchart shown in ESM Fig. 1).

3.2 Study Characteristics

The characteristics of the included studies are summarized in Table 1. The inclusion and exclusion criteria of each study as well as the endpoints, both primary and secondary, are presented in ESM Table 3. A total of 41,204 patients were included, of whom 20,592 were allocated to the VSDAPT arm and 20,612 were allocated to the DAPT > 3 months arm. Two studies only included ACS patients [18, 19], while the remaining six studies included patients with both ACS and CCS. One-month DAPT was selected in four studies, whereas 3-month duration was chosen in the remaining four studies in the intervention arm. The One-Month DAPT trial used aspirin as monotherapy after the shortened regimen [20]. One study included only patients under high bleeding risk [21]. The follow-up duration was 24 months in two trials and 12 months in the remaining six trials [14, 18]. All endpoints were evaluated during the 1-year follow-up period.

3.3 Patient Characteristics

The baseline characteristics of the study patients are shown in Table 2 and did not vary significantly among the included studies and populations. Women were underrepresented in all trials, representing < 30% of the total patients, except the One-Month DAPT and the MAnagement of high bleeding risk patients post bioresorbable polymer coated STEnt implantation with an abbReviated versus prolonged DAPT regimen (MASTER-DAPT) trials [20, 21]. More than half of the patients presented with ACS. Six of the included trials included at least 10% of patients with ST-elevation myocardial infarction (STEMI).

Table 2 Patient characteristics

Variable	GLOBAL LEADERS[14]		SMART CHOICE[15]		STOP-DAPT-2[16]		TWI-LIGHT[17]		REDUCE[18]		TICO[19]		One-Month DAPT[20]		MASTER DAPT[21]	
	SHT	STD	SHT	STD	SHT	STD	SHT	STD	SHT	STD	SHT	STD	SHT	STD	SHT	STD
Patients (*n*)	7980	7988	1495	1498	1500	1509	3555	3564	751	745	1527	1529	1507	1513	2295	2284
Age (years)	64.5	64.6	64.6	64.4	68.1	69.1	65.2	65.1	61	60	61	61	67	67	76.1	76
Female (%)	23.4	23.1	27.3	25.8	21.1	23.5	23.8	23.9	17.4	22.7	21	20	31	31	30.7	30.8
BMI (kg/m^2)	28.2	28.2	24.5	24.7	24.4	24.2	28.6	28.5	–	–	24.9	24.9	24.7	24.7	27.3	27.4
Smoking (%)	25.9	26.3	28.4	24.5	26.6	20.6	20.4	23.1	42.1	42.7	36	38	17	16	38.2	37.5
HTN (%)	74	73.3	61.6	61.3	73.7	74	72.6	72.2	50.7	50.7	50	51	67	66	76.9	78.2
DM (%)	25.7	24.9	38.2	36.8	39	38	37.1	36.5	21.6	19.5	27	27	37	38	32.9	34.3
Dyslipidemia (%)	69.3	70	45.1	45.5	74.4	74.8	60.7	60.2	46.3	44.9	61	60	81	82	67.2	68.1
PAD (%)	6	6.7	–	–	6.4	6.6	6.9	6.8	–	–	–	–	–	–	10.6	10.6
CKD (%)	13.9	13.5	2.9	3.5	5.5	5.6	16.8	16.7	–	–	19	22	13	14	18.2	20.1
Previous PCI (%)	32.7	32.7	11.5	11.8	33.5	35.1	42.3	42	11.7	9.8	9	8	16	18	25.9	26
ACS (%)	47	46.8	58.2	58.2	37.7	38.6	63.9	65.7	100	100	100	100	38	41	49.1	47.4
STEMI (%)	13.3	12.9	11	10	19.4	17.9	0	0	49.3	45.2	36	36	–	–	11.9	11.6
NSTEMI (%)	21.1	21.1	16	15.4	5.4	6.6	28.8	30.8	35.6	41	35	32	–	–	25.9	24.4
UA (%)	12.6	12.7	31.2	32.8	12.9	14.2	35.1	34.9	15.2	13.8	29	32	35	38	11.3	11.4
CCS (%)	53	53.2	41.8	41.8	62.3	61.4	29.5	28	0	0	0	0	62	59	40.2	40.6
No. of stents	–	–	–	–	1.3	1.3	–	–	–	–	1.37	1.37	1.3	1.3	1.47	1.76
Total length of stents (mm)	–	–	38	37.8	30.3	30.5	40.1	39.7	23	23	35	35	31	31	39.3	39.7

ACS acute coronary syndrome, *BMI* body mass index, *CCS* chronic coronary syndrome, *CKD* chronic kidney disease, *DAPT* dual antiplatelet therapy, *DM* diabetes mellitus, *HTN* hypertension, *NSTEMI* non-ST elevation myocardial infarction, *PAD* peripheral arterial disease, *PCI* percutaneous coronary intervention, *SHT* short duration DAPT, *STD* standard duration DAPT, *STEMI* ST-elevation myocardial infarction, *UA* unstable angina

3.4 Primary Endpoint-Net Adverse Clinical Events

The incidence of NACE was available for six trials, with a total of 18,117 patients. The Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention (TWILIGHT) trial did not provide data about NACE, while GLOBAL LEADERS presented data for only 2 years of follow-up of NACE [14, 17]. NACE occurred in 479 patients treated with the VSDAPT regimen and 567 patients in the control group. VSDAPT resulted in 17% odds reduction of NACEs (OR 0.83, 95% Cl 0.74–0.95). There was no statistically significant heterogeneity between studies ($p = 0.35$) (Fig. 1).

3.5 Secondary Endpoints

3.5.1 Major Adverse Cardiovascular Events

All trials, except the One-Month study, provided adequate data about MACE. A total of 1221/38,184 patients experienced at least one MACE, as defined in each trial, during follow-up. No statistically significant difference was observed between the two study arms (OR 0.92, 95% Cl 0.82–1.03). There was no statistically significant heterogeneity between studies ($p = 0.32$) (Fig. 2).

3.5.2 All-Cause and Cardiovascular Mortality

Data about all-cause mortality were available for all included studies, while GLOBAL LEADERS was the only study that did not provide results about cardiovascular mortality. Pooled analysis showed no significant difference between the two arms, for both all-cause (OR 0.88, 95% CI 0.75–1.03) (Fig. 3a) and cardiovascular mortality (OR 0.80, 95% CI 0.62–1.03) (Fig. 3b). The heterogeneity among trials was low for both endpoints ($p = 0.37$ and $p = 0.65$, respectively) (Fig. 4).

3.5.3 Major Bleeding

Data on major bleeding were available in the total population of the present meta-analysis. Major bleeding was considered as bleeding classified according to the BARC 3–5 guidelines, except in the Short-term Dual Anti Platelet Therapy in Patients With ACS Treated With the COMBO Dual-therapy Stent (REDUCE) trial, which was included in the BARC 2–5 guidelines [18]. As displayed in the figure, the abbreviated regimen decreased the risk of major bleeding by 29% at 1-year follow-up (1.6% vs. 2.2%; OR 0.71, 95% Cl 0.61–0.82; $I^2 = 45\%$, $p = 0.08$).

3.5.4 Myocardial Infarction and Stroke

All eight studies involving a total of 41,204 patients reported data about myocardial infarction and stroke. We estimated that 1.9% (398/20,592) of the intervention group and 1.8% (377/20,612) of the control arm suffered a MI, with a calculated pooled OR of 1.06 (95% CI 0.92–1.22). Moreover, 122/20,592 patients who received VSDAPT and 131/20,612 patients who received >3 months of DAPT experienced a stroke during the duration of the study, with a pooled OR of 0.93 (95% CI 0.73–1.19). There was no statistically significant heterogeneity between studies ($p = 0.59$ and $p = 0.12$, respectively, for MI and stroke) (Fig. 5).

3.5.5 Stent Thrombosis and Repeat Revascularization

All eight studies reported data on stent thrombosis, while five of the studies reported data about the urgency of revascularization. No statistically significant difference with low heterogeneity was observed between the two arms for both stent thrombosis (OR 1.26, 95% CI 0.95–1.65; $I^2 = 0\%$, $p = 0.54$) (Fig. 6a) and repeat revascularization (OR 0.99, 95% CI 0.88–1.10, $I^2 = 6\%$, $p = 0.37$) (Fig. 6b).

3.6 Trial Sequential Analysis

TSA included six RCTs reporting NACE outcomes, with a total sample size of $n = 18{,}117$ with clinical follow-up at 1 year. This shows the cumulative curve of the Z-score statistic and the O'Brien–Fleming trial sequential monitoring boundaries to control statistical errors against the available sample size. Clearly, the cumulative Z-curve crosses the external alpha-spending boundaries, and the required information size (cumulative patient sample) has been achieved (ESM Fig. 2)

3.7 Risk-of-Bias Assessment, Sensitivity, and Meta-Regression Analysis

A risk-of-bias summary and graph were prepared according the RoB 2.0 tool and are presented in ESM Fig. 3. All included studies were in the lower categories for risk of bias.

Publication bias was assessed using funnel plots. Symmetric distribution of the mean effect size was noticed in funnel plots for all endpoints, suggesting low risk of publication bias of the included studies (ESM Fig. 4). The statistical significance of the overall results did not change through the sensitivity analyses, confirming the robustness of our findings.

Meta-regression analysis for ACS patients showed no significant association between percentage ACS in the treated population and the observed effect size, as the coefficient of the regression line is -0.0014 ± 0.0031 ($p = 0.656$) (ESM Fig. 5).

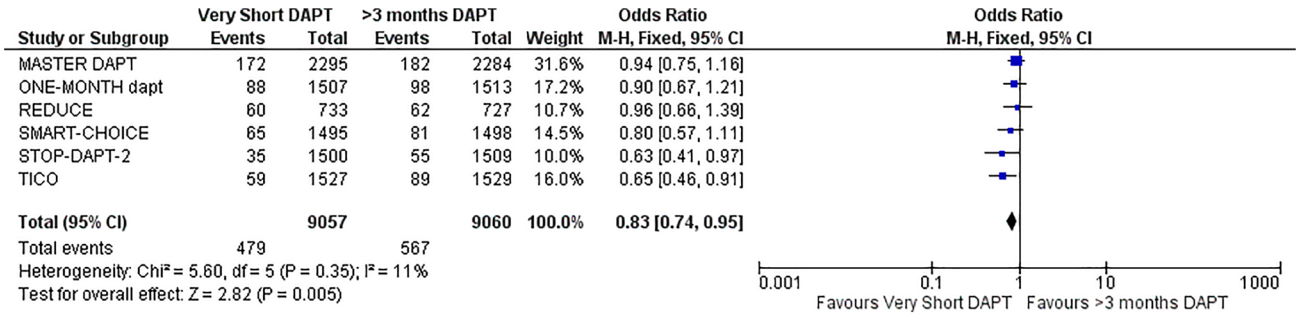


Fig. 1 Forest plot demonstrating the effect of very short-term versus > 3 months of DAPT on net adverse clinical events, with odds ratios and 95% CIs. *CI* confidence interval, *DAPT* dual antiplatelet therapy, *M-H* Mantel–Haenszel, *df* degrees of freedom

4 Discussion

To the best of our knowledge, our systematic review and meta-analysis is the first to include more than 40,000 patients undergoing PCI with DES in the era of VSDAPT. The newer generation of DESs with thin struts, and the advancement of intracoronary imaging, have resulted in better stent deployment, high PCI success rates, and low risk of thrombotic complications [7, 22]. According to our findings, a very short (≤ 3 months) DAPT duration significantly decreased the risk for NACEs and major bleeding, without increasing the risk of ischemic events.

VSDAPT was recently introduced in clinical practice, and describes early (≤ 90 days) discontinuation of DAPT. Whereas there are numerous systematic reviews and meta-analyses on DAPT duration post PCI, only two included VSDAPT as the intervention arm [23, 24]. Benenati et al. were the first to perform a meta-analysis of VSDAPT [24]. They included seven RCTs with 37,785 patients, showing a benefit of abbreviated DAPT on bleeding risk. Verdoia and colleagues included five RCTs with approximately 38,000 patients with ACS or CCS [23]. Similar to our study, they found a benefit of abbreviated DAPT duration on major bleeding.

However, none of these meta-analyses included the three most recent, large-scale RCTs. Kim et al. compared the 3-month DAPT plus ticagrelor per se for the remaining 9 months with ticagrelor-based 12-month DAPT in patients with ACS [19]. The TICO trial showed a modest but statistically significant result in favor of 3-month DAPT followed by ticagrelor monotherapy. Hong et al. investigated whether 1 month of DAPT followed by aspirin after PCI with polymer-free drug-coated stent (PF-DCS) implantation is non-inferior to 6–12 months of DAPT after biodegradable-polymer DES (BP-DES) placement [20]. They found that the abbreviated DAPT regimen was non-inferior to > 3 months of DAPT but these findings should be validated with other stent types. The most recent RCT included in the present systematic review and meta-analysis is the MASTER-DAPT trial, in which Valgimigli et al. compared the abbreviated versus standard-of-care DAPT regimen in patients with high bleeding risk, supporting that 1-month of DAPT is non-inferior for the prevention of NACE [21].

Our systematic review and meta-analysis was the first to use NACE as the primary endpoint. An increasing number of trials studying antithrombotic treatments use this novel composite endpoint. In contrast with MACE, NACE includes major bleeding so as to cover a wider spectrum of adverse events, both thrombotic and hemorrhagic.

In addition, ours is one of the first meta-analyses to include a TSA, showing that the cumulative sample size has been achieved, and hence strengthening the power of our results.

Our meta-analysis tried to cover the entire range of patients with coronary disease, either presented acutely or on a chronic basis. While it could be supposed that this could add heterogeneity among the populations, and inconsistency of the results, our meta-analysis showed that the ACS did not alter the overall effect size, supporting that VSDAPT is feasible and safe even for ACS patients. Nevertheless, the majority of patients included in our meta-analysis suffered from ACS, while a significant proportion of patients presented with STEMI. These findings are in accordance with the existing literature; a recent meta-analysis with nine RCTs and more than 25,000 patients showed that VSDAPT has similar efficacy for preventing ischemic events with decreased bleeding risk compared with 6–12 months of DAPT [25].

The selection of antiplatelet agents after discontinuation of DAPT remains controversial. Most studies used a potent P2Y12 inhibitor for a more successful platelet inhibition. Giacoppo et al. did not achieve to exact a clear conclusion in their recent, large-scale network meta-analysis [26]. Ticagrelor has been considered an acceptable option after short-term DAPT [27]. In their recent network meta-analysis, Ullah et al. showed that 3 months of DAPT followed by ticagrelor monotherapy was associated with the best outcomes, independently of the indication of the procedure

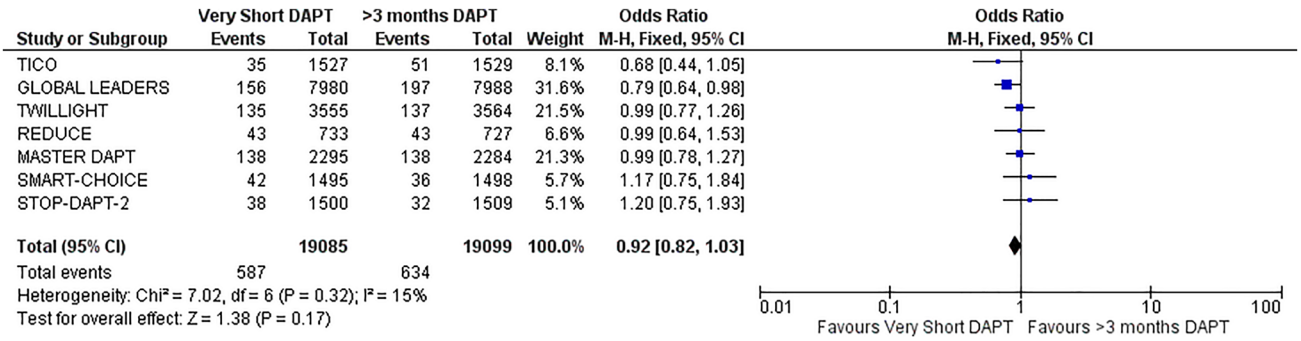


Fig. 2 Forest plot demonstrating the effect of very short-term versus > 3 months of DAPT on major adverse clinical events, with odds ratios and 95% CIs. *CI* confidence interval, *DAPT* dual antiplatelet therapy, *M-H* Mantel–Haenszel, *df* degrees of freedom

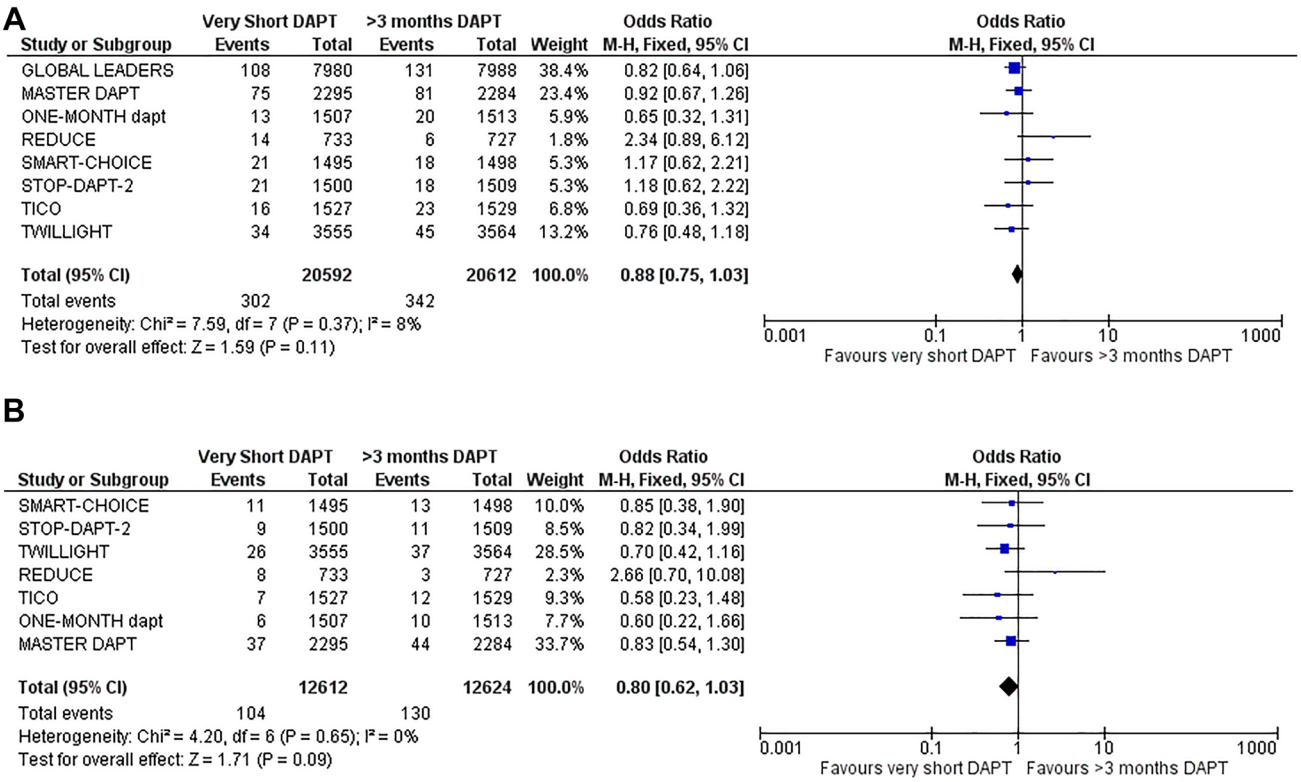


Fig. 3 Forest plot demonstrating the effect of very short-term versus > 3 months of DAPT on **(A)** all-cause and **(B)** cardiovascular mortality, with odds ratios and 95% CIs. *CI* confidence interval, *DAPT* dual antiplatelet therapy, *M-H* Mantel–Haenszel, *df* degrees of freedom

[28]. However, more studies comparing ticagrelor with aspirin and another P2Y12 inhibitor as monotherapy after a short course of DAPT are required. Finally, based on the PANTHER analysis results and the HOST-EXAM trial, the use of P2Y12 inhibitors instead of aspirin monotherapy seems to be a reasonable choice, especially in young CCS patients with a previous PCI and low bleeding risk or a high risk of gastrointestinal bleeding [29].

Our findings are in accordance with the current European Society of Cardiology guidelines that support the very short duration of DAPT for both ACS and CCS patients under special circumstances [4, 30]. Taking into consideration the fact that many of the analyzed studies included ACS patients, 1- or 3-month DAPT duration could be a feasible option for acute patients with high bleeding risk [31].

Our meta-analysis supports a strategy of VSDAPT mainly with potent P2Y12 inhibitor monotherapy, likely

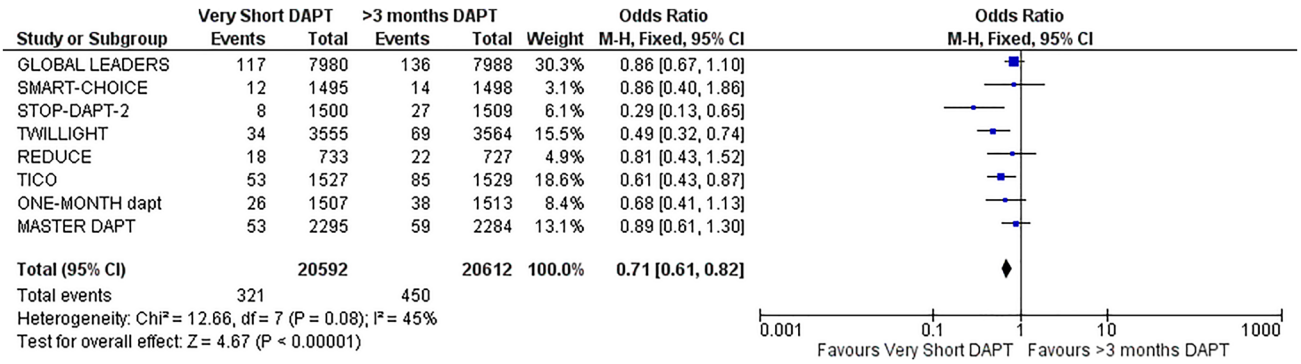


Fig. 4 Forest plot demonstrating the effect of very short-term versus > 3 months of DAPT on major bleedings, with odds ratios and 95% confidence intervals. *CI* confidence interval, *DAPT* dual antiplatelet therapy, *M-H* Mantel–Haenszel, *df* degrees of freedom

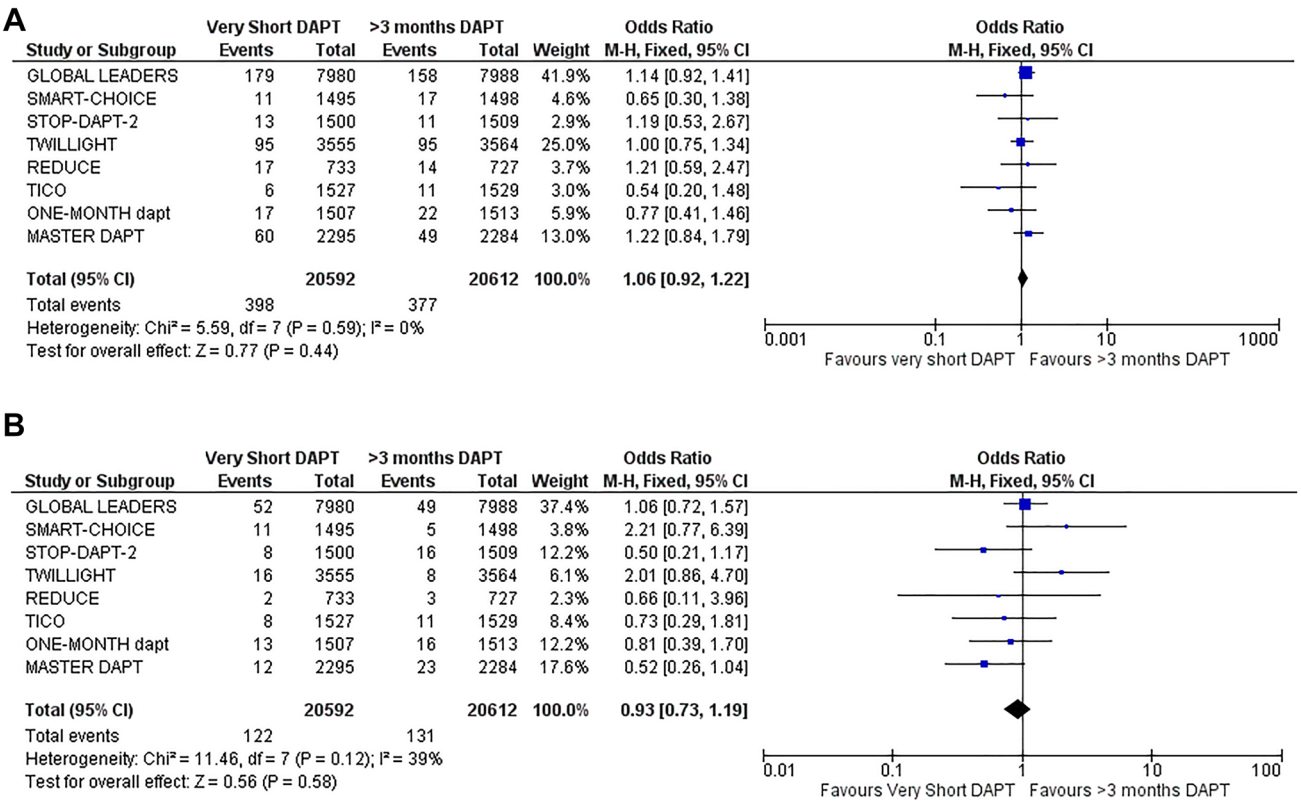


Fig. 5 Forest plot demonstrating the effect of very short-term versus > 3 months of DAPT on **a** myocardial infarction and **b** stroke, with odds ratios and 95% CIs. *CI* confidence interval, *DAPT* dual antiplatelet therapy, *M-H* Mantel–Haenszel, *df* degrees of freedom

ticagrelor according to the existing literature, as a safe option in patients treated with new-generation DES. Certainly, further investigation is needed regarding patients' clinical profiles that may derive maximum benefit from such a strategy, the most appropriate P2Y12 inhibitor monotherapy, and the optimal DAPT duration.

4.1 Limitations

Our systematic review and meta-analysis has limitations. First, this was a study-level meta-analysis and thus the absence of patient-level data and individualized baseline characteristics did not allow the estimation of their impact

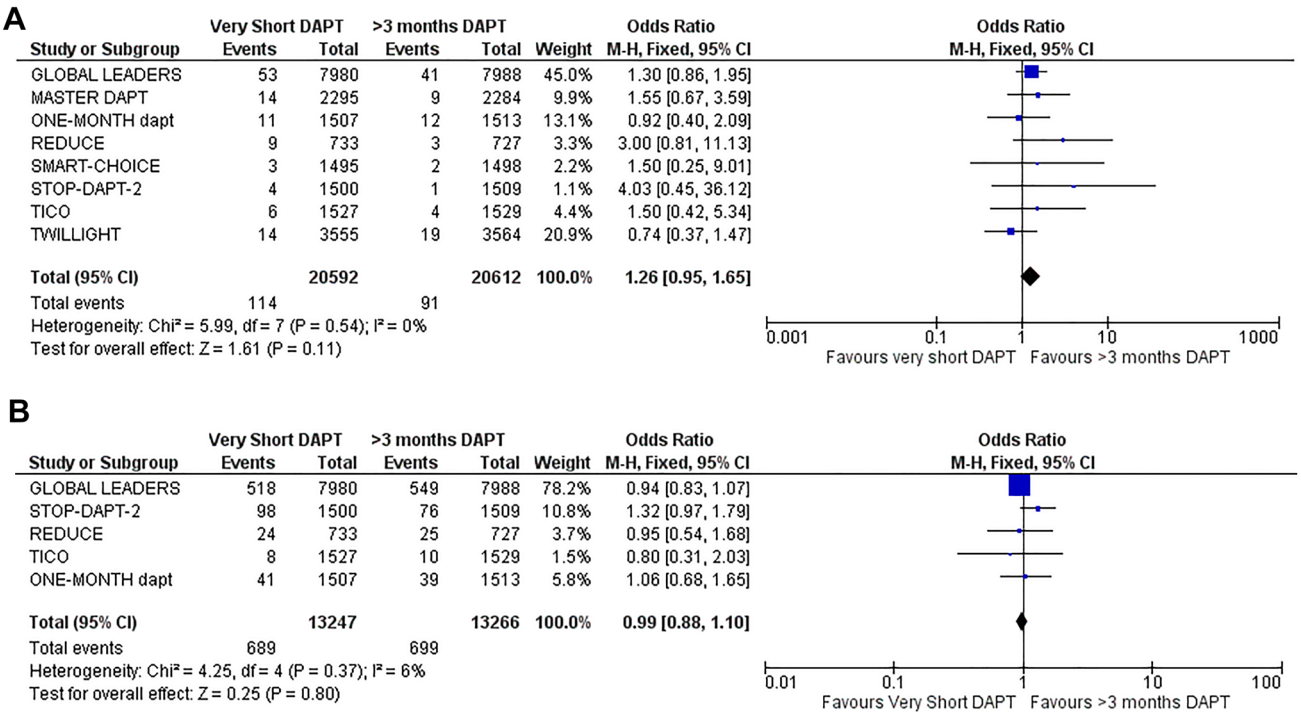


Fig. 6 Forest plot demonstrating the effect of very short-term versus > 3 months of DAPT on **a** stent thrombosis and **b** revascularization, with odds ratios and 95% CIs. *CI* confidence interval, *DAPT* dual antiplatelet therapy, *M-H* Mantel–Haenszel, *df* degrees of freedom

on outcomes. Second, our systematic review and meta-analysis synthesizes data from patients with both ACS and CCS who presented with different bleeding and thrombotic profiles. However, low-to-moderate heterogeneity was found in all analyzed trials, therefore the wide variety of clinical presentations did not affect the quality and confirmed that a very short duration of DAPT could be administered for patients with ACS and CCS. Moreover, the meta-regression analysis showed that no significant association between percentage ACS in the treated population and the observed effect size existed. Third, the definition of the composite outcomes differed slightly among the included trials. However, a consensus has not been achieved on the definition and validity of the composite outcome of NACEs or MACEs, although it would be useful for comparing the antithrombotic regimens. For this reason, we comprehensively presented the definition of each trial in ESM Table 3.

5 Conclusions

The present meta-analysis of patients undergoing PCI with DES indicates that VSDAPT (≤ 3 months) significantly decreases the rate of NACE and major bleeding, without increasing the risk of ischemic events or mortality, compared with > 3 months of DAPT duration. The odds of NACE and major bleeding were reduced by 17% and 29%, respectively. Overall, our meta-analysis supports the very short term of DAPT, but the duration and P2Y12 inhibitor selection should be tailored to individual benefit-risk profiles.

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Declarations

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Conflict of interest Grigorios Tsigkas has received advisory board/lecturing fees from Astra Zeneca, Menarini, Pfizer, and Boehringer Ingelheim. Konstantinos Toutouzas has received honorarium from Sanofi Adventist. Dimitrios Alexopoulos has received advisory board/lecturing fees from Astra Zeneca, Bayer, Pfizer, Boehringer Ingelheim, Medtronic, Biotronik, and Chiesi Hellas. Emmanouil S. Brilakis has received consulting/speaker honoraria from Abbott Vascular, American Heart Association (Associate Editor Circulation), Amgen, Asahi Intecc, Biotronik, Boston Scientific, Cardiovascular Innovations Foundation (Board of Directors), ControlRad, CSI, Elsevier, GE Healthcare, IMDS, InfraRedx, Medicure, Medtronic, Opsens, Siemens, and Teleflex; and research support from Boston Scientific, GE Healthcare. He is also an owner of Hippocrates LLC; and a shareholder of MHI Ventures, Cleerly Health, and Stallion Medical. Periklis Davlouros has received advisory board/lecturing fees from Astra Zeneca, Bayer, Menarini, Pfizer, and Boehringer Ingelheim. Anastasios Apostolos, Ai-

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Availability of data and material Not applicable.

Code availability Not applicable.

Ethical approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Authors contributions GT, AA, and PD designed the analysis. AA, AT, and DC collected the data. AA and KK performed the analysis. GT and AA wrote the manuscript. KT, DA, ESB, and PD reviewed the manuscript. All authors approved the final manuscript.

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