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Meta-Analysis of Short vs. Prolonged Dual Antiplatelet Therapy after Drug-Eluting Stent Implantation and Role of Continuation with either Aspirin or a P2Y12 Inhibitor Thereafter

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Aim: The optimal duration of dual antiplatelet therapy (DAPT) after drug-eluting stent (DES) implantation is an ongoing debate and novel data has emerged. The aim of this meta-analysis was to assess outcomes of short vs. control DAPT duration. In addition, the role of single antiplatelet therapy (SAPT) after DAPT with either aspirin or P2Y12 inhibitor monotherapy was analyzed.

Methods: The authors searched MEDLINE and Cochrane databases and proceedings of international meetings for randomized controlled trials (RCT) comparing ≤ 3 months with ≥ 6 months DAPT after DES implantation. The primary and co-primary outcomes of interest were definite or probable stent thrombosis (ST) and bleeding. In addition, we performed an analysis on studies who continued with either aspirin or P2Y12 monotherapy after DAPT.

Results: 9 RCTs comprising 41,864 patients were included and we analyzed a short DAPT duration of median 1.5 months vs. 12.1 months in the control group. The risk for ST was similar with short vs. control DAPT duration (0.5 vs. 0.5%; hazard ratio 1.17[95% CI 0.89-1.54]; $p=0.26$). Bleeding was significantly reduced with short vs. control DAPT duration (1.9 vs. 3.0%; 0.65[0.54-0.77]; $p<0.0001$).
ST was not different between short vs. control DAPT duration in the analysis of the 4 RCTs who continued with aspirin after DAPT and the 5 P2Y12 RCTs, respectively, and no heterogeneity was detected ($p=0.861$). Bleeding was also reduced with short vs. control DAPT in both the aspirin (1.2 vs. 1.7%; 0.71[0.51-0.99]; $p=0.04$) and P2Y12 inhibitor studies (2.1 vs. 3.4%; 0.62[0.47-0.80]; $p=0.0003$) and no heterogeneity was detected ($p=0.515$).

Conclusions: Our meta-analysis shows that short DAPT ≤ 3 months followed by SAPT reduces bleeding and is not associated with an increase in ST. The results were consistent within the aspirin and P2Y12 SAPT studies.

Key words: Dual antiplatelet therapy, Drug-eluting stent, Aspirin, P2Y12 inhibitor

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is recommended in patients who undergo drug-eluting stent (DES) implantation for coronary artery disease (CAD) to prevent ischemic events[1]. This therapy, however, is associated with an increased bleeding rate which may lead to adverse outcomes[2]. While the risk of stent thrombosis (ST) is highest in the early phase after percutaneous coronary intervention (PCI) and declines over time[3], the risk of bleeding increases with length of therapy[4].

Current guidelines recommend at least 6 months DAPT after stent implantation with the possibility to

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shorten DAPT to 1-3 months according to the patients' risk for bleeding[1, 5]. The optimal length of DAPT after stent implantation is, however, an ongoing debate and several trials have evaluated a very short DAPT duration of ≤ 3 months. Whether this short DAPT protects sufficiently against ischemic events and adequately reduces bleeding events is still unclear because of limited statistical power of the individual trials and mixed results.

Clinicians need to determine optimal DAPT duration for their patients and do also define which single antiplatelet therapy (SAPT) will follow thereafter and this has traditionally been aspirin. The role of aspirin is currently challenged by the concept, that SAPT with a $P2Y_{12}$ inhibitor may have superior antithrombotic efficacy as compared to aspirin and may even be associated with lower bleeding rates[6].

Aim

Against this background, we performed this meta-analysis to investigate benefits and risks of a short DAPT duration (≤ 3 months) after coronary stent placement in patients with stable and unstable CAD.

Furthermore, we separately analyzed ischemic and bleeding events in the corresponding trials who continued with either aspirin or the $P2Y_{12}$ inhibitor as SAPT after short DAPT.

Methods

Data Sources and Searches

We searched MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), proceedings of international meetings and relevant websites (www.escardio.org, www.theheart.org, www.clinicaltrialresults.org, www.tctmd.com) without restricting language or publication status. The references listed in all eligible studies were checked to identify further citations. The last search was performed on February 2nd, 2021. Search terms included the keywords and the corresponding Medical Subject Headings for: "dual antiplatelet therapy", "drug eluting stent", and "randomized trial". Inclusion criteria were: (1) randomized design, (2) total number of participants >1,000, (3) DAPT duration ≤ 3 months in experimental arm, (4) DAPT duration ≥ 6 months in control arm, and (5) use of drug-eluting stents. Trials who were investigating outcomes in patients treated with bare-metal stents (BMS) were excluded.

Study Selection and Quality Assessment

Two investigators (SL and PB) independently assessed publications for eligibility at title and/or abstract level, with divergences resolved by a third investigator (NS). Studies that met inclusion criteria were selected for further analysis. Freedom from bias was independently evaluated for each study by the same investigators in accordance with The Cochrane Collaboration method[7]. Composite quality scores were not assigned[8].

Data Extraction and Outcome Variables

The primary outcome was definite or probable stent thrombosis (ST). The co-primary endpoint was bleeding. The main bleeding definitions across trials differed substantially and not every trial reported comparable bleeding definitions. While some trials analyzed mainly major bleeding events, other trials focused on a broader bleeding definition as their main outcome. The main bleeding outcome of the corresponding trial was therefore used for this analysis to increase the sample size.

Secondary outcomes were mortality, cardiac death, myocardial infarction (MI) and stroke. All endpoints were evaluated in the intention-to-treat population up to 1 year, in accordance to definitions reported in the original protocols.

Data Synthesis and Analysis

We summarized the distribution of patient characteristics in individual trials by calculating means (continuous variables) and proportions (categorical variables). We used the hazard ratios (HRs) and corresponding 95% confidence intervals (CI) reported in individual trials. In the two trials in which no HRs were reported[9, 10], the absolute number of events and the provided log-rank p-value were used to calculate HRs with 95% CIs according to the method of Parmar *et al.*[11]. In one trial[12], neither HRs nor log-rank *p*-value for cardiac death were provided; in this case, the absolute number of events was used to calculate odds ratios (ORs) with 95% CIs. We obtained pooled HRs from the inverse variance random-effects model. The heterogeneity across trials was estimated using the I^2 statistic and [95% CIs], with values around 25%, 50% and 75% indicating low, moderate or high heterogeneity, respectively[13]. The between-study variance was calculated according to the DerSimonian–Laird method. Risk estimates from random and fixed model effects are displayed in the figures, while results from the random-effects model are only reported in the text.

We also assessed whether the treatment effect of monotherapy that followed DAPT was dependent on its type — aspirin or $P2Y_{12}$ inhibitor. For this purpose, we performed separate analyses by pooling the 4

studies which continued with aspirin monotherapy after initial short DAPT duration and the 5 studies which continued with $P2Y_{12}$ monotherapy after short DAPT duration. The pooled HRs obtained by these 2 separate analyses were checked for significant heterogeneity.

All analyses were performed using R (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria). A two-sided p value <0.05 was considered as statistically significant. This meta-analysis was reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[14] **(Supplemental Fig. 1 and Supplemental Table 1)**. This meta-analysis was registered with PROSPERO (CRD42021231234; https://www.crd.york.ac.uk/prospero/)

Results

Eligible Studies

The flow diagram for the trial selection process is shown in **Supplemental Fig. 1**. After application of inclusion/exclusion criteria, 9 trials were included in this meta-analysis: 8 trials published as full-length manuscripts[9, 10, 12, 15-19] and one trial as a meeting presentation[20].

In these trials, a total of 41,864 patients were included and randomized to either short DAPT duration (≤ 3 months, $n=20,915$) or control DAPT duration (≥ 6 months, $n=20,949$).

The main characteristics of the patients included in the studies are reported in **Table 1**. Briefly, patients with significant coronary artery disease (CAD) undergoing PCI plus stenting were randomized to short vs. control DAPT duration. In seven studies, the randomization to DAPT regimens took place at the time of PCI or during the initial index hospital stay, in one study mostly at the index procedure or within 3 months[18] and in one study 3 months after the index procedure[17] **(Supplemental Table 2)**. In this latter case, all patients experiencing major bleeding or ischemic adverse events after PCI were excluded before subsequent random allocation.

Seven trials included stable and unstable patients with CAD, while two studies included only patients with ACS[12, 16]. All patients were loaded with either 300-600 mg clopidogrel or 60 mg Prasugrel (20mg in Asian populations) or 180 mg Ticagrelor, followed by either 75 mg clopidogrel once daily or prasugrel 10 mg once daily (5 mg in patients ≥ 75 years or <60 kg; 3.75 mg in Asian populations) or 90 mg ticagrelor twice daily. Most patients were loaded with 75-500 mg of aspirin. Patients received 75-100 mg aspirin per day in 7 trials and up to 200 mg aspirin per day in 2 trials[15, 19].

Short DAPT was given for 3 months in six trials and for 1 month in three trials[10, 19, 20]. Control DAPT was given for 6-12 months in one trial[20], for 12 months in seven trials and for 15 months in one trial[17].

Aspirin monotherapy was given after short DAPT in four trials[9, 15, 16, 20]. P2Y12 monotherapy was given in five trials after short DAPT until the end of the study[10, 12, 17-19].

Anticoagulation during coronary interventions was accomplished through the administration of either unfractionated heparin or bivalirudin in all patients.

All interventions were performed in accordance with standard care including the administration of glycoprotein IIb/IIIa inhibitors, stent deployment optimization, or use of intravascular imaging techniques, at the operators' discretion. All subjects enrolled received treatments on top of other cardioactive therapies (e.g. beta-blockers, statins, etc.).

Patients were treated with newer generation DES in seven trials, while earlier DES were also used in two trials[9, 15] **(Table 1)**. Common key exclusion criteria among trials were cardiogenic shock, inability to take DAPT, the need for chronic oral anticoagulation, a bleeding diathesis or a planned short-term surgery. Per protocol endpoints definitions are listed in detail **(Supplemental Table 3)**.

Clinical features among included patients were well-balanced among treatment arms in all studies. The mean age among patients enrolled ranged from 61 to 69 years, the percentage of females from 20 to 37%, the percentage of patients with a diagnosis of diabetes mellitus at admission from 25 to 38% and the percentage of patients with ACS from 32 to 100%. The median DAPT duration was 1.5 vs. 12.1 months for the short and control DAPT groups, respectively. The risk of bias among studies is reported in the **Supplemental Table 4**.

Clinical endpoints were adjudicated by an independent event adjudication committee (EAC) in seven trials. In GLOBAL LEADERS only Q-wave myocardial infarction (MI) was centrally adjudicated[10] and the yet not published one-month DAPT trial did not yet report whether events were adjudicated by an independent EAC.

Clinical Endpoints

All trials contributed to the analysis either for primary or secondary endpoints. A total of 41,864 patients were available for final calculations.

The primary endpoint of ST occurred in 212 patients (0.5%). The risk for ST was similar with

Table 1. Main characteristics of patients enrolled among trials included in the study

Trial	GLOBAL LEADERS	One-month DAPT	OPTIMIZE	REDUCE	RESET	SMART-CHOICE	STOPDAPT-2	TICO	TWILIGHT
Patients	15968	3020	3119	1496	2117	2993	3009	3056	7119
Age – years	64.5	67.0	61.6	60.5	62.4	64.5	68.6	61.0	65.1
Women – no.(%)	3714 (23.3)	933 (31)	1145 (36.7)	300 (20.1)	770 (36.4)	795 (26.6)	672 (22.3)	628 (20.5)	1698 (23.8)
BMI (kg/m^2)	28.2	NA	NA	NA	25.0	24.6	24.3	24.9	28.5
Diabetes – no.(%)	4038/15957 (25.3)	1135 (37.6)	1103 35.4	307/1494 (20.5)	621 (29.3)	1122 (37.5)	1159 (38.5)	835 (27.3)	2620 (36.8)
Arterial hypertension – no. (%)	11715/15914 (73.6)	2009 (66.5)	2721 (87.2)	754/1488 (50.7)	1310 (61.9)	1840 (61.5)	2221 (73.8)	1541 (50.4)	5154/7118 (72.4)
Dyslipidemia – no. (%)	10768/15465 (69.6)	2454 (81.3)	1905 (61.1)	679/1490 (45.6)	1245 (58.8)	1352 (45.2)	2244 (74.6)	1846 (60.4)	4303 (60.4)
Current smoker– no (%)	4169 (26.1)	NA	559 (17.9)	627/1480 (42.4)	508 (24.0)	791 (26.4)	710 (23.6)	1142 (37.4)	1548/7115 (21.8)
Ejection fraction, %	NA	63	NA	NA	64.1	60.0	59.8	NA	NA
Previous PCI– no. (%)	5221/15954 (32.7)	521 (17.3)	624 (20.0)	161 (10.8)	69 (3.3)	NA	1032 (34.3)	262 (8.6)	2998 (42.1)
Prior CABG – no. (%)	943/15955 (5.9)	44/3020 (1.5)	239/3119 (7.7)	42 (2.8)	8 (0.4)	NA	59 (2.0)	18 (0.6)	710/7118 (10.0)
Stable CAD– no. (%)	8481 (53.1)	1828/3020 (60.5)	2123 (68.1)	0	961 (45.4)	1250 (41.8)	1861 (61.9)	0	2503/7117 (35.2)
Multivessel disease– no. (%)	NA	1745 (57.8)*	809† (25.9)	523/1495 (35.0)	910 (43.0)*	1483 (49.5)	NA	1703 (55.7)	4466/7119 (62.7)
Lesion Type B2/C – no. (%)	NA	NA	1526/4120 (37.0)‡	NA	1842/2687 (68.6)	NA	490/638 (76.8)§	NA	NA
Number of treated lesions	20841	3604	4120	NA	2687	3734	NA	3779	NA
LAD treated (%)	8666/20841 (41.6)	2001/3604 (55.5)	1946/4120 (47.2)	689/1495 (46.1)	1429/2687 (53.2)	1853/3734 (49.6)	1682/3009 (55.9)	1821/3779 (48.2)	4003/7119 (56.2)
Stent/lesion	1.2	1.3‖	1.2	NA	NA	NA	1.3	1.1	NA
Stent length/lesion (mm)	24.8	31‖	32.7‖	23.0#	22.8	37.9‖	30.4#	35‖	NA
P2Y$_{12}$ Inhibitor LD	Ticagrelor 180 mg or Clopidogrel 600 mg	NA	300 to 600 mg Clopidogrel	Ticagrelor 180 mg or Prasugrel 60 mg or Clopidogrel at least 300 mg.**	300 mg Clopidogrel	300- or 600 mg Clopidogrel (In ACS patients 60 mg prasugrel or 180 mg ticagrelor)	NA	180 mg Ticagrelor	NA
Aspirin LD	325 mg	NA	300 to 500 mg	At least 300 mg	At least 75 mg	300 mg	As in clinical practice	300 mg	NA
Glycoprotein IIb/IIIa inhibitors use n. (%)	NA	NA	NA	NA	NA	NA	NA	197/3056 (6.4)	NA
Type of DES used	Biolimus A9-eluting stent	BioFreedom (experimental arm) Biomatrix or Ultimaster (control arm)	Endeavor zotarolimus-eluting stent	Combo	Endeavor zotarolimus (experimental arm) Cypher, Xience, Resolute (control arm)	Cobalt chromium everolimus-eluting stent (Xience); platinum-chromium everolimus-eluting stent (Promus, Synergy); sirolimus-eluting stent (Orsiro, Biotronik)	Cobalt-chromium everolimus eluting stent (Xience, Abbott vascular)	Bioresorbable polymer sirolimus-eluting stent (Orsiro, Biotronik AG)	Second generation DES

BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; DES, drug-eluting stent; LAD, left anterior descending; LD, loading dose; PCI, percutaneous coronary intervention; NA, not available
*Including ≥ 2-vessel disease †Multivessel PCI ‡Lesion type C §Only 638 lesions analyzed ‖Indicates stent per patient, not per lesion
#Total stent length **Ticagrelor and Prasugrel were preferred over Clopidogrel.

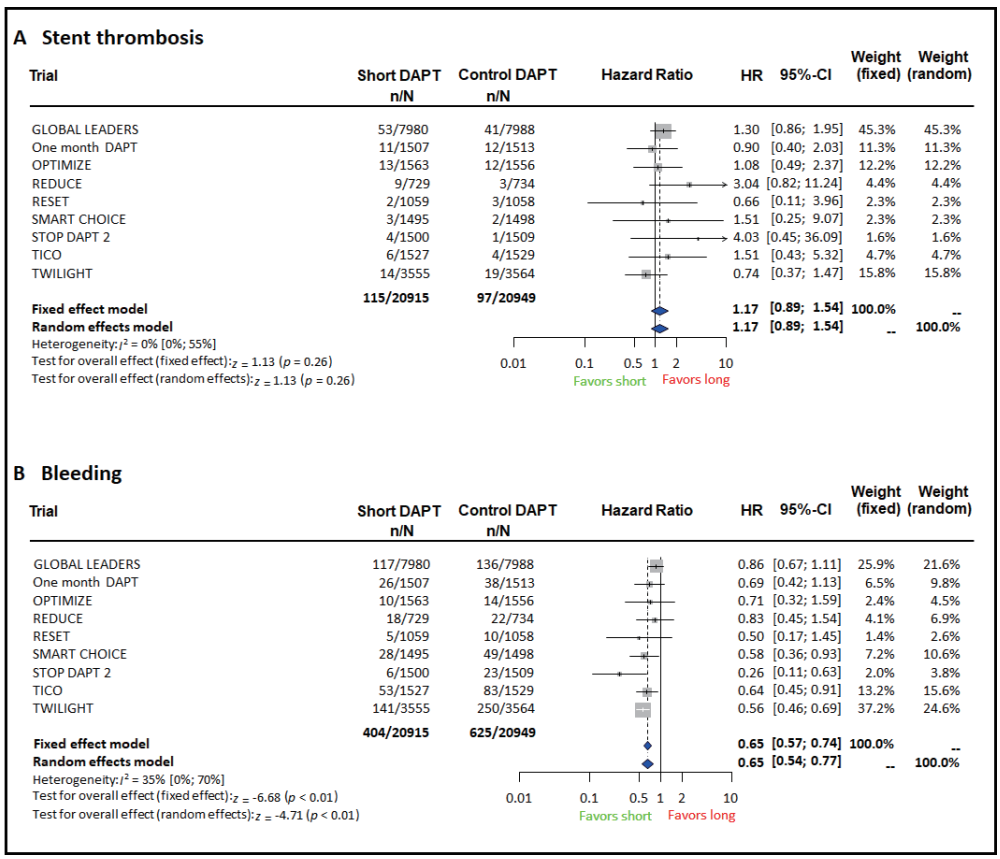

Fig. 1. Forest plot of the primary endpoints, (A) definite or probable stent thrombosis and (B) bleeding in short DAPT vs. control DAPT arm

The squares indicate the point estimate [hazard ratio (HR)] and the lines represent the 95% confidence intervals (CI). The size of each square is proportional to the statistical weight of a trial in the meta-analysis; diamond indicates the effect estimate derived from meta-analysis. The arrow indicates a CI value beyond the shown axis limit. DAPT, dual antiplatelet therapy.

short vs. control DAPT duration (0.5 vs. 0.5%; hazard ratio (HR) 1.17 [95% confidence interval (CI) 0.89- 1.54]; p=0.26, **Fig. 1A**).

The co-primary endpoint of bleeding occurred in 1029 patients (2.5%). Bleeding was significantly reduced with short vs. control DAPT duration (1.9 vs. 3.0%; HR [95% CI] 0.65 [0.54- 0.77]; p<0.0001, **Fig. 1B**).

The secondary endpoint of all-cause death occurred in 589 patients (1.4%). The risk for all-cause death was similar between short and control DAPT durations (1.3 vs. 1.5%; HR [95% CI] 0.88 [0.74-1.04]; p=0.13, **Fig. 2**). Cardiac death occurred in 220 patients (0.5%). The risk for cardiac death was similar between short and control DAPT durations (0.5 vs. 0.6%; HR [95% CI] 0.80 [0.61-1.04]; p=0.10, **Supplemental Fig. 2**). Myocardial infarction occurred in 763 patients (1.8%). The risk of MI was similar between short and control DAPT durations (1.9 vs. 1.8%; HR [95% CI] 1.05 [0.91-1.21]; p=0.53, **Supplemental Fig. 2**). Stroke occurred in 240 patients (0.6%). The risk of stroke was similar between short and control DAPT durations (0.6 vs. 0.6%; HR [95% CI] 1.01 [0.77-1.33]; p=0.94, **Supplemental Fig. 2**).

Aspirin Monotherapy vs. P2Y12 Monotherapy after Initial DAPT

We also analyzed the primary and secondary endpoints separately in the 4 studies which continued with aspirin and in the 5 studies which continued with P2Y12 monotherapy after short DAPT duration.

The aspirin monotherapy studies included 9,719 patients with a DAPT duration of 1.8 vs. 10.9 months for the short vs. control group, respectively. The P2Y12 monotherapy studies included 32,145 patients with a DAPT duration of 1.4 vs 12.6 months for the short vs. control group, respectively. ST was not significantly different between short and control DAPT durations in both the aspirin (0.7% vs 0.6%; HR 1.13 [0.69-1.86]; p=0.63) and P2Y12 groups (0.5% vs. 0.4%; HR 1.19 [0.86-1.65]; p=0.30, **Fig. 3**). No heterogeneity between aspirin and P2Y12 groups was detected

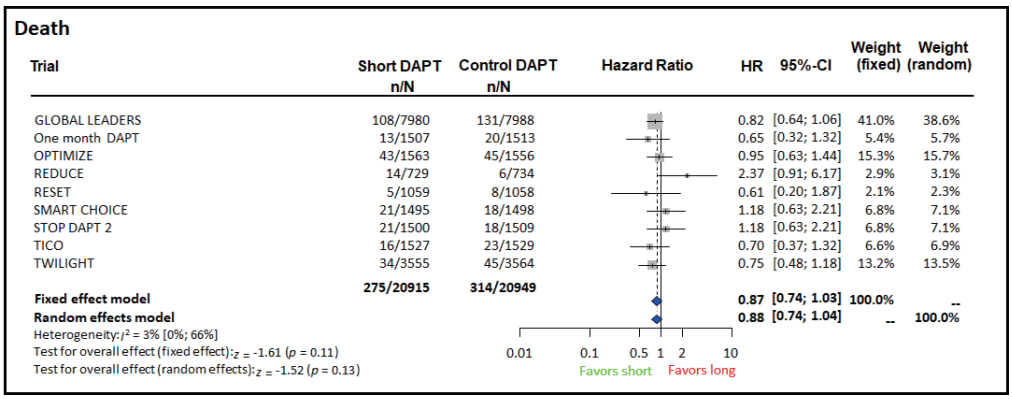

Fig. 2. All-cause mortality in patients with short vs. control DAPT after percutaneous coronary intervention

The squares indicate the point estimate [hazard ratio (HR)] and the lines represent the 95% confidence intervals(CI). The size of each square is proportional to the statistical weight of a trial in the meta-analysis; diamond indicates the effect estimate derived from meta-analysis. DAPT, dual antiplatelet therapy.

(p=0.861).

Bleeding was significantly reduced with short vs. control DAPT duration in the aspirin monotherapy studies (1.2 vs. 1.7%; HR [95% CI] 0.71 [0.51-0.99]; p=0.04) as well as in the P2Y$_{12}$ monotherapy studies (2.1 vs. 3.4%; HR [95% CI] 0.62 [0.47-0.80]; p=0.0003, **Fig. 3**). No heterogeneity between aspirin and P2Y$_{12}$ groups was detected (p=0.515). Neither all-cause mortality nor the ischemic endpoints such as cardiac death, MI or stroke were significantly different in these separate analyses **(Table 2)**. No heterogeneity between the aspirin and P2Y$_{12}$ groups was detected across endpoints.

Discussion

We performed a meta-analysis of 9 trials which included 41,864 patients who underwent DES implantation and received a short DAPT duration of median 1.5 months vs. longer DAPT of median 12.1 months. The main findings are that I) short DAPT does not increase the rates of ST, all-cause death, cardiac death, MI and stroke; II) bleeding rates are higher with longer DAPT durations; III) short DAPT reduces bleeding rates in patients receiving aspirin as well as P2Y$_{12}$ monotherapy after initial DAPT.

The optimal duration of DAPT is of great importance and an early meta-analysis comparing 6 months vs. 1 year vs. longer than 1 year DAPT durations has found the following: DAPT duration beyond 1 year reduced MI and ST but was associated with an increased mortality, while 6 months DAPT vs. 12 months DAPT had similar rates of ischemic events including mortality, MI and ST but was associated with lower rates of major bleeding[21].

Several trials have therefore evaluated an even shorter DAPT duration of ≤ 3 months compared with ≥ 6 months of DAPT which are included in the present study. None of these nine trials showed an increase in ischemic events with the shorter DAPT duration; however, these trials were not adequately powered to assess rare events such as ST properly. In our meta-analysis we could show that ST and ischemic events such as cardiac death, MI or stroke are not increased with a DAPT duration of ≤ 3 months. Moreover, this result was consistent in patients who continued with aspirin monotherapy[9, 15, 16, 20] as well as in those who continued with P2Y$_{12}$ inhibitor monotherapy[10, 12, 17-19].

Our analysis confirms and extends the findings of previous meta-analyses which have also assessed short DAPT with subsequent SAPT with either aspirin or a P2Y$_{12}$ inhibitor[22, 23]. These analyses have also found that ischemic events were not increased with short DAPT. While their analyses mainly found a bleeding reduction with short DAPT and subsequent P2Y12 inhibitor therapy, our analysis did also show that patients who continued with aspirin were also at significantly lower risk for bleeding. This may be attributed to the fact that they had different inclusion criteria[23], that the "One-Month DAPT study" was not included[22, 23] and that different bleeding definitions were applied.

It is of interest that bleeding rates were numerically higher in the P2Y$_{12}$ monotherapy trials as compared to the aspirin monotherapy trials. However, it is difficult to compare these numbers because patient populations, the used P2Y$_{12}$ inhibitor and bleeding definitions differed. The results of our meta-analysis neither favor aspirin nor P2Y$_{12}$ monotherapy because both strategies reduce bleeding events without an increase in ischemic events. Ticagrelor

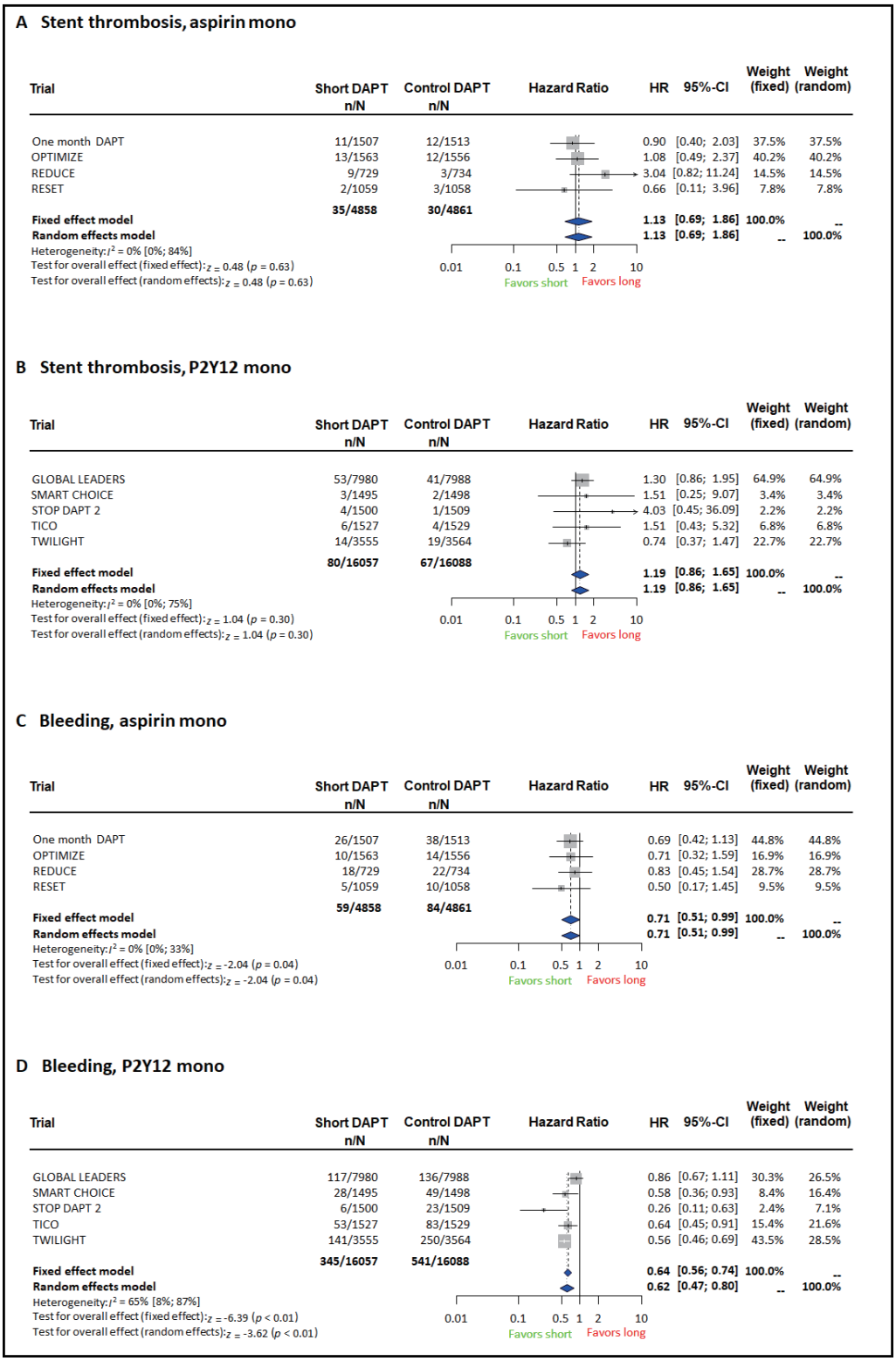

Fig. 3. Outcomes of patients with short vs. control DAPT after percutaneous coronary interventions

A) Stent thrombosis in trials with aspirin monotherapy after DAPT; B) Stent thrombosis in trials with P2Y$_{12}$ monotherapy after DAPT; C) Bleeding in trials with aspirin monotherapy after DAPT; D) Bleeding in trials with P2Y$_{12}$ monotherapy after DAPT. The squares indicate the point estimate [hazard ratio (HR)] and the lines represent the 95% confidence intervals(CI). The size of each square is proportional to the statistical weight of a trial in the meta-analysis; diamond indicates the effect estimate derived from meta-analysis. The arrow indicates a CI value beyond the shown axis limit. DAPT, dual antiplatelet therapy; mono, monotherapy.

Table 2. Clinical endpoints according to aspirin and P2Y12 groups

Endpoints	Aspirin mono* HR [95% CI]	P2Y12 mono HR [95% CI]	*p* for heterogeneity
Stent thrombosis	1.13 [0.69-1.86]	1.19 [0.86-1.65]	0.861
Bleeding	0.71 [0.51-0.99]	0.62 [0.47-0.80]	0.515
Death	0.95 [0.59-1.54]	0.85 [0.71-1.03]	0.681
Cardiac death	0.91 [0.53-1.54]	0.72 [0.51-1.04]	0.496
Myocardial infarction	1.04 [0.77-1.42]	1.05 [0.89-1.23]	0.988
Stroke	0.86 [0.51-1.46]	1.08 [0.67-1.74]	0.528

*Mono, monotherapy; CI, confidence interval; HR, hazard ratio

monotherapy was compared with aspirin monotherapy in the SOCRATES trial in patients with ischemic stroke and found no difference regarding bleeding[24] or ischemic events[25]. The multicenter HOST-EXAM trial found that clopidogrel monotherapy, compared with aspirin monotherapy during the chronic maintenance period after PCI with DES, significantly reduced the risk of ischemic as well as bleeding events[26]. This is of great interest and may lead to a paradigm change, if this result is confirmed in further trials. The role of aspirin is further challenged in the ongoing STOPDAPT-3 trial (NCT04609111) that evaluates an aspirin-free regimen with prasugrel after PCI in high risk patients.

It is speculated that patients with ACS may benefit from longer DAPT duration because of systemic antithrombotic properties which are effective beyond the implanted stent. In the present study we did not specifically analyze ACS patients, but in the two included trials who studied only ACS patients[12, 16], 3 months DAPT was not associated with an increase in ischemic events. One explanation may come from the ADAPT-DES registry, which has observed, that ST risk in patients with MI was greatest in the first 30 days post-PCI and was observed predominantly among those with increased high platelet reactivity on clopidogrel[27]. The other seven trials from our meta-analysis reported subgroup analyses on ACS patients regarding the primary combined endpoint. However, the primary combined endpoint varied among those trials and a meaningful comparison was therefore not feasible.

Several meta-analyses have found that longer than 12 months DAPT duration leads to a reduction in ischemic events such as MI and ST[23, 28]. This effect is, however, offset by higher bleeding rates and some analyses have even found higher rates of non-cardiac death[28] with this very long therapy. We, therefore, believe that DAPT durations beyond 12 months should be reserved to patients with a high ischemic risk, such as those with recurrent ischemic events who tolerate DAPT well.

Limitations

There are some limitations of this study. Our meta-analysis generated evidence from study level data. As outlined above, the main bleeding definitions across trials differed substantially and not every trial reported comparable bleeding definitions. It is known that not only major but also clinically relevant non major bleeding is associated with adverse clinical outcomes[2, 29]. We, therefore, used the main bleeding outcome of the corresponding trial for this analysis and also included broader bleeding definitions in order to increase sample size. Most of the trials randomized patients during the initial hospital stay, while two trials randomized patients up to three months after PCI. Some higher risk patients who have experienced events during this time frame have therefore been excluded and as a consequence the results of this analysis may not be generalizable to these higher risk patients. Patients were treated with a number of different DES types and the majority received newer generation DES. Although this reflects real world practice, it remains possible that efficacy and safety of the analyzed DAPT duration varies for the individual DES type. There was heterogeneity of different P2Y12 inhibitors during and after DAPT. We cannot rule out that clinical outcomes in the DAPT groups may differ with newer P2Y12 inhibitors as compared to clopidogrel and this needs to be evaluated in further trials.

Conclusion

Our meta-analysis shows that short DAPT ≤ 3 months followed by SAPT reduces bleeding and is not associated with an increased risk for ST, mortality or other ischemic events. The results were consistent within the aspirin and P2Y12 inhibitor monotherapy groups. To further assess the optimal antiplatelet therapy during and after DAPT, specifically designed randomized trials are needed.

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This was an investigator-initiated analysis and the analysis was not funded externally.

Conflicts of Interest

Stefanie Schüpke: Lecture fees from Daichii Sankyo and Biopas Laboratoires, Else Kröner-Memorial grant from the Else Kröner-Fresenius-Stiftung, Consulting Fees from Bayer Vital GmbH. (all modest)

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The other authors report no conflicts of interest.

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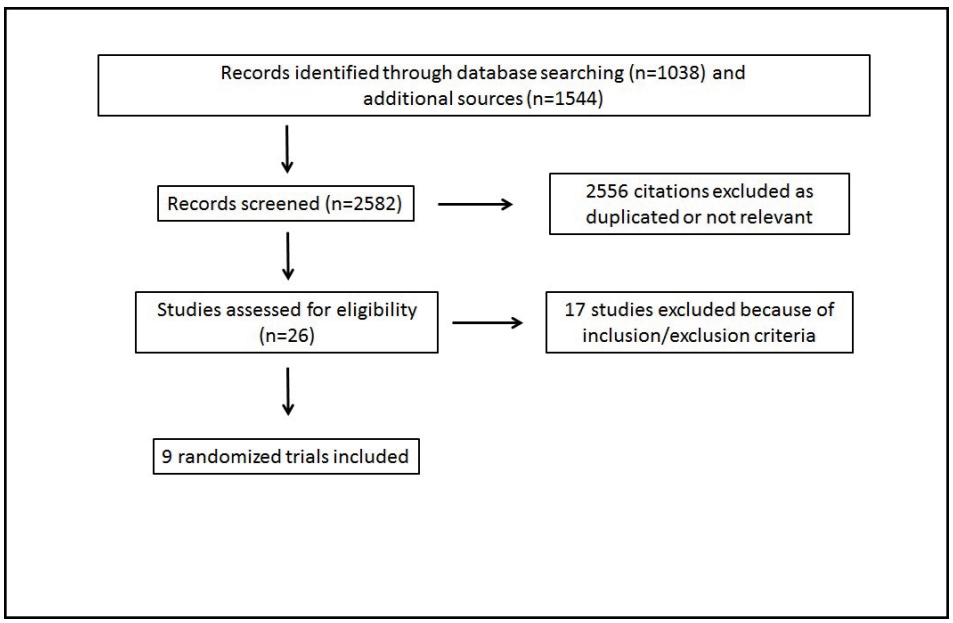


Supplemental Fig. 1. PRISMA flow diagram of the study selection process

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Supplemental Table 1. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1, 2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	Table S4, page 2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	2, 3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis	2, 3
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Table S4, page 2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	2, 3
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure S1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	Page 3, table 1, S2, S3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table S4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 1, 2, S2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Figure 1, 2, S2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table S4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 2, figure 3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	page 6
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	page 8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	page 8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	page 9

Supplemental Table 2. Main characteristics of the trials included in the study

Trial	Study design	Time to randomization	Stratification	Assigned therapies	Key inclusion criteria	Key exclusion criteria	Primary endpoints	Secondary endpoints
GLOBAL LEADERS	Randomized, open-label, multicenter trial	After coronary angiography but before PCI	By center and clinical presentation (stable CAD vs. ACS)	75-100 mg/d ASA+ 90 mg Ticagrelor twice daily for 1 month, followed by 23 months of ticagrelor monotherapy vs. standard DAPT with 75-100 mg ASA + either 75 mg/d clopidogrel or 2x 90 mg ticagrelor for 12 months, followed by aspirin monotherapy for 12 months	- Age ≥ 18; - any clinical indication for PCI (stable CAD or ACS)	- Intolerance to aspirin, P2Y12 inhibitors, bivalirudin, stainless steel or biolimus; - intake of a strong CYP3A4 inhibitor; - need for oral anticoagulation therapy; - overt major bleeding	Composite of all-cause death or non-fatal new Q-wave myocardial infarction at 24 months	- BARC type 3 to 5 bleeding - other secondary endpoint included the individual components of the primary endpoint; a composite endpoint of all-cause death, new Q-wave MI, or stroke; MI; stroke; any revascularization; and definite stent thrombosis.
One-month DAPT	Randomized, open-label, noninferiority multicenter trial	At PCI		1-month DAPT followed by aspirin monotherapy vs. 6-12 months DAPT followed by aspirin monotherapy	- Patients undergoing PCI for stable or unstable ischemic heart disease - ≥ 19 years of age - significant de novo coronary lesion	- acute MI - complex lesion - cardiogenic shock or previous cardiopulmonary resuscitation	Composite of cardiac death, nonfatal MI, target-vessel revascularization, stroke, or major bleeding	- all-cause death - cardiac death - nonfatal MI - TVR - stent thrombosis - stroke - major bleeding
Optimize	Multicenter, open-label, active-controlled, randomized clinical trial	At PCI	By the presence of diabetes mellitus	Aspirin 100-200 mg daily + clopidogrel 75 mg daily for 3 months, followed by therapy with aspirin alone vs. aspirin 100-200 mg daily + clopidogrel 75 mg daily for 12 months.	- > 18 years of age - clinical indication for PCI - lesion located in a native major epicardial vessel or a major side branch ≥ 2.50 mm (by visual estimation) or arterial conduit. - at least one stenosis ≥ 50% (by visual estimation)	- ST-segment elevation MI presenting for primary or rescue PCI - PCI with bare-metal stents in nontarget lesions < 6 months prior to the index procedure - previous treatment with any DES - scheduled elective surgery within 12 months after the index procedure - known hypersensitivity to aspirin, clopidogrel or both - lesion located in a saphenous vein graft - in-stent restenosis of a DES.	A composite of all-cause death, MI, stroke, or major bleeding	- stent thrombosis, - target lesion and target vessel revascularization, - MACE (including death from any cause, MI, emergent CABG or TLR) - any bleeding
Reduce	Prospective, open-label, multicenter, randomized, investigator-initiated study	At index PCI (before discharge)	By site	3-month DAPT with ASA 75 mg + either ticagrelor 90 mg twice daily or prasugrel 10 mg daily* or clopidogrel 75 mg daily vs. 12-month DAPT (ASA 75 mg + either ticagrelor 90 mg twice daily or prasugrel 10 mg daily or clopidogrel 75 mg daily).	- patients older than 18 years - patients diagnosed with ACS - successful COMBO stent implantation	- patients presenting with cardiogenic shock - major bleeding complications or contraindication to DAPT - patients who have been treated with another DES	- composite of all-cause death, myocardial infarction, stent thrombosis, stroke, target vessel revascularization or bleeding (BARC 2, 3, 5) at 12 months.	- bleeding (BARC 2,3,5) at 12 months - all-cause mortality, MI, ST, stroke, TVR, bleeding at 24 months - mortality at 12 months and 24 months - any MI at 12 and 24 months etc.

(Cont. Supplemental Table 2)

Trial	Study design	Time to randomization	Stratification	Assigned therapies	Key inclusion criteria	Key exclusion criteria	Primary endpoints	Secondary endpoints
Reset	Prospective, open-label, randomized trial	At PCI	By participating center and 4 clinical or lesion characteristics: diabetes mellitus; acute coronary syndrome; treatment of a short lesion (stent length ≤ 24mm); and treatment of a long lesion (≥ 28 mm)	E-ZES with 3-month DAPT (ASA 100 mg daily + 75 mg Clopidogrel) vs. other DES with 12-month DAPT (ASA 100 mg daily + 75 mg Clopidogrel)	- coronary artery disease including stable angina, unstable angina and acute myocardial infarction - age 20 years or older - significant coronary artery stenosis (>50% by visual estimation)	- Contraindication to antiplatelet agents & bleeding history within prior 3 months - prior history of cerebral vascular accidents, peripheral artery occlusive disease, thrombo-embolic disease, stent thrombosis - LVEF <40% - cardiogenic shock - severe renal or hepatic dysfunction	- composite of death from cardiovascular causes, myocardial infarction, stent thrombosis, ischemia-driven target-vessel revascularization, or bleeding at 1-year post-procedure.	- Individual components of the primary endpoint - the composite of all-cause death, myocardial infarction or stent thrombosis.
SMART-CHOICE	Investigator-initiated, multicenter, open-label, noninferiority, randomized study.	At index procedure or at a follow-up visit within 3 months after the index procedure.	- By clinical presentation (stable ischemic heart disease or acute coronary syndrome), -enrolling center, - type of P2Y12 inhibitor used (clopidogrel, prasugrel, or ticagrelor) and -type of stent used	Aspirin 100 mg daily + either clopidogrel 75 mg daily, or prasugrel 10 mg daily, or ticagrelor 90 mg twice daily for 3 months, followed by the respective P2Y12 inhibitor monotherapy for 6 or 12 months vs. aspirin 100 mg daily + 1 P2Y12 inhibitor (either clopidogrel, prasugrel, or ticagrelor) for 12 months.	- age at least 20 - written informed consent - successful percutaneous coronary intervention with DES for stable ischemic heart disease or acute coronary syndrome - one or more coronary stenosis of 50% or more in a native coronary artery.	- hypersensitivity or contraindication to any of the following:Aspirin, Clopidogrel, Prasugrel, Ticagrelor, Everolimus, Sirolimus - hemodynamic instability or cardiogenic shock - active pathological bleeding including gastrointestinal or genitourinary bleeding - Drug-eluting stent implantation within 12 months before index procedure.	Composite of all-cause death, myocardial infarction, or stroke at 12 months after the index procedure.	- individual components of the primary end point at 12-months - cardiac death at 12-month, - target lesion revascularization, - any revascularization at 12 months, - stent thrombosis at 12 months, - BARC bleeding type 2 to 5, - each component of primary and secondary end points at 2 and 3 years.
Stop DAPT- 2	Multicenter, open-label, randomized trial	Before hospital discharge, after index PCI	By participating center.	- either aspirin 81-200 mg/d and clopidogrel 75 mg/d (in 62% of patients) or aspirin 81-200 mg/d and prasugrel 3,75 mg/d (in 38% of patients) for 1 month, followed by monotherapy with the respective P2Y12 inhibitor alone for 5 years vs. aspirin + clopidogrel for 12 months.	- PCI with a cobalt chromium everolimus-eluting stent - no plan for staged PCI	- need for oral anticoagulation or antiplatelet therapy other than aspirin and P2Y12 receptor blockers, - history of intracranial bleeding, and - known intolerance to clopidogrel	- composite of cardiovascular death, myocardial infarction, ischemic or hemorrhagic stroke, definite stent thrombosis, and TIMI major or minor bleeding at 12 months.	- composite of cardiovascular death, myocardial infarction, ischemic or hemorrhagic stroke, or definite stent thrombosis - TIMI major or minor bleeding
TICO	Randomized, investigator-initiated, multicenter, unblinded trial	After PCI	According to the presence of diabetes and ST-elevation myocardial infarction	Aspirin 100 mg/d + 90 mg ticagrelor twice daily for 3 months, followed by ticagrelor monotherapy vs. aspirin 100 mg daily + ticagrelor 90 mg twice daily for 12 months.	- Age ≥ 19 - Patients who received bioresorbable polymer sirolimus-eluting stent - Provision of informed consent	- age >80 years - increased risk of bleeding - need for oral anticoagulation therapy - life expectancy < 1 year	Composite of major bleeding and major adverse cardiac and cerebrovascular events (death, myocardial infarction, stent thrombosis, stroke, or target-vessel revascularization)	- Each component of the primary outcome - cardiac or non-cardiac death - stent thrombosis - any bleeding (TIMI minor or major)

(Cont. Supplemental Table 2)

Trial	Study design	Time to randomization	Stratification	Assigned therapies	Key inclusion criteria	Key exclusion criteria	Primary endpoints	Secondary endpoints
TWILIGHT	Randomized, double-blind placebo-controlled, multicenter trial	After 3 months	According to site	90 mg ticagrelor twice daily + aspirin 81-100 mg daily for 3 months, followed by ticagrelor + placebo for 12 months vs. 90 mg ticagrelor twice daily + aspirin 81-100 mg daily for 3+12 months.	- High risk patients who have undergone successful elective or urgent PCI with at least one locally approved drug eluting stent discharged on DAPT with aspirin and ticagrelor of at least 3 months intended duration	- <18 years of age - contraindication to aspirin - contraindication to ticagrelor - planned surgery within 90 days - planned coronary revascularization within 90 days - need for chronic oral anticoagulation - prior stroke - life expectancy <1 year - unable or unwilling to provide informed consent -women of child bearing potential	BARC type 2, 3, or 5 bleeding	- First occurrence of death from any cause, nonfatal MI, or nonfatal stroke. - Secondary bleeding end points included BARC type 3 or 5 bleeding; TIMI major or minor bleeding; GUSTO moderate, severe, or life-threatening bleeding; or major bleeding as defined by ISTH

ACS, acute coronary syndrome; ARC, Academic Research Consortium; BARC, Bleeding Academic Research Consortium; CAD, coronary artery disease, CYP3A4, cytochrome P450 3A4; DAPT, dual antiplatelet therapy; DES, drug-eluting stent, E-ZES, endeavor zotarolimus-eluting stent; GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; ISTH, International Society on Thrombosis and Haemostasis; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; MI, myocardial infarction, PCI; percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

*(5 mg if >75 years, or <60 kg)

Official titles and acronyms: GLOBAL LEADERS: Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs.aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent; One -month DAPT: One-month dual antiplatelet therapy followed by aspirin monotherapy vs. 6-12 months DAPT followed by aspirin monotherapy after drug-eluting stent implantation; OPTIMIZE: Three vs. Twelve Months of Dual Antiplatelet Therapy After Zotarolimus-Eluting Stents; REDUCE: The Randomised Evaluation of short-term DUal antiplatelet therapy in patients with acute coronary syndrome treated with the COMBO dual-therapy stEnt; RESET: REal Safety and Efficacy of 3- month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation; SMART-CHOICE: Effect of P2Y12 Inhibitor Monotherapy vs. Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention; STOPDAPT-2: Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel vs. 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI; TICO: Effect of Ticagrelor Monotherapy vs. Ticagrelor With Aspirin on Major Bleeding and Cardiovascular Events in Patients With Acute Coronary Syndrome; TWILIGHT: Ticagrelor with or without Aspirin in High-Risk Patients after PCI.

Supplemental Table 3. Definitions of clinical outcomes according to protocols of trials included in the study

Trial	Cardiovascular death	Myocardial Infarction	Stent thrombosis	Stroke	Bleeding
GLOBAL LEADERS	Cardiovascular mortality includes unclear causes of death	According to the Joint ESC/ACCF/AHA/ WHF Task Force universal definition of MI	NA	Any ischemic and hemorrhagic stroke	According to BARC definition (BARC 3 or 5)
One-month DAPT	NA	NA	NA	NA	According to STEEPLE criteria
Optimize	Any unknown cause of death or death that cannot be clearly attributed to a non-cardiac cause will be considered cardiac.	According to WHO definition	According to ARC criteria	Classified as hemorrhagic or ischemic. Defined as acute neurological event with duration ≥ 24 hours with confirmation by CT or MRI or pathological confirmation.	Modified REPLACE-2 and GUSTO criteria
Reduce	NA	According to the Joint ESC/ACCF/AHA/ WHF Task Force universal definition of MI	According to ARC criteria	NA	According to BARC criteria (BARC 2,3,5)
Reset	All deaths are considered cardiovascular deaths unless a definite non-cardiovascular cause can be established.	Defined as the presence of clinical symptoms, electrocardiographic change or abnormal imaging findings of myocardial infarction combined with an increase in creatine kinase myocardial band fraction to greater than three times the upper limit of the normal range or troponin-T/ troponin-I more than the 99th percentile of the upper normal limit, unrelated to an interventional procedure.	According to ARC criteria	NA	According to TIMI criteria (TIMI major or minor)
SMART-CHOICE	All deaths were considered cardiac unless a definite non-cardiac cause could be established	Defined as elevated cardiac enzyme levels (cardiac troponin or myocardial band fraction of creatine kinase)	Stent thrombosis was defined as definite or probable stent thrombosis according to the Academic Research Consortium (ARC) criteria	Stroke was defined as any nonconvulsive focal or global neurologic deficit of abrupt onset lasting for more than 24 hours or leading to death, which was caused by ischemia or hemorrhage within the brain.	According to BARC definition (BARC 2-5)

(Cont. Supplemental Table 3)

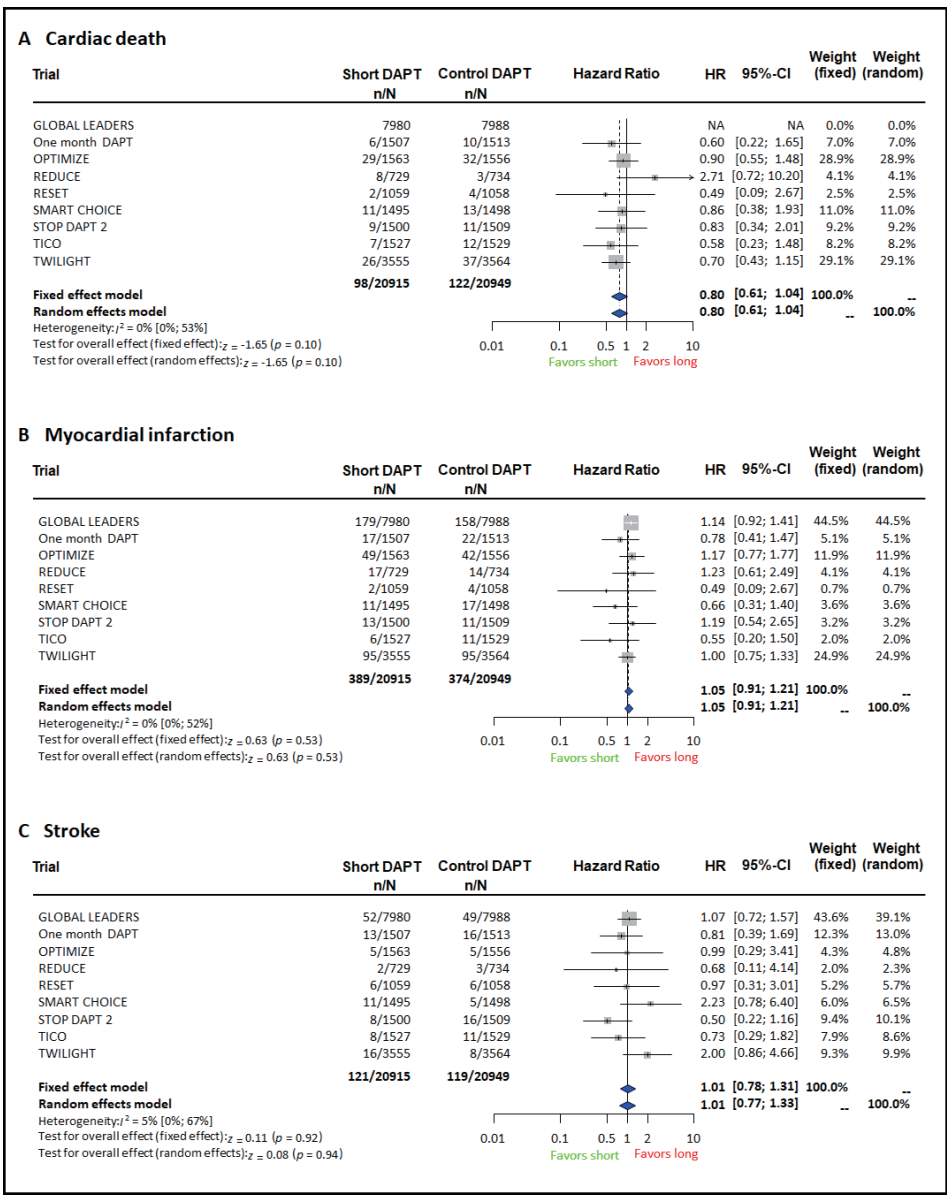
Trial	Cardiovascular death	Myocardial Infarction	Stent thrombosis	Stroke	Bleeding
Stop DAPT-2	(According to ARC classification) Any death due to proximate cardiac cause (e.g. myocardial infarction, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all procedure related deaths including those related to concomitant treatment. All deaths are considered cardiac unless a non-cardiac cause can be established.	According to ARC criteria	According to ARC criteria	Acute onset of a neurological deficit that persists for at least 24 hours and is the result of a disturbance of the cerebral circulation due to ischemia or hemorrhage.	According to TIMI criteria (TIMI major or minor)
TICO	Cardiac death was defined as death due to myocardial infarction, cardiac perforation or pericardial tamponade; arrhythmia or conduction abnormality; stroke within 30 days of the procedure or related to the procedure; death due to a procedural complication; or any cause of death in which a cardiac cause was not excluded.	According to the Joint ESC/ACCF/AHA/ WHF Task Force universal definition of MI Defined as symptoms, electrocardiographic changes, or abnormal imaging findings, combined with a creatinine kinase MB fraction above the upper normal limits of a troponin T or I level greater than the 99th percentile of the upper normal limit.	According to ARC criteria	Defined as an acute cerebrovascular event that caused death, a neurological deficit lasting more than 24 hours, or an acute infarction shown by imaging studies.	According to TIMI criteria (TIMI major or minor)
TWILIGHT	Cardiovascular death includes unwitnessed death and death of unknown cause.	According to the Joint ESC/ACCF/AHA/ WHF Task Force universal definition of MI	According to ARC criteria	Defined as an acute symptomatic episode of neurological dysfunction, more than 24 hours in duration in the absence of therapeutic intervention or death, due to cerebral, spinal or retinal tissue injury as evidenced by neuroimaging or lumbar puncture.	According to BARC definition (2,3 or 5)

ARC, Academic Research Consortium; BARC, Bleeding Academic Research Consortium; GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; TIMI, Thrombolysis in Myocardial Infarction:

Supplemental Table 4. Assessment of risk of bias

Trial	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Description of incomplete outcome data	Selective outcome reporting	Sample size calculation	Funding source
GLOBAL LEADERS	Yes (blocks, stratum)	Yes (IWRS)	No	No (only Q-wave MI was centrally adjudicated)	Yes (flow diagram)	No	Yes (superiority-design)	Yes (investigator-initiated, industry-funded)
One-month DAPT	NA	NA	No	NA	Yes (flow diagram)	No	Yes (noninferiority design)	NA
Optimize	Yes (blocks, stratum)	Yes	No	Yes (Independent CEC)	Yes (flow diagram)	No	Yes (noninferiority design)	Yes (investigator-initiated, cosponsored by an independent clinical research organization and industry)
Reduce	Yes (blocks, stratum)	Yes (computer-generated)	No	Yes (Independent CEC)	Yes (flow diagram)	No	Yes (noninferiority design)	Yes (investigator-initiated, industry-funded)
Reset	Yes (stratum)	Yes (IWRS)	No	Yes (Independent CEC)	Yes (flow diagram)	No	Yes (noninferiority design)	Yes (investigator-initiated, combined funding)
SMART -CHOICE	Yes (blocks, stratum)	Yes (web-based)	No	Yes (Independent CEC)	Yes (flow diagram)	No	Yes (noninferiority design)	Yes (investigator-initiated, combined funding)
Stop DAPT-2	Yes (stratum)	Yes (web-based)	No	Yes (Independent CEC)	Yes (flow diagram)	No	Yes (noninferiority design)	Yes (investigator-initiated, industry-funded)
TICO	Yes (blocks, stratum)	Yes (computer-generated)	No	Yes (Independent CEC)	Yes (flow diagram)	No	Yes (superiority-design)	Yes (investigator-initiated, industry-funded)
TWILIGHT	Yes (blocks, stratum)	Yes (computer-generated)	Yes	Yes (Independent CEC)	Yes (flow diagram)	No	Yes (superiority-design)	Yes (investigator-initiated, industry-funded)

IWRS: interactive web-based response system; CEC: Clinical event committee. Official titles and acronyms are reported in Supplemental Table 2.



Supplemental Fig. 2. Secondary outcomes of patients with short vs. control DAPT after percutaneous coronary interventions. A) Cardiac death B) Myocardial infarction C) Stroke

The squares indicate the point estimate [hazard ratio (HR)] and the lines represent the 95% confidence intervals. The size of each square is proportional to the statistical weight of a trial in the meta-analysis; diamond indicates the effect estimate derived from meta-analysis. The arrow indicates a CI value beyond the shown axis limit