JOURNAL OF COMMUNITY HOSPITAL INTERNAL MEDICINE PERSPECTIVES
2019, VOL. 9, NO. 1, 9–17
https://doi.org/10.1080/20009666.2018.1562853

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

OPEN ACCESS Check for updates

Best duration of dual antiplatelet therapy after drug-eluting stent implantation: an updated network meta-analysis of randomized controlled trials

Mahmoud Barbarawi[a], Babikir Kheiri[a], Yazan Zayed[a], Ahmed Aburahma[a], Mohammed Osman[a], Owais Barbarawi[b], Michael Hicks[a], Mustafa Hassan[c], Mohammad L. Alkotob[c] and Ghassan Bachuwa[a]

[a]Department of Internal Medicine, Hurley Medical Center/Michigan State University, Flint, MI, USA; [b]Department of Internal Medicine, Mutah University, Al-Karak, Jordan; [c]Department of Cardiology, Hurley Medical Center/Michigan State University, Flint, MI, USA

ABSTRACT

Background: Drug-eluting stent(DES) implantation is the main interventional treatment for coronary artery disease, and dual antiplatelet therapy(DAPT) remains the gold standard strategy to prevent ischemic events. However, the optimal duration of DAPT after DES implantation remains controversial. Therefore, we aimed to evaluate the best duration of DAPT following DES implantation.

Method: We searched PubMed, Embase, Cochrane Library, and clinicaltrials.gov for all randomized clinical trials(RCTs) that compared different durations of DAPT after DES implantation. Major adverse cardiac events(MACE) and major bleeding were the primary and secondary outcomes, respectively.

Results: We included 16 RCTs (n = 42,993). The mean age of included patients was 63.1 ± 10.1. The primary outcome was statistically significant for lower MACE in patients who received DAPT for 24–48 months (mo) following DES when compared with those who received 3–6 mo of DAPT (odds ratio [OR] 0.75; 95% credible interval [CI] 0.58–0.97). There was nonstatistically significant difference in MACE when comparing those who received 12 mo of DAPT to those taking either 3–6 mo of DAPT (OR 0.86; 95% CI 0.69–1.08) or 24–48 mo of DAPT (OR 0.87; 95% CI 0.72–1.05). In contrast, major bleeding was significantly lower in those who received 3–6 mo of DAPT (OR 0.32; 95% CI 0.17–0.54) and 12 mo of DAPT (OR 0.43; 95% CI 0.27–0.63) than in those who received 24–48 mo of DAPT.

Conclusion: In patients who undergo DES implantation, a longer duration of DAPT is associated with lower MACE, despite the increased risk of major bleeding events. Therefore, individualizing the duration of DAPT after DES according to the patient's risk of bleeding and recurrent ischemia is recommended.

ARTICLE HISTORY
Received 22 July 2018
Accepted 18 December 2018

KEYWORDS
Dual antiplatelet; drug eluting stent; aspirin; clopidogrel; antiplatelet duration; meta-analysis

1. Introduction

The efficacy of percutaneous coronary intervention (PCI) has improved significantly with the use of drug-eluting stents (DESs). However, the concern regarding their safety, specifically stent thrombosis, is rising. Although the rate of stent thrombosis is generally low, its occurrence is potentially fatal [1–3]. Current PCI guidelines recommend dual antiplatelet therapy (DAPT) with aspirin and thienopyridine as the cornerstone of treatment after DES implantation [4,5]. The first 6–12 months (mo) post–coronary stent implantation hold the highest risk of thrombotic complications [1,6,7]. Therefore, DAPT is recommended during this 'ischemic phase'. The use of DAPT during the 'maintenance phase', however, is associated with an increased bleeding risk [5]. Strategies to reduce bleeding risk, such as reducing the DAPT duration, have emerged, especially with the establishment of a new, safer generation of DESs [8,9]. In contrast, patients with a stenosed stent, diabetes, or low bleeding risk may experience the benefit of prolonged (more than a year) DAPT without a similar bleeding risk [8–11].

Multiple randomized clinical trials (RCTs) have evaluated the safety and efficacy of different DAPT durations with conflicting results [12–15]. Previous meta-analyses and systematic review have also shown mixed results [16–19]. Therefore, we conducted our network meta-analysis to evaluate the safety and efficacy of various DAPT durations in patients undergoing DES implantation.

2. Methodology

2.1. Literature search and data source

An electronic literature search was performed independently by two authors (A.A. and Y.Z.) according

CONTACT Mahmoud Barbarawi, Mahmoud.albarbarawi@gmail.com Department of Internal Medicine, Hurley Medical Center/Michigan state university, One Hurley Plaza, Flint, MI 48503, USA
Supplemental data for this article can be accessed here.

to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) Statement 2015. We comprehensively searched PubMed, Embase, Cochrane Library, and clinicaltrials.gov from inception to 8 March 2018. Any disagreement was resolved by a discussion between the two authors and in consultation with a third author (M.B.). Neither language nor demographic restrictions were applied. Furthermore, references of the relevant studies and meta-analyses were reviewed for possible eligibility. The search terms were: 'drug eluting stent*', 'DES', 'stent', 'dual antiplatelet', 'DAPT', 'aspirin', 'clopidogrel', 'Plavix', 'P2Y12', 'thienopyridines', 'ticagrelor', 'prasugrel.'

Studies were first screened by their titles and abstracts for eligibility. Then, full texts of the eligible studies were reviewed before exclusion. The search process is detailed in Figure 1. The electronic search was archived through Mendeley and is available on request. Our study was a systematic review and meta-analysis and thus did not require institutional review board (IRB) approval.

2.2. Study selection and data extraction

We included only RCTs that compared long-term versus short-term DAPT after PCI and their effect on various clinical outcomes. The duration of DAPT was classified into three categories: 3–6 mo, 12–24 mo, and 24–36 mo. Retrospective studies were excluded to reduce biases and eliminate confounding variables. The main outcome of each included RCT and the baseline patient characteristics are shown in Tables 1 and 2.

2.3. Quality assessment

We performed a quality assessment for the included RCTs. We assessed the included RCTs for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. We classified studies as low-risk for bias only if all the described items were adequately described as low-risk. Quality assessment results are attached in the online supplemental data.

2.4. Data extraction

Two authors (A.A., M.B.) independently and separately extracted the data from the included studies into a predesigned form. Any disagreement was resolved by a discussion between the two reviewers and a third investigator (Y.Z.).

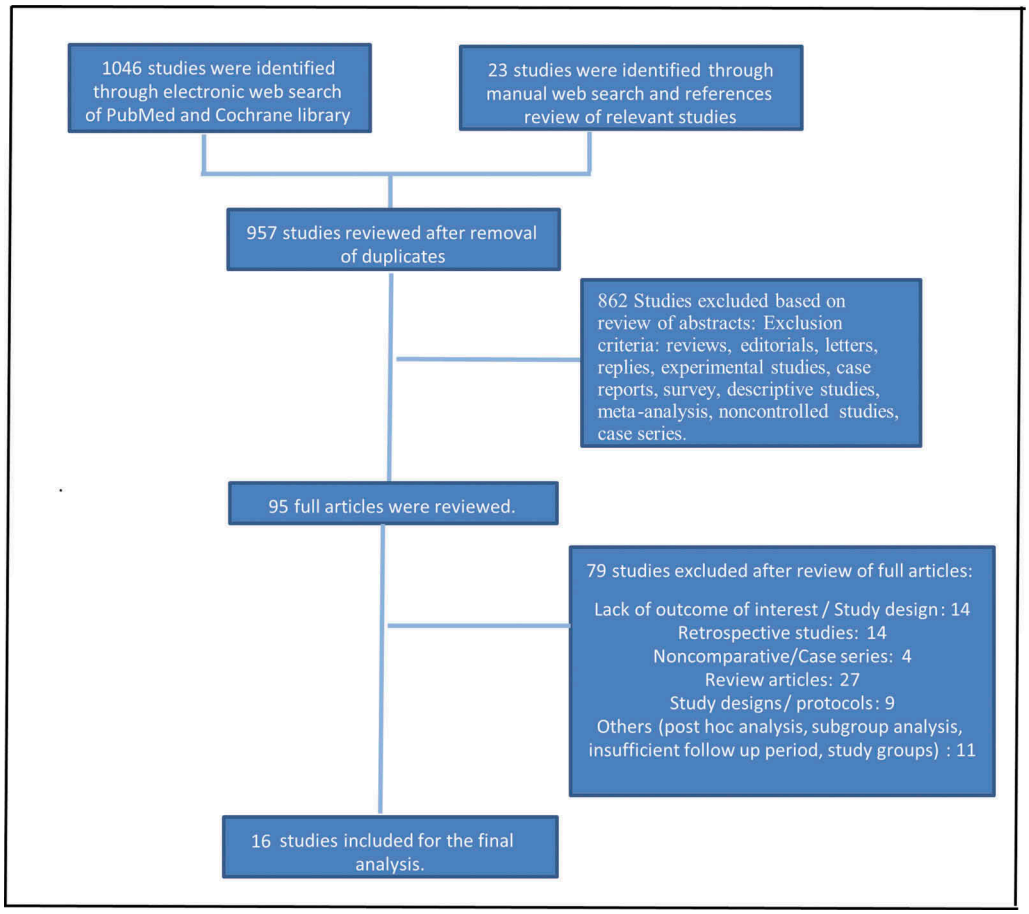

Figure 1. Preferred reporting items for systematic reviews and meta-analyses chart of the studies selection process.

Table 1. Details of the randomized clinical trials.

Name of study/Author	Number of patients	Follow up duration	Treatment duration	Study population	Study period	Primary Outcome
EXCELLENT/Gwon et al. 2012	1443	*12 months	6 months vs 12 months	Exclude recent MI (within 72 h)	2008–2009	Composite of cardiac death, myocardial infarction, or target vessel revascularization
PRODIGY/Valgimigli et al. 2012	1443	*24 months	6 months vs 24 months	Any PCI	2006–2008	Cumulative incidence of death of any cause, nonfatal myocardial infarction, or cerebrovascular accident
RESET/Kim et al. 2012	2117	*12 months	3 months vs 12 months	Any PCI	2009–2010	Composite of death from cardiovascular cause, myocardial infarction, stent thrombosis, ischemia-driven target-vessel revascularization, or bleeding
OPTIMIZE/Feres et al. 2013	3119	*12 months	3 months vs 12 months	STEMI excluded	2010–2012	Composite of death from any cause, MI, stroke, or major bleeding
SECURITY/Colombo et al. 2014	1399	*21.4 months	6 months vs 12 months	Exclude STEMI	2009–2014	Composite of cardiac death, MI, stroke, definite or probable stent thrombosis, or BARC criteria type 3 or 5 bleeding
ARCTIC-Interruption/Collet et al. 2014	1259	**17 months	12 months vs 30 months	Planned PCI, no STEMI	2011–2012	Composite of all-cause death, myocardial infarction, stroke or transient ischemic attack, urgent coronary revascularization, and stent thrombosis
DES LATE/Lee et al. 2014	5045	**4 months	12 months vs 36 months	Any PCI	2007–2011	Composite of death resulting from cardiac causes, myocardial infarction, or stroke
DAPT/Mauri et al. 2014	9961	*17 months	12 months vs 30 months	Any PCI	2009–2011	Cumulative incidence of definite or probable stent thrombosis and of major Adverse cardiovascular and cerebrovascular events (defined as the composite of death, myocardial infarction, or stroke)
OPTIDUAL/Helft et al. 2015	1385	**33.9 months	12 months vs 48 months	Any PCI	2009–2013	Net adverse clinical events defined as the composite of all-cause mortality, non-fatal myocardial infarction, stroke, or major bleeding
ISAR-SAFE/Schu¨pke. 2015	4000	**6.6 months	6 months vs 12 months	Any PCI	2008–2014	Composite of death, myocardial infarction, stent thrombosis (definite or probable), stroke, or TIMI major bleeding
ITALIC/Gilard et al. 2015	1822	*12 months	6 months vs 24 months	Any PCI	2012–2013	Composite of death, MI, repeat emergency TVR, stroke, or major TIMI bleeding
I LOVE IT-2/Han et al. 2016	1829	*18 months	6 months vs 12 months	Any PCI	n/a	Cardiac death, target vessel myocardial infarction, or clinically indicated target lesion revascularization
IVUS-XPL/Hong et al. 2016	1400	*12 months	6 months vs 12 months	Any PCI	2010–2014	Composite of cardiac death myocardial infarction, stroke, or TIMI major bleeding
NIPPON/Nakamura et al. 2017	3307	**14.5 months	6 months vs 18 months	Any PCI	2011–2015	Composite of all cause death, Q-wave or non–Q-wave MI, cerebrovascular events, and major bleeding events.
OPTIMA-C/Lee et al. 2017	1367	*12 months	6 months vs 12 months	STEMI excluded	2011–2014	Composite of cardiac death, Target vessel related MI, Ischemia-driven target lesion revascularization
SMART-DATE/Hahn et al. 2018	2712	*18 months	6 months vs 12 months	Acute ACS PCI	2012–2015	Composite of major adverse cardiac and cerebrovascular events, defined as a composite of all-cause mortality, myocardial infarction, or stroke

Abbreviation. ARCTIC; Double Randomization of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and Interruption Versus Continuation of Double Antiplatelet Therapy; BARC: Bleeding Academic Research Consortium; DAPT: Dual Antiplatelet Therapy; DES LATE: Duration of Clopidogrel Therapy After Drug-Eluting Stent; EXCELLENT: The Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; I LOVE IT: Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization; ISAR-SAFE: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; MI: myocardial infarction; ITALIC: Is There A LIfe for DES After Discontinuation of Clopidogrel; IVUS-XPL: Impact of Intravascular Ultrasound Guidance on Outcomes of XIENCE PRIME Stents in Long Lesions; NIPPON: Nobori Dual Antiplatelet Therapy as Appropriate Duration; OPTIDUAL: Optimal Duration of Dual Antiplatelet Therapy After Drug-eluting Stent Implantation; OPTIMA-C: Optimal Duration of Clopidogrel in Second-Generation Drug-Eluting Stents; OPTIMIZE: OPTIMIZE IDE for the Treatment of ACS; PCI: Percutaneous coronary intervention; PRODIGY: Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia; RESET: REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation; SECURITY; Second-Generation Drug-Eluting Stent Implantation Followed by 6- Versus 12-Month Dual Antiplatelet Therapy; SMART-DATE: Safety of 6-month Duration of Dual Antiplatelet Therapy After Acute Coronary Syndromes; STEMI: ST-elevation myocardial infarction; TIMI: Thrombolysis in Myocardial Infarction.

*mean

**median

Table 2. Demographic features.

	Duration	Age(year)	Male (n)	DM	HTN	Dyslipidemia	Current smoker	Previous MI	Previous PCI	Previous CABG	CVA	PVD	Stable angina	Unstable Angina/NSEMI	STEMI
EXCELLENT	Long 721	62.4 ± 10.4	461	278	532	550	186	27	62	7	48	-	346	349	26
	Short 722	63.0 ± 9.6	470	272	525	543	198	47	67	11	47	-	353	350	19
PRODIGY	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
RESET	Long 1058	62.4 ± 9.8	665	305	650	634	241	17	32	6	-	-	490	422	146
	Short 1059	62.4 ± 9.4	682	316	660	611	267	19	37	2	-	-	471	432	156
OPTIMIZE	Long 1556	61.9 ± 10.6	982	549	1371	952	269	542	279	128	38	46	143	84	-
	Short 1563	61.3 ± 10.4	992	554	1350	953	290	541	327	111	38	43	134	84	-
SECURITYL 717 S 682	Long 717	65.5 ± 10.1	551	223	510	436	172	144	116	39	-	-	368	229	-
	Short 682	64.9 ± 10.2	529	216	508	446	139	135	132	38	-	-	341	213	-
ARCTIC-Interruption	Long 635	64 ± 7	503	222	388	426	152	186	249	35	38	-	-	-	-
	Short 624	64 ± 8	504	198	376	428	147	197	273	47	28	-	-	-	-
DES LATE	Long 2531	62.5 ± 10.0	1749	709	1479		693	103	313	-	15	-	1011	930/268	314
	Short 2514	62.3 ± 10.1	1749	709	1423		722	92	276	-	89	-	956	971/266	314
DAPT trial	Long 5020	61.8 ± 10.2	3778	1556	3796	-	1222	1092	1518	568	155	284	1882	838/776	534
	Short 4961	61.6 ± 10.1	3657	1481	3649	-	1210	1026	1529	581	169	284	1870	825/767	511
OPTIDUAL trial	Long 695	64.1 ± 10.8	568	213	396	-	425	119	180	37	29	34	240	66/99	74
	Short 690	64.2 ± 11.5	547	222	417	-	399	122	186	35	25	45	207	63/117	82
ISAR-SAFE	Long 2003	67.2 ± 6.5	1612	484	1830	1748	306	491	-	149	-	-	956	438/203	166
	Short 1997	67.2 ± 7.9	1611	495	1797	1747	292	516	-	152	-	-	969	429/207	158
ITALIC	Long 910	61.5 ± 11.1	721	344	589	611	480	134	205	45	26	-	378	149/65	3
	Short 912	61.7 ± 10.9	737	331	595	612	464	142	220	61	25	-	375	143/67	1
I-LOVE-IT 2	Long 920	60.0 ± 10.0	632	203	596	215	352	145	60	4	87	10	139	520/98	126
	Short 909	60.4 ± 10.2	611	211	554	230	333	156	77	4	84	13	130	527/103	122
IVUS-XPL	Long 701	64 ± 9	494	257	455	456	165	29	73	14	-	-	358	231	112
	Short 699	63 ± 9	470	249	443	473	171	34	72	22	-	-	356	237	106
NIPPON	Long 1653	67.2 ± 9.9	1312	635	1209	1132	967	159	432	29	48	44	734	330/26	196
	Short 1654	67.4 ± 9.6	1304	619	1177	1130	990	201	413	22	41	62	805	296/33	198
OPTIMA-C	Long 684	64.4 ± 10.3	464	203	437	195	184	25	71	-	-	-	339	254/90	-
	Short 683	62.810.8	478	199	426	204	184	18	59	-	-	-	336	253/95	-
SMART-DATE	Long 1355	62.2 ± 11.9	1028	379	654	336	536	23	*52		58	-	-	416/425	514
	Short 1357	62.0 ± 11.5	1016	365	669	322	506	30	*65		52	-	-	420/428	509

Abbreviation. ARCTIC; Double Randomization of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and Interruption Versus Continuation of Double Antiplatelet Therapy; CAPG: coronary artery bypass graft; CVA: Cerebrovascular accident; DAPT: Dual Antiplatelet Therapy; DES LATE: Duration of Clopidogrel Therapy After Drug-Eluting Stent; DM: Diabetes Meletus; EXCELLENT: The Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; HTN: Hypertension; I LOVE IT: Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization; ISAR-SAFE: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; MI: myocardial infarction; ITALIC: Is There A LIfe for DES After Discontinuation of Clopidogrel; IVUS-XPL: Impact of Intravascular Ultrasound Guidance on Outcomes of XIENCE PRIME Stents in Long Lesions; Long: long duration of DAPT; MI: myocardial infarction; NIPPON: Nobori Dual Antiplatelet Therapy as Appropriate Duration; NSTEMI: Non-ST-elevation myocardial infarction; OPTIDUAL: Optimal Duration of Dual Antiplatelet Therapy After Drug-eluting Stent Implantation; OPTIMA-C: Optimal Duration of Clopidogrel in Second-Generation Drug-Eluting Stents; OPTIMIZE: OPTIMIZE IDE for the Treatment of ACS; PCI: Percutaneous coronary intervention; PRODIGY: Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia; PVD: Peripheral vascular disease; RESET: REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation; SECURITY; Second-Generation Drug-Eluting Stent Implantation Followed by 6- Versus 12-Month Dual Antiplatelet Therapy; Short: Shorter duration of DAPT; SMART-DATE: Safety of 6-month Duration of Dual Antiplatelet Therapy After Acute Coronary Syndromes; STEMI: ST-elevation myocardial infarction.

*number of both previous PCI and CABG.

2.5. Outcomes

The primary outcome was the incidence of major adverse cardiac events (MACE) and incidence of major bleeding between different durations of DAPT. The definitions of MACE and major bleeding events are shown in **supplementary material Tables S1**.

2.6. Data synthesis

We conducted our network meta-analysis using the Markov Chain Monte Carlo (MCMC) simulation with a little informative prior distributions and likelihood function to derive the posterior distribution of the parameter. We assessed convergence using the Brooks-Gelman-Rubin method as well as the Monte-Carlo error to check if the error was <5% of the standard deviation of the effect estimates and between-study variance. Random effects for the consistency model were reported as odds ratios (ORs) and Bayesian 95% credible intervals (CI). We converted the relative treatment effects to a probability of the best, second best, third best, and so on, as well as the ranking of each treatment. We combined both results to estimate the surface under the cumulative ranking curve (SUCRA). Inconsistency was assessed by comparing the deviance residuals and deviance information criteria (DIC) statistics in fitted consistency and inconsistency models to identify any loops in the treatment network where inconsistency was present. We analyzed our data using NetMetaXL v1.6.1 and WinBUGS software v1.4.3 (Imperial College and Medical Research Council).

3. Results

Sixteen RCTs were included in the analysis with a total of 42,993 patients; 30.1% were treated for 3–6 mo, 46.9% for 12 mo, and 23% for 24–48 mo. The baseline demographics are shown in Table 2. The mean age of patients included in the trials was 63.1 ± 10.1 years. Overall, 31.3% of patients had diabetes and 67.3% had hypertension. The procedural characteristics of each RCT are shown in **supplementary material Tables S2**. The most stented artery was the left anterior descending (LAD) artery. Both first- and second-generation stents were used, in various proportions, in these RCTs.

There was a significant improvement in MACE in patients treated with DAPT for 24–48 mo following DES when compared with those treated for 3–6 mo (OR 0.75; 95% CI [0.58–0.97]). In contrast, improvement in MACE was not significantly different when those treated with 24–48 mo of DAPT following DES were compared with those treated with 12 mo of DAPT (OR 0.86; 95% CI [0.69–1.08]). Also, there was no significant improvement in MACE in patients treated with 12 months of DAPT when compared with patients treated with DAPT for 3–6 months (OR 0.87, 95% CI [0.72–1.05]), as illustrated in Figure 2.

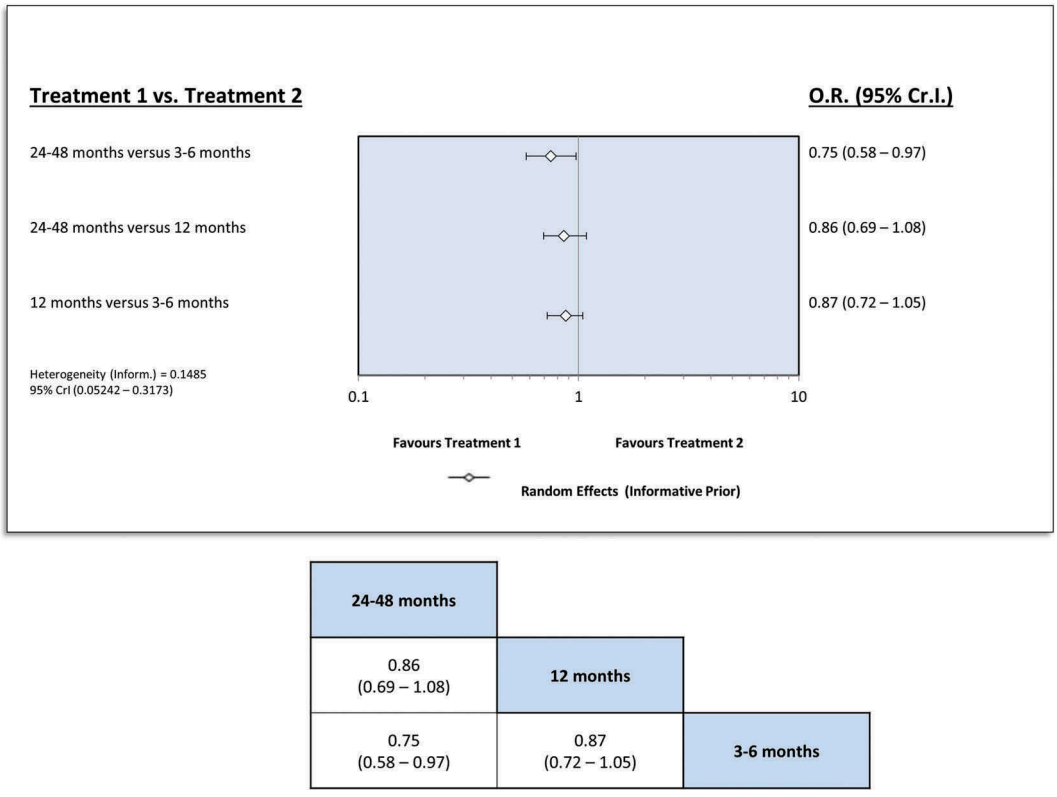

Figure 2. Forest plots summarizing the major adverse cardiac events between the competing treatments duration. Random effects model was used to report the odds ratios (ORs) with 95% credible intervals (CIs).

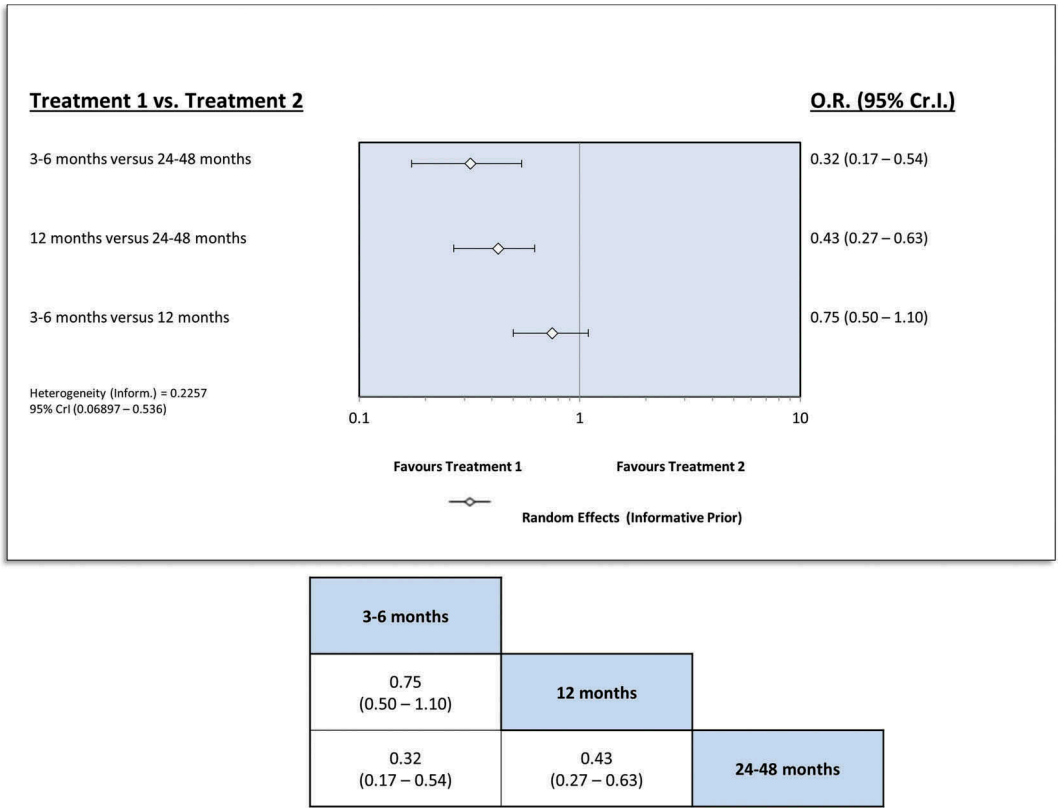

Figure 3. Forest plots summarizing the major bleeding events between the competing treatments duration. Random effects model was used to report the odds ratios (ORs) with 95% credible intervals (CIs).

The effect of duration of DAPT following DES on the bleeding risk was also studied. Compared with patients treated with 24–48 mo of DAPT following DES, those treated with either 3–6 mo (OR 0.32, 95% CI [0.17–0.54]) or 12 months of DAPT (OR 0.43, 95% CI [0.27–0.63]) experienced lower bleeding risk. On the other hand, there was no significant improvement in risk of major bleeding when 12 months of DAPT was compared with 3–6 months of DAPT (OR 0.75, 95% CI [0.50–1.10]), as illustrated in Figure 3.

4. Discussion

In the present network meta-analysis of 16 RCTs to evaluate the safety and efficacy of various DAPT durations in DES-treated PCI patients, we had several notable findings [12–15,20–31]. First, long-duration DAPT (≥24 mo) reduces the composite ischemic vascular events significantly when compared with short-duration DAPT (3–6 mo). Second, there is a trend of improved composite ischemic vascular events with longer DAPT as 12 mo was better than 3–6 mo and ≥24 mo was better than both 3–6 mo and 12 mo. Third, there is a higher bleeding risk when longer duration DAPT is used, as there was a significant increase in major bleeding with long-duration DAPT (≥24 mo) when compared with shorter duration DAPT (3–6 mo and 12 mo). Thus, our findings support the use of long-duration DAPT in patients with high risk of thrombotic events and short-duration DAPT in high bleeding-risk patients.

Despite the advances in the treatment of coronary artery disease, recurrent stent thromboses remain problematic [32,33]. The introduction of DAPT (aspirin and a P2Y12 receptor antagonist) has mitigated the risk of early and late thrombosis after coronary stent implantation, yet the duration of DAPT remains controversial [34]. Although most of the previously published meta-analyses have supported the use of short-duration DAPT because of the lower associated bleeding risk without an apparent increase in ischemic vascular events, some meta-analyses were consistent with our finding and supported the use of longer durations of DAPT after DES implantation to reduce ischemic vascular events [19,35]. The time-dependent nature of DAPT on risk of ischemic vascular events has also been demonstrated in a previous meta-analysis [36].

Six trials evaluated the efficacy of DAPT when used for more than 12 mo [12,13,23,24,27,31]. All of them showed a lower incidence of composite ischemic events compared to shorter durations of DAPT with the exception of Lee et al and Valgimigli et al, who showed a higher incidence of these events with long DAPT [12,27]. A recently published individual data meta-analysis by Lee et al may explain the unexpected findings in these two studies, however [37]. The majority of deaths in these trials were associated with a higher rate of Type II MI, a condition that is not affected by DAPT,

indicating that many of these deaths may not have been related to a true cardiac event [38]. It should be noted that the DAPT Trial – the largest of these trials – reported a significantly lower incidence of vascular events with long DAPT [13]. Furthermore, a subgroup analysis of patients treated by everolimus-eluting stents – the most commonly used stent – resulted in significant reduction of stent thrombosis and MI [39].

In our study, there was no significant difference in the rate of ischemic events with 12 mo of DAPT, which is the current recommended duration after DES implantation, when compared with using DAPT for 6 mo or less following DES [5]. This result was inconsistent with three of the included trials [21,22,28]. This incongruity could be explained by the inclusion of low-risk patients and short duration of follow-up implemented by these trials. Also, several trials were limited by low event rates, which raise the possibility of bias [22,28]. In contrast, Hahn et al included only patients with acute coronary syndrome (ACS) and showed a lower rate of composite ischemic events in the 12 mo DAPT group [15]. This may highlight the importance of longer duration DAPT in patients with ACS, as they have a higher rate of recurrent ischemic events than patients with stable coronary artery disease [32,33]. More trials with exclusively ACS patients are required, however, before solid conclusions can be made regarding the optimal duration of DAPT after DES implantation in such patients.

In our meta-analysis, the benefit of prolonging DAPT was precluded by a higher risk of bleeding, which was consistent across all of the included trials. Although bleeding risk has been associated with higher mortality, both a recently published analysis by Udell et al and Mauri et al concluded that the risk of fatal bleeding was not significantly higher in a longer duration DAPT arm when compared with a shorter duration DAPT arm [13,16,40]. Furthermore, one study showed a comparable risk of noncardiac death between 6 mo and 12 mo of DAPT, even though the major bleeding risk was higher with longer DAPT [37]. Thus, it remains controversial as to whether or not reported bleeding risk should affect clinical decision-making when it comes to duration of DAPT following DES.

Although our results support longer duration DAPT after DES implantation to reduce risk of ischemic events, it is important to note that there has been a recent influx of new generation DESs, which inherently carry different thrombosis risks, as well as several different combinations of DAPT.

4.1. Limitations

Our analysis has some limitations that should be acknowledged. First, we did not have access to patient-level data. Second, the definition of MACE varied between the clinical trials; however, we could not find any significant heterogeneity in the analysis ($I^2 < 15$). Third, there were inconsistencies in the definition of bleeding events among the included studies. Fourth, the included trials assessed different CAD presentations (stable vs ACS). Finally, clopidogrel was the main thienopyridine used in most of the included trials; therefore, generalizability of the current results to other P2Y12 blockades is limited.

5. Conclusions

In patients who undergo DES implantation, longer durations of DAPT after DES implantation are associated with lower rates of composite ischemic vascular events, especially with durations longer than 24 mo. Longer duration DAPT is associated with a higher rate of bleeding, however.

Acknowledgments

We would like to thank Katherine Negele, editorial assistant, research department, Hurley Medical Center, for assistance with manuscript editing.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Mahmoud Barbarawi http://orcid.org/0000-0001-8218-2466
Babikir Kheiri http://orcid.org/0000-0003-1747-2859
Yazan Zayed http://orcid.org/0000-0002-0179-512X
Mohammed Osman http://orcid.org/0000-0001-5097-5568

References

[1] Schulz S, Schuster T, Mehilli J, et al. Stent thrombosis after drug-eluting stent implantation: incidence, timing, and relation to discontinuation of clopidogrel therapy over a 4-year period. Eur Heart J. 2009;30(22):2714–2721.
[2] Armstrong EJ, Feldman DN, Wang TY, et al. Clinical presentation, management, and outcomes of angiographically documented early, late, and very late stent thrombosis. JACC Cardiovasc Interv. 2012;5(2):131–140.
[3] Holmes DRJ, Kereiakes DJ, Garg S, et al. Stent thrombosis. J Am Coll Cardiol. 2010;56(17):1357–1365.
[4] Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European society of cardiology (ESC) and of the European. Eur Heart J. 2018;39(3):213–260.

[5] Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: A report of the American college of cardiology/American heart association task force on clinical practice guidelines. J Thorac Cardiovasc Surg. 2016;152(5):1243–1275.
[6] Airoldi F, Colombo A, Morici N, et al. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. Circulation. 2007;116(7):745–754.
[7] Roy P, Bonello L, Torguson R, et al. Temporal relation between clopidogrel cessation and stent thrombosis after drug-eluting stent implantation. Am J Cardiol. 2009;103(6):801–805.
[8] Bhatt DL, Fox KAA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med. 2006;354(16):1706–1717.
[9] Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357(20):2001–2015.
[10] Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361(11):1045–1057.
[11] Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. Circulation. 2016;134(10):e123–e155.
[12] Lee CW, Ahn J-M, Park D-W, et al. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: a randomized, controlled trial. Circulation. 2014;129(3):304–312.
[13] Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med. 2014;371(23):2155–2166.
[14] Han Y, Xu B, Xu K, et al. Six versus 12 months of dual antiplatelet therapy after implantation of biodegradable polymer sirolimus-eluting stent: randomized substudy of the I-LOVE-IT 2 trial. Circ Cardiovasc Interv. 2016;9(2):e003145.
[15] Hahn J-Y, Song YB, Oh J-H, et al. 6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial. Lancet. 2018 Mar;391:1274–1284.
[16] Udell JA, Bonaca MP, Collet J-P, et al. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. Eur Heart J. 2016;37(4):390–399.
[17] D'Ascenzo F, Iannaccone M, Saint-Hilary G, et al. Impact of design of coronary stents and length of dual antiplatelet therapies on ischaemic and bleeding events: a network meta-analysis of 64 randomized controlled trials and 102 735 patients. Eur Heart J. 2017;38(42):3160–3172.
[18] Sawaya FJ, Morice M-C, Spaziano M, et al. Short- versus long-term dual antiplatelet therapy after drug-eluting stent implantation in women versus men: A sex-specific patient-level pooled-analysis of six randomized trials. Catheter Cardiovasc Interv. 2017;89(2):178–189.
[19] Rozemeijer R, Voskuil M, Greving JP, et al. Short versus long duration of dual antiplatelet therapy following drug-eluting stents: a meta-analysis of randomised trials. Neth Heart J. 2018 Mar;26:242–251.
[20] Collet J-P, Silvain J, Barthelemy O, et al. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial. Lancet. 2014;384(9954):1577–1585.
[21] Gwon H-C, Hahn J-Y, Park KW, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the efficacy of Xience/Promus versus Cypher to reduce late loss after stenting (EXCELLENT) randomized, multicenter study. Circulation. 2012;125(3):505–513.
[22] Schulz-Schupke S, Byrne RA, Ten Berg JM, et al. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. Eur Heart J. 2015;36(20):1252–1263.
[23] Helft G, Steg PG, Le Feuvre C, et al. Stopping or continuing clopidogrel 12 months after drug-eluting stent placement: the OPTIDUAL randomized trial. Eur Heart J. 2016;37(4):365–374.
[24] Gilard M, Barragan P, Noryani AAL, et al. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: the randomized, multicenter ITALIC trial. J Am Coll Cardiol. 2015;65(8):777–786.
[25] Hong S-J, Shin D-H, Kim J-S, et al. 6-month versus 12-month dual-antiplatelet therapy following long everolimus-eluting stent implantation: the IVUS-XPL randomized clinical trial. JACC Cardiovasc Interv. 2016;9(14):1438–1446.
[26] Lee B-K, Kim J-S, Lee O-H, et al. Safety of six-month dual antiplatelet therapy after second-generation drug-eluting stent implantation: OPTIMA-C randomised clinical trial and OCT substudy. EuroIntervention J Eur Collab with Work Gr Interv Cardiol Eur Soc Cardiol. 2018;13(16):1923–1930.
[27] Valgimigli M, Campo G, Monti M, et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation. 2012;125(16):2015–2026.
[28] Kim B-K, Hong M-K, Shin D-H, et al. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (Real safety and efficacy of 3-month dual antiplatelet therapy following endeavor zotarolimus-eluting stent implantation). J Am Coll Cardiol. 2012;60(15):1340–1348.
[29] Feres F, Costa RA, Abizaid A, et al. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. JAMA. 2013;310(23):2510–2522.
[30] Colombo A, Chieffo A, Frasheri A, et al. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. J Am Coll Cardiol. 2014;64(20):2086–2097.
[31] Nakamura M, Iijima R, Ako J, et al. Dual antiplatelet therapy for 6 versus 18 months after biodegradable polymer drug-eluting stent implantation. JACC Cardiovasc Interv. 2017;10(12):1189–1198.
[32] Loh JP, Pendyala LK, Kitabata H, et al. Comparison of outcomes after percutaneous coronary intervention among different coronary subsets (stable and unstable angina pectoris and ST-segment and non-ST-segment

myocardial infarction). Am J Cardiol. 2014;113 (11):1794–1801.
[33] Kukreja N, Onuma Y, Garcia-Garcia HM, et al. The risk of stent thrombosis in patients with acute coronary syndromes treated with bare-metal and drug-eluting stents. JACC Cardiovasc Interv. 2009;2(6):534–541.
[34] Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. JAMA. 2007;297(2):159–168.
[35] Cassese S, Byrne RA, Tada T, et al. Clinical impact of extended dual antiplatelet therapy after percutaneous coronary interventions in the drug-eluting stent era: a meta-analysis of randomized trials. Eur Heart J. 2012;33(24):3078–3087.
[36] Gajulapalli RD, Dias S, Pattanshetty DJ, et al. Optimal duration of dual antiplatelet therapy after drug eluting stent implantation: a network meta-analysis. Anatol J Cardiol. 2017;18(4):251–260.
[37] Lee S-Y, Hong M-K, Palmerini T, et al. Short-term versus long-term dual antiplatelet therapy after drug-eluting stent implantation in elderly patients: a meta-analysis of individual participant data from 6 randomized trials. JACC Cardiovasc Interv. 2018;11 (5):435–443.
[38] Anderson JL, Morrow DA. Acute myocardial infarction. N Engl J Med. 2017;376(21):2053–2064.
[39] Hermiller JB, Krucoff MW, Kereiakes DJ, et al. Benefits and risks of extended dual antiplatelet therapy after everolimus-eluting stents. JACC Cardiovasc Interv. 2016;9(2):138–147.
[40] Mauri L, Elmariah S, Yeh RW, et al. Causes of late mortality with dual antiplatelet therapy after coronary stents. Eur Heart J. 2016;37(4):378–385.