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Optimal duration of dual antiplatelet therapy after drug eluting stent implantation: a network meta-analysis

Rama Dilip Gajulapalli, Sofia Dias[1], Deepak J. Pattanshetty[2], Ganesh Athappan[3]

Department of Medicine, Cleveland Clinic; Cleveland-Ohio-*USA*
[1]School of Social and Community Medicine, University of Bristol; Bristol-*UK*
[2]Case Western University, Metro Health; Cleveland-Ohio-*USA*
[3]Department of Interventional Cardiology, Temple University Hospital; Philadelphia-PA-*USA*

Abstract

Objective: There has been much debate regarding the optimal duration of dual antiplatelet therapy (DAPT) cover after drug eluting stent (DES) implantation. We aimed to assess the relative benefits of shorter and longer durations of DAPT coverage.
Methods: We performed a network meta-analysis (NMA) of all the randomized clinical trials (RCT) comparing different time durations of DAPT cover.
Results: We included 11 unique trials with a total of 33,458 patients; the longest duration of follow-up was 48 months and the shortest was 3 months. NMA results demonstrated that compared with 12 months, longer DAPT of 30 months reduced the hazard ratio (HR) of stent thrombosis (HR, 0.29; 95% CrI, 0.17–0.49). There was no difference in mortality between shorter and longer durations of DAPT except for 30 vs. 48 months (HR, 0.48; 95% CrI, 0.23–0.98). Compared with 12 months, longer DAPT of 30 months reduced the risk of myocardial infarction (HR, 0.47; 95% CrI, 0.37–0.61). Results also demonstrated that compared with 12 months, a shorter-term DAPT reduced the risk of major bleeding (6 months: HR, 0.53; 95% CrI, 0.29–0.98), whereas longer-term DAPT increased the risk of major bleeding (30 months: HR, 1.61; 95% CrI, 1.21–2.15).
Conclusion: As expected, bleeding was less in the shorter duration regimens, whereas the ischemic outcomes were better in the longer duration ones. *(Anatol J Cardiol 2017; 18: 251-60)*
Keywords: DAPT, PCI, ST, Network meta-analysis

Introduction

The optimal duration of dual antiplatelet therapy (DAPT) after drug eluting stent (DES) implantation has remained in contention, with the recently updated guidelines from major American cardiology societies recommending a minimum of 6 months of aspirin in combination with a P2Y12 inhibitor after DES implantation (1) bringing them in line with the European societies' recommendations (2) and marking a departure from the past. Shorter DAPT comes with the risk of late and very late stent thrombosis (3, 4), whereas prolonged DAPT comes with an elevated risk of bleeding (5). Defining the fine balance between ischemic benefits and bleeding risks has been elusive thus far. Multiple randomized control trials have shown short-term DAPT to be non-inferior to the current recommended duration of 12 months with similar ischemic outcomes and a lower risk of bleeding (6–9). Conversely, randomized controlled trials on prolonged DAPT beyond 12 months have shown a significant reduction of ischemic events but at the expense of increased bleeding (10).

We therefore conducted a network meta-analysis (NMA) to assess the safety and efficacy of varied durations of DAPT after DES. NMA allows the synthesis of direct and indirect evidence to produce measures of treatment efficacy and ranking of different interventions, while preserving randomization of included trials. This allows an estimation of relative effect estimates for treatments for which no head-to-head comparisons currently exist and can also improve the precision of existing estimates.

Methods

Study design and definitions

In this NMA, we compared four outcomes: all-cause mortality, myocardial infarction (MI), stent thrombosis (ST), and major bleeding (MB), for variable durations of DAPT (short and prolonged). Trials comparing variable durations of DAPT were iden-

Address for correspondence: Ganesh Athappan, Division of Interventional Cardiology
Temple University Hospital, 3401 N Broad Street, Philadelphia, PA 19131-*USA*
E-mail: ganeshathappan@gmail.com
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Table 1. Definitions/criteria of primary endpoint, major bleeding, and stent thrombosis

Study names	Primary endpoint	Major bleeding	ST
DAPT	Death, MI, or Stroke	GUSTO	ARC
ITALIC	Death, MI, TVR, Major bleeding, or stroke	TIMI	ARC
RESET	Death, MI, ST, TVR, or Bleeding	TIMI	ARC
ARCTIC	Death, MI, TVR, ST, and Stroke	STEEPLE	ARC
SECURITY	Death, MI, ST, Stroke, and Bleeding	BARC	ARC
EXCELLENT	Death, MI, and TVR	TIMI	ARC
DES LATE	Death, MI, and Stroke	TIMI	ARC Definite
OPTIMIZE	Death, MI, Stroke, and Major bleeding	GUSTO	ARC
PRODIGY	Death, MI, and Stroke	TIMI, BARC, or BleedScore	ARC
ISAR-SAFE	Death, MI, Stroke, ST, and Major bleeding	TIMI	ARC
OPTIDUAL	Death, MI, Stroke, and Major bleeding	ISTH	ARC

ARC - academic research consortium; BARC - bleeding academic research consortium; GUSTO - global use of strategies to open occluded arteries; ISTH - international society on thrombosis and hemostasis; MI - myocardial infarction; ST - stent thrombosis (All presumed Definite/Probable unless stated otherwise); TIMI - thrombolysis in myocardial infarction; TVR - target vessel revascularization

tified and analyzed. We restricted our analyses to randomized controlled trials. The present NMA review was done according to PRISMA guidelines for performing NMA (11).

Search strategy

The authors collected data from four online databases: Medline (PubMed), Cochrane Collaboration of Clinical Trials, Clinicaltrials.gov, and Google Scholar. The searches were limited by date and extended from 2000 to October 25, 2015. The search objective was to identify all randomized controlled trials comparing varying durations of DAPT.

The search terms used were "DAPT," "dual antiplatelet," "clopidogrel," "Plavix," "thienopyridiene," and "P2Y12 inhibitors." We limited the search to English language reports and randomized controlled trials. We screened citations at the title and abstract level and retrieved full reports if they were randomized trials comparing variable durations of DAPT after DES implantation and provided information on all-cause mortality, MI, ST, and bleeding. The full texts of all potential articles were reviewed in detail. The bibliography of retained studies was used to seek additional relevant studies.

Inclusion and exclusion criteria

Studies were included if the following criteria applied: (a) comparative trials of variable DAPT duration, (b) enrolled patients with DES implantation, and (c) reported on at least one of the following outcomes: all-cause mortality, MI, MB, or ST. When two similar studies were reported from the same institution or author, the most recent publication or the most relevant one was included in the analysis.

Studies were excluded if any of the following criteria applied: (a) nonrandomized studies, (b) enrolled patients with no DES implantation, (c) outcomes of interest were not clearly reported or were impossible to extract or calculate from the published results, (d) single-arm studies, or (e) duplicate publications.

Study end-point

The end points analyzed were all-cause mortality, bleeding, MI, and ST. All end points were evaluated according to per protocol and individual study definitions (Table 1).

Statistical analysis

A Bayesian NMA, using noninformative priors, was conducted on the hazard ratio (HR) scale to account for the varying follow-up times across studies. Relative effect estimates are presented as median HRs and 95% credible intervals (CrI). Both fixed and random effects models were fitted and compared based on residual deviance and deviance information criteria (DIC) (12, 13). The model with the smallest DIC was preferred as being the best compromise between fit and complexity. A small difference in DIC between the fixed and random effects models (3–5 points) implies that the better fit obtained by adding random effects does not justify the additional complexity, in which case we would report the results from a fixed effects model's results. Between-studies heterogeneity estimates from random effects models are presented as median and 95% CrI.

A DAPT duration of 12 months was selected as the reference treatment to aid interpretation, although results are not sensitive to this choice (14).

Inconsistency, that is the agreement between direct and indirect evidence on the same comparisons, was tested in the single available closed loop of treatment comparisons by comparing the direct and indirect estimates obtained from an unrelated mean effects model (14). This technique allows estimation of relative effects based only on direct RCT data, which can then be compared to the indirect evidence generated according to the Bucher method (15). The difference between these contributions can be quantified using a Bayesian p-value indicating the probability that there are differences in relative effects calculated using direct and indirect evidence.

Probabilities of each outcome on the reference treatment were calculated by pooling the evidence from all RCTs that compared it using a separate random effects meta-analysis model (16). These probabilities were then used to calculate the expected number of people who need to receive DAPT at each duration to incur (or avoid) an event at a given time point [number needed to treat (NNT) and number needed to harm (NNH)] (13). Ranking probabilities for each treatment and outcome were also calculated.

The statistical analyses were conducted in WinBUGS 1.4.3 (The BUGS Project, MRC Biostatistics Unit, University of Cambridge, UK) (17) using the code adapted from the Dias et al. (18–20). Noninformative priors were used for all relative treatment effects and heterogeneity parameters. Three independent chains were run and checks for convergence and autocorrelation were carried out using the Brooks–Gelman–Rubin tools and by inspecting trace and autocorrelation plots. All results were based on postconvergence 150.000 iterations (50.000 on each of the three independent chains).

Results

Using the keyword search, 18,467 reports were identified of which 1122 relevant publications were selected by screening at the abstract and title level (Fig. 1). By applying the inclusion and exclusion criteria, 10 unique trials were selected for the meta-analysis. The OPTIDUAL trial was also included as a late addition based on it meeting the appropriate criteria. These 11 unique trials included a total of 33,458 patients. The longest duration of follow-up was 48 months while the shortest was 3 months. The majority of the dual antiplatelet agents were aspirin or acetylsalicylic acid and clopidogrel, while prasugrel was sparingly used. All the included trials reported end points including ST, MI, mortality, and bleeding. The main study details and clinical characteristics of enrolled patients are shown in Table 2a, b.

There were two studies that compared 3 months vs. 12 months, three that compared 6 months vs. 12 months, two that compared 6 months vs. 24 months, three that compared 12 vs. 30 months (DES LATE, which compared 12 months vs. 36 months was included for ease of comparison), and one that compared 12 vs. 48 months of DAPT after DES implantation. The treatment network is presented in Figure 2.

Fixed effect models were found to fit the data well for all outcomes, thus all results presented are from fixed effect models. There was no evidence of inconsistency between direct and indirect evidence for any outcome with Bayesian p-values ranging from 0.09 (ST) to 0.82 (bleeding). The probability rankings of the treatment durations for each outcome are shown in Figure 3. We also assessed the quality of outcome and interpretations using the GRADE recommendation (Table 3a, b). The probabilities and numbers needed to treat based on our NMA are provided in Tables 4 and 5.

Stent thrombosis (Fig. 4a)

NMA results demonstrated that compared with 12 months, longer DAPT of 30 months reduced HR of ST (HR, 0.29; 95%

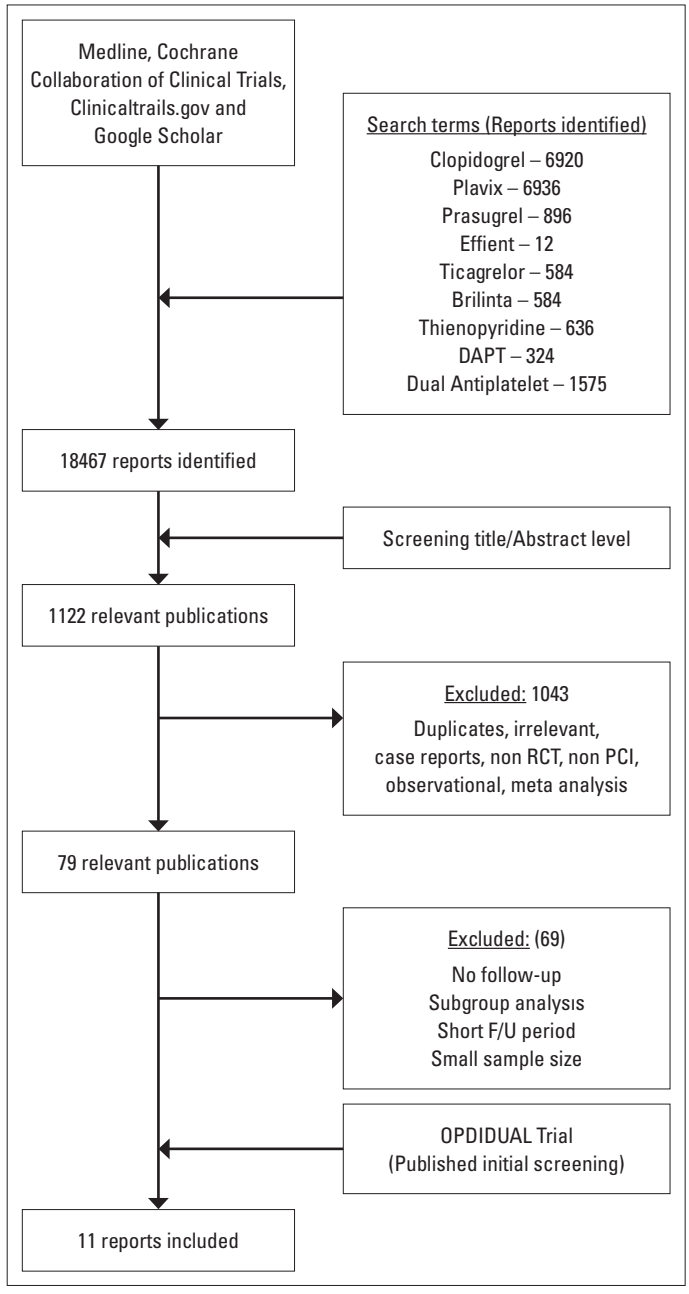

Figure 1. Flowchart showing selection of studies

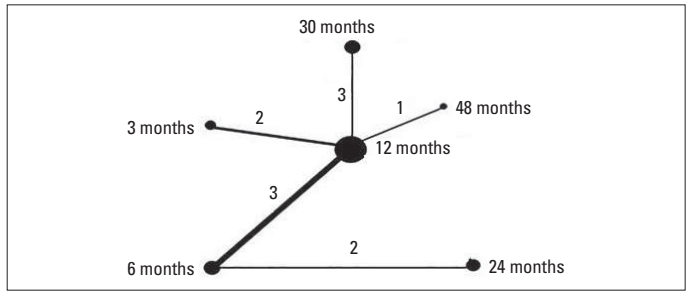

Figure 2. Network plot. Nodes represent DAPT durations and lines represent direct comparisons of different durations in included trials. The numbers on the lines and line thickness represent the number of studies makin those comparisons, the width of the nodes is proportional to the number of patients randomised to those durations

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Table 2a. Study characteristics of the randomized trials

Study names	Year	Comparison (Time of DAPT use in months)	N		Age, years		Sex		DM		Clopidogrel		Prasugrel	
			S	L	S	L	S	L	S	L	S	L	S	L
DAPT	2014	12 vs. 30	4941	5020	62	62	26	25	30	31	65	65	35	35
ITALIC	2014	6 vs. 24	912	910	62	62	19	21	36	38	99	98	1	2
RESET	2012	3 vs. 12	1059	1058	62	62	36	37	30	29	100	100	0	0
ARCTIC	2014	12 vs. 30	624	635	64	64	19	20	36	31	91	91	9	9
SECURITY	2014	6 vs. 12	682	717	65	66	22	23	30	31	98	99	<1	<1
EXCELLENT	2012	6 vs. 12	722	721	63	62	35	36	38	37	99	100	0	0
DES LATE	2014	12 vs. 36	2514	2531	62	63	30	31	28	28	100	100	0	0
OPTIMIZE	2013	3 vs. 12	1563	1556	61	62	37	37	35	35	100	100	0	0
PRODIGY	2012	6 vs. 24	983	987	68	68	24	23	24	25	100	100	0	0
ISAR-SAFE	2015	6 vs. 12	1997	2003	67	67	19	20	25	24	100	100	0	0
OPTIDUAL	2015	12 vs. 48	690	695	64	64	21	18	32	31	100	100	0	0

Age given in Mean or Median as provided; DAPT - dual antiplatelet treatment; DM - diabetes mellitus %; L - longer duration group; N - number of subjects; NA - not available; S - short duration group; Sex - female %; vs - versus; year, study published

Table 2b. Study characteristics of the randomized trials

Study names	Stents per patient	ACS	DES generation		Type of study	Independent adjudication
			First	Second		
DAPT	1.45	43	38	60	Double blinded RCT	Yes
ITALIC	1.6	24	0	100	Open Label RCT	Yes
RESET	1.3	54	21	85	Open Label RCT	Yes
ARCTIC	–	–	40	60	Open Label RCT	Yes
SECURITY	1.6	38	0	100	Open Label RCT	Yes
EXCELLENT	1.6	52	25	75	Open Label RCT	Yes
DES LATE	1.3*	61	64	30	Open Label RCT	Yes
OPTIMIZE	1.6	32	0	100	Open Label RCT	Yes
PRODIGY	1.86	75	25	50	Open Label RCT	Yes
ISAR-SAFE	1.68	40	10	89	Double blinded RCT	Yes
OPTIDUAL	1.5	34	35	60	Open Label RCT	Yes

ACS - acute coronary syndrome; DES - drug eluting stent; RCT - randomized controlled trial; ACS&DES figures given in %

CrI, 0.17–0.49). Similarly, 30 months of DAPT was better than 3 months of DAPT to prevent ST (HR, 0.29; 95% CrI, 0.12–0.70). The probability that 30 months of DAPT is the best of the durations compared at reducing ST is 96%. There was no difference in ST between 3 months vs. 12, 6, 24, or 48 months; 6 months vs. 12, 24, 30, or 48 months; 24 months vs. 48 months; and 30 months vs. 48 months. The number needed to prevent one ST with 30 months of DAPT compared with 12 months was 327 (95% CrI, 116–939) vs. 816 (95% CrI, 287–2346).

Mortality (Fig. 4b)

NMA results demonstrated that there was no difference in mortality between short and longer durations of DAPT except for 30 months vs. 48 months (HR, 0.48; 95% CrI, 0.23–0.98), indicating that 48 months duration reduces mortality compared with 30 months. The probability that 48 months of DAPT is the best of the durations compared at reducing mortality is 73%. The number needed to cause harm or one mortality event with 48 months of DAPT compared with 12 months was 84 (95% CrI, 619–165) vs. 325 (95% CrI, 2409–640). There was no significant effect noted when 30 months was compared with 12 months.

MI (Fig. 4c)

NMA results demonstrated that compared with 12 months, longer DAPT of 30 months reduced the hazard risk (HR) of MI (HR, 0.47; 95% CrI, 0.37–0.61). Similarly 30 months of DAPT was better than 3 (HR, 0.42; 95% CrI, 0.26–0.68), 6 (HR, 0.47; 95% CrI,

Table 3a. GRADE assessment

Outcome	Type of evidence	Quality	Consistency	Directness	Effect size	Overall grade
Stent thrombosis	4+	0	0	0	0	3
Myocardial infarction	4+	0	0	0	0	3
Mortality	4+	0	0	0	0	3
Bleeding	4+	0	0	0	0	3

Table 3b. GRADE assessment scoring system (Adapted from BMJ Clinical Evidence 2012*)

Type of evidence		
Scored on	+4	RCT
	+2	Observational evidence
Quality		
Based on	Blinding and allocation, follow-ups, withdrawals, sparse data, and methodological concerns	
Score	0	No problems
	–1	Problem with 1 element
	–2	Problem with 2 elements
	–3	Problem with 3 or more elements
Consistency		
Based on	Degree of consistency of effect between or within studies	
Score	+1	Evidence of dose response across or within studies
	0	All/most studies show similar results
	–1	Lack of agreement between studies
Directness		
Based on	The generalizability of population and outcomes from each study to population of interest	
Score	0	Population and outcomes broadly generalizable
	–1	Problem with 1 element
	–2	Problem with 2 or more elements
Effect size		
Based on	The reported OR/RR/HR for comparison	
Score	0	Not all effect sizes >2 or <0.5 and significant; or if OR/RR/HR not significant
	+1	Effect size >2 or <0.5 for all studies/meta-analyses included in comparison and significant
	+2	Effect size >5 or <0.2 for all studies/meta-analyses included in comparison and significant
Final GRADE score:	High (4 points overall), Moderate (3 points), Low (2 points), and Very low (one or less).	

(*http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665072.html). HR - hazards ratio; OR - odds ratio; RCT - randomized controlled trial, RR - relative risk

0.30–0.72), or 24 months (HR, 0.54; 95% CrI, 0.34–0.86) of DAPT to prevent MI. There was no difference in MI between 30 and 48 months of DAPT (HR, 1.42; 95% CrI, 0.63–3.21). There was no difference in MI between the other durations of DAPT. The probability that 30 months of DAPT is the best of the durations compared at preventing MI is 80%. The number needed to prevent one MI with 30 months of DAPT compared with 12 months was 91 (95% CrI, 51–165) vs. 225 (95% CrI, 126–411).

Bleeding (Fig. 4d)

NMA results demonstrated that compared with 12 months, shorter DAPT reduced the risk of MB (6 months: HR, 0.53; 95% CrI, 0.29–0.98), whereas longer DAPT increased HR of MB (30 months: HR, 1.61; 95% CrI, 1.21–2.15). Similarly, 3 months of DAPT was better than 24 months (HR, 2.50; 95% CrI, 1.08–5.85) and 30 months (HR, 2.66; 95% CrI, 1.25–5.72). Six months DAPT was also better than 24 months (HR, 2.85; 95% CrI, 1.48–5.44) and 30 months (HR, 3.02; 95% CrI, 1.54–6.00) of DAPT to prevent MB. The duration with the highest probability of being the best of the durations compared at preventing bleeding is 6 months, with 57% probability. The number needed to cause harm or one MB event with 30 months of DAPT compared with 12 months was 139 (95% CrI, 434–64) vs. 343 (95% CrI, 1076–157).

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Table 4. Probability of an event and 95% CrI at given time points

	Stent thrombosis		Bleeding		MI		Mortality	
Months	Median	95% CrI	Median	95% CrI	Median	95% CrI	Median	95% CrI
3	0.000	(0.000, 0.001)	0.002	(0.001, 0.003)	0.002	(0.001, 0.004)	0.002	(0.001, 0.003)
6	0.001	(0.000, 0.002)	0.004	(0.002, 0.006)	0.004	(0.002, 0.007)	0.004	(0.003, 0.006)
12	0.002	(0.001, 0.004)	0.008	(0.005, 0.012)	0.009	(0.005, 0.015)	0.008	(0.005, 0.013)
24	0.004	(0.001, 0.009)	0.015	(0.010, 0.023)	0.017	(0.010, 0.029)	0.017	(0.011, 0.026)
48	0.007	(0.002, 0.017)	0.030	(0.019, 0.046)	0.034	(0.019, 0.057)	0.033	(0.022, 0.050)

Reference treatment (12 months duration); CrI, credible interval; MI, myocardial infarction. Probabilities of each outcome on the reference treatment were calculated by pooling the evidence from all RCTs that compared it using a separate random effects meta-analysis model

Table 5. NNT for an additional event

	Stent thrombosis		Bleeding		MI		Mortality	
Months	Median	95% CrI	Median	95% CrI	Median	95% CrI	Median	95% CrI
3	3259	(1145, 9377)	1362	4289,621	894	(497, 1637)	1288	(9577, 2542)
6	1630	(573, 4690)	683	(2147,312)	448	(250, 820)	646	(4800, 1274)
12	816	(287, 2346)	343	(1076,157)	225	(126, 411)	325	(2409, 640)
24	409	(144, 1173)	173	(541,79)	113	(64, 207)	164	(1216, 323)
30	327	(116, 939)	139	(434,64)	91	(51,165)	***	***
48	205	(73, 588)	88	(273,41)	58	(33, 104)	84	(619, 165)

NNT for an additional event compared with 12 months; CrI - credible interval; MI - myocardial infarction. Probabilities used to calculate the expected number of people who need to receive DAPT at each duration

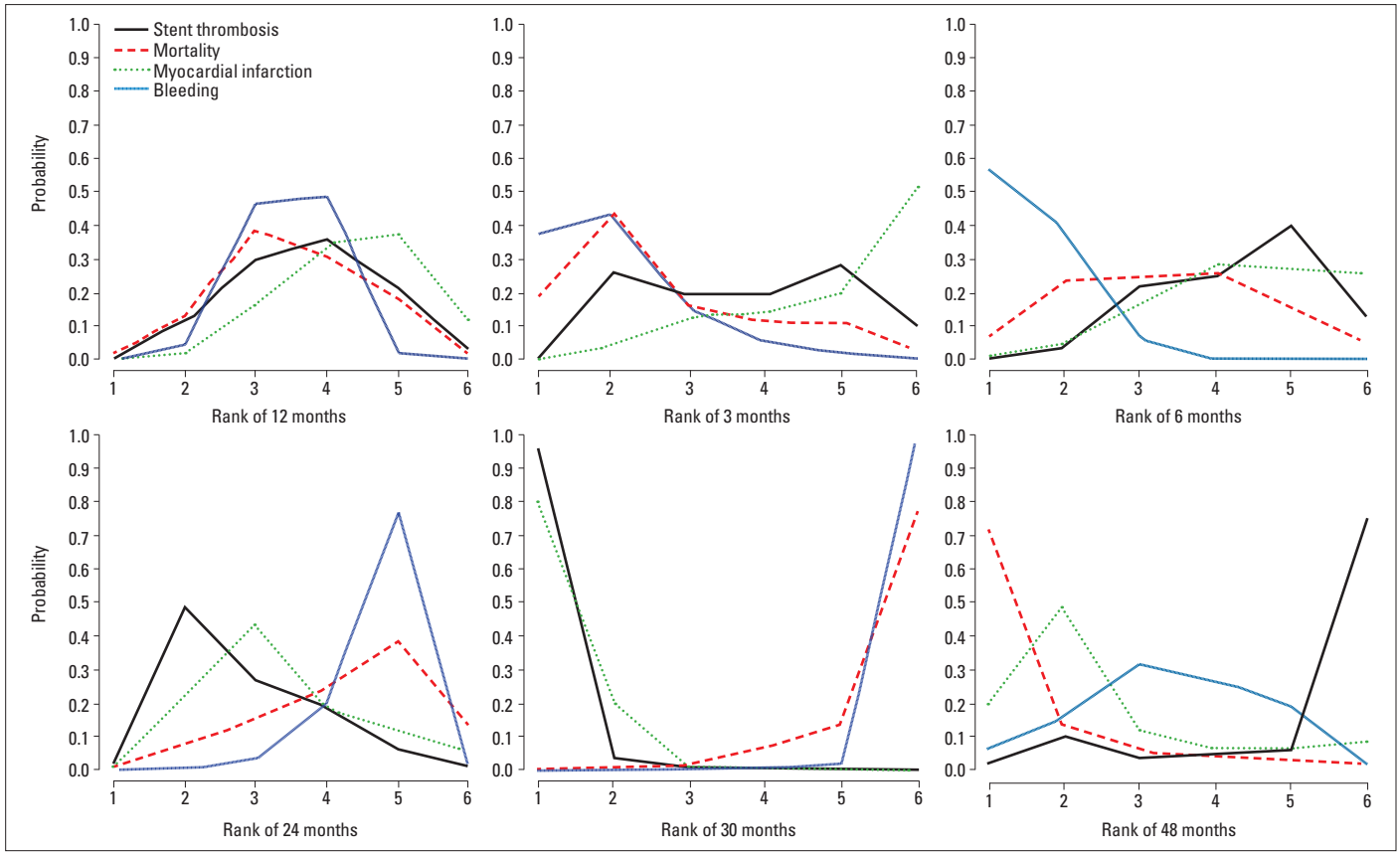

Figure 3. Rankogram probability plots

a

Duration in months		Network Meta-Analysis HR of Y compared X	
X	Y	Median	95%CrI
12	3	1.01	(0.49, 2.06)
12	6	1.12	(0.59, 2.14)
12	24	0.82	(0.43,1.57)
12	30	0.29	(0.17, 0.49)
12	48	3.01	(0.29, 31.31)
3	6	1.11	(0.42, 2.94)
3	24	0.82	(0.31, 2.15)
3	30	0.29	(0.12, 0.70)
3	48	2.98	(0.26, 34.62)
6	24	0.73	(0.49, 1.10)
6	30	0.26	(0.11, 1.10)
6	48	2.68	(0.24, 30.34)
24	30	0.35	(0.15, 0.81)
24	48	3.65	(0.32, 41.44)
30	48	10.35	(0.94, 114.10)

HR>1 favors X; HR<1 favors Y

b

Duration in months		Network Meta-Analysis HR of Y compared X	
X	Y	Median	95%CrI
12	3	0.87	(0.59, 1.29)
12	6	0.99	(0.68, 1.42)
12	24	1.09	(0.78,1.53)
12	30	1.36	(1.00, 1.85)
12	48	0.65	(0.34, 1.24)
3	6	1.13	(0.66, 1.93)
3	24	1.25	(0.75, 2.10)
3	30	1.56	(0.95, 2.58)
3	48	0.75	(0.35, 1.60)
6	24	1.11	(0.82, 1.49)
6	30	1.38	(0.86, 2.22)
6	48	0.66	(0.32, 1.39)
24	30	1.25	(0.79,1.97)
24	48	0.60	(0.29, 1.24)
30	48	0.48	(0.23, 0.98)

HR>1 favors X; HR<1 favors Y

c

Duration in months		Network Meta-Analysis HR of Y compared X	
X	Y	Median	95%CrI
12	3	1.12	(0.75, 1.66)
12	6	1.07	(0.71, 1.45)
12	24	0.87	(0.59,1.28)
12	30	0.47	(0.37, 0.61)
12	48	0.67	(0.31, 1.45)
3	6	0.91	(0.53, 1.55)
3	24	0.78	(0.45, 1.36)
3	30	0.42	(0.26, 0.68)
3	48	0.60	(0.25, 1.44)
6	24	0.86	(0.60, 1.23)
6	30	0.47	(0.30, 0.72)
6	48	0.66	(0.28, 1.55)
24	30	0.54	(0.34, 0.86)
24	48	0.77	(0.33, 1.83)
30	48	1.42	(0.63, 3.21)

HR>1 favors X; HR<1 favors Y

d

Duration in months		Network Meta-Analysis HR of Y compared X	
X	Y	Median	95%CrI
12	3	0.61	(0.30, 1.22)
12	6	0,53	(0.29, 0.98)
12	24	1,52	(0.95, 2.42)
12	30	1.61	(1.21, 2.15)
12	48	0.98	(0.47, 2.05)
3	6	0.88	(0.35, 2.24)
3	24	2.50	(1.08, 5.85)
3	30	2.66	(1.25, 5.72)
3	48	1.62	(0.58, 4.51)
6	24	2.85	(1.48, 5.44)
6	30	3.02	(1.54, 6.00)
6	48	1.84	(0.70, 4.81)
24	30	1.06	(0.61, 1.85)
24	48	0.65	(0.27, 1.56)
30	48	0.61	(0.27, 1.35)

HR>1 favors X; HR<1 favors Y

Figure 4. Hazard ratios (HR) of stent thrombosis (a), mortality (b), myocardial infarction (c) and bleeding (d).

Discussion

DAPT after PCI has been a cornerstone as it has been shown to be beneficial in reducing complications including ST. It is a class I A recommendation from major societies including the American College of Cardiology (1). However, the optimal duration of DAPT after PCI has been a source of discussion with varying consensus.

The study herein is the largest meta-analysis to be reported in the literature and the only one to compare as many different durations of DAPT (3, 6, 12, 24, 30, and 48 months). We have performed an NMA comparing different durations of DAPT from studies incorporating nearly 30,000 patients undergoing PCI with DES implantation. Our findings are consistent with the current thoughts on DAPT: longer duration of DAPT is associated with increased risk of bleeding and reduced risk of ST and MI. We also found no difference in mortality between shorter or longer duration of DAPT. However, we were able to delve further into the data and show that one significantly reduced risks of ST and MI are only seen with durations of DAPT >24 months and that

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while preventing one myocardial infarction and one ST with 30 months of DAPT, approximately 3 and 11 patients, respectively, developed one MB complication.

As shown by the majority of previous studies, incidence of ST tended to decrease as the DAPT duration increased (21–23). However, our analysis showed that ST rates were significantly lower only when DAPT was continued for 30 months when compared with any duration up to and including 24 months. It would seem that the advantage is highest when compared with durations of 3, 6, or 12 months. Comparisons of differing DAPT durations up to 24 months did not have any statistical benefit. It may seem that continuing DAPT beyond 24 months may reduce continued rates of very late ST. In the included trials, PCI patients with both 1st and 2nd generation DES were enrolled. Since late and very late ST has been shown to be more significant in 1st generation DES compared with 2nd generation DES, it can be speculated that the continuation of DAPT beyond 2 years reduced the elevated rates of very late ST in 1st generation DES, contributing to the overall statistical benefit. The combined analysis of all SPIRIT studies (24) showed the risk of definite and probable ST after the 1st year and up to the 3rd year to be 0.4% with EES and 0.70% with PES, respectively. The lower risk of late ST with second-generation DES compared with first-generation DES challenges the need for prolonged DAPT to prevent stent thrombosis. In our analysis, the number needed to prevent one ST by prolonging DAPT for 30 months as opposed to the standard therapy was 327. Therefore, whether prolonged DAPT duration has clinical significance in preventing ST post 2nd generation DES remains debatable.

Similar to ST, MI rates seem to improve with longer duration of DAPT (10). DAPT coverage of 30 months had the lowest rates of MI. In our analysis, the number needed to prevent one MI by prolonging DAPT for 30 months as opposed to the standard therapy was 91. In the PEGASUS trial (25), patients who were 1–3 years post-MI and had specific high-risk characteristics (aged ≥65 years and had diabetes mellitus, second prior spontaneous MI, multi-vessel CAD, and chronic renal dysfunction) were enrolled to receive either DAPT or aspirin alone for a median follow-up of 33 months. Both 90 mg and 60 mg of ticagrelor significantly reduced MI (HR, 0.83; 95% CrI, 0.72–0.95) over the study period compared with aspirin alone. However, reduction in MI was accompanied by increased MB (1.85% vs. 1.09%; RR, 1.73; 95% CrI, 1.19–2.50; p = 0.004; NNH, 132). In our analysis, the prevention of one MI with prolonged DAPT was estimated to occur at the expense of three major bleeds.

As expected, longer duration of DAPT increased the risk of MB. Bleeding during 3 months or 6 months of DAPT was less than that at 12, 24, or 30 months. The only discrepancy was the lack of significant difference between 3 months vs. 12 months of DAPT (HR, 0.61; 95% CrI, 0.30–1.22). Standard 12 months duration of DAPT was similarly better than prolonged DAPT. Recent analysis by Palmerini et al. (26) concluded that at 1 year, bleeding was lower with shorter duration (<6 months) compared with 1 year of therapy and there was no significant difference in MACE. We have been able to show that the trends for bleeding worsen as the duration of DAPT coverage lengthens up to 30 months compared with just 1 year. While we did not look specifically at MACE, we were able to show that the mortality risk did not differ at various time intervals, irrespective of the duration of therapy. This reinforces the findings by Palmerini et al. (26) albeit over a longer term. Another recent analysis by Giustino et al. (22) showed that longer duration DAPT correlated to lower risk of ST and MI and increased the bleeding risk.

In the DAPT trial (10), prolonged DAPT was however associated with an increased risk of noncardiac death. Similarly, in the meta-analysis by Palmerini et al. (26), prolonged DAPT was associated with increased mortality. Our meta-analysis incorporates the OPTIDUAL study published by Helft et al. (27), which randomized 1385 patients to DAPT with clopidogrel for 12 months vs. 48 months. They found a trend toward decreased mortality without statistical significance in the long term DAPT group but also saw no increase in bleeding risk with longer therapy. However, we found no mortality benefit with longer duration DAPT compared with shorter duration. Though ST and MI rates were reduced with longer duration DAPT, this did not lend a mortality benefit. This could be due to higher bleeding risk negating any mortality benefit of reduced ST and MI rates. One aspect to note was that compared to 30 months, 48 months therapy seemed to reduce mortality but the risk of ST, bleeding, or MI was no different. It is unclear if this pertains to only cardiac deaths or combined mortality. Prior analysis seems to suggest that while longer DAPT lowers many complications, some risks seem to plateau over time including very late ST (28). Whether the 48 month duration in particular was helpful in preventing cerebrovascular events is unclear.

Study limitations

Without access to patient level data, we were unable to further assess the effect of differing antiplatelet agents (clopidogrel vs. ticagrelor vs. prasugrel). We were also unable to assess the effect of stent generation on patient outcomes and the risk of ST and MI. In fact, the lack of this data and lack of standardization across studies may obscure the complete clinical picture and actual risk and benefits of DAPT duration.

Although we carried out NMA on the HR scale, which accounts for the different duration of follow-up in each study, this assumes proportional hazards throughout the period of study. Individual patient data would allow exploration of other assumptions.

Conclusion

In this NMA of randomized trials comparing different durations of DAPT after DES implantation, we found that there is probably no benefit in extending DAPT beyond 12 months. The

lower frequency of MI and ST likely comes at the price of increased MB. Based on our calculation of NNT vs. NNH, 30 months of DAPT may have an unnecessarily high risk of bleeding in comparison to the more modest reduction in the risk of MI or ST. DAPT after DES implantation should be limited to 6 months as suggested by various updated guidelines recently. Prolonging DAPT beyond this time period may have benefits in some patients but is independent of stent implantation.

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