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# Duration of dual antiplatelet therapy after percutaneous coronary intervention with drug-eluting stent: systematic review and network meta-analysis

Shang-He-Lin Yin,<sup>1,2</sup> Peng Xu,<sup>2</sup> Bian Wang,<sup>2</sup> Yao Lu,<sup>1</sup> Qiao-Yu Wu,<sup>1</sup> Meng-Li Zhou,<sup>1,2</sup> Jun-Ru Wu,<sup>1,2</sup> Jing-Jing Cai,<sup>1,3</sup> Xin Sun,<sup>4</sup> Hong Yuan<sup>1,3</sup>

<sup>1</sup>Center of Clinical Pharmacology, Third Xiangya Hospital, Central South University, Changsha, 410013, Hunan, China

<sup>2</sup>Xiangya School of Medicine, Central South University, Changsha, Hunan, China

<sup>3</sup>Department of Cardiology, Third Xiangya Hospital, Central South University, Changsha, Hunan, China

<sup>4</sup>Chinese Evidence-based Medicine Centre and CREAT Group, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University and Collaborative Innovation Centre, Chengdu, Sichuan, China

Correspondence to: H Yuan yuanhong01@csu.edu.cn (ORCID 0000-0002-9452-2189)

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## ABSTRACT

### OBJECTIVE

To evaluate the efficacy and safety of standard term (12 months) or long term (>12 months) dual antiplatelet therapy (DAPT) versus short term (<6 months) DAPT after percutaneous coronary intervention (PCI) with drug-eluting stent (DES).

### DESIGN

Systematic review and network meta-analysis.

### DATA SOURCES

Relevant studies published between June 1983 and April 2018 from Medline, Embase, Cochrane Library for clinical trials, PubMed, Web of Science, ClinicalTrials.gov, and Clinicaltrialsregister.eu.

### REVIEW METHODS

Randomised controlled trials comparing two of the three durations of DAPT (short term, standard term, and long term) after PCI with DES were included. The primary study outcomes were cardiac or non-cardiac death, all cause mortality, myocardial infarction, stent thrombosis, and all bleeding events.

### RESULTS

17 studies (n=46 864) were included. Compared with short term DAPT, network meta-analysis showed that long term DAPT resulted in higher rates of major bleeding (odds ratio 1.78, 95% confidence interval 1.27 to 2.49) and non-cardiac death (1.63, 1.03 to 2.59); standard term DAPT was associated with higher rates of any bleeding (1.39, 1.01 to 1.92). No noticeable difference was observed in other primary endpoints. The sensitivity analysis revealed that the risks of non-cardiac death and bleeding were further increased for ≥18 months of DAPT compared with

short term or standard term DAPT. In the subgroup analysis, long term DAPT led to higher all cause mortality than short term DAPT in patients implanted with newer-generation DES (1.99, 1.04 to 3.81); short term DAPT presented similar efficacy and safety to standard term DAPT with acute coronary syndrome (ACS) presentation and newer-generation DES placement. The heterogeneity of pooled trials was low, providing more confidence in the interpretation of results.

### CONCLUSIONS

In patients with all clinical presentations, compared with short term DAPT (clopidogrel), long term DAPT led to higher rates of major bleeding and non-cardiac death, and standard term DAPT was associated with an increased risk of any bleeding. For patients with ACS, short term DAPT presented similar efficacy and safety with standard term DAPT. For patients implanted with newer-generation DES, long term DAPT resulted in more all cause mortality than short term DAPT. Although the optimal duration of DAPT should take personal ischaemic and bleeding risks into account, this study suggested short term DAPT could be considered for most patients after PCI with DES, combining evidence from both direct and indirect comparisons.

### SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42018099519.

## Introduction

Dual antiplatelet therapy (DAPT), with aspirin and a P2Y<sub>12</sub> receptor inhibitor, is a basis for the care of patients after percutaneous coronary intervention (PCI).<sup>1-3</sup> The recommended duration of DAPT for patients after drug-eluting stent (DES) implantation is ≥12 months for patients with acute coronary syndrome (ACS), and six months for patients with stable coronary artery disease.<sup>2,3</sup> Despite these recommendations, the optimal timing of switching from DAPT to a single antiplatelet therapy continues to be a matter of debate, owing to refinements in DES technologies and the advent of potent P2Y<sub>12</sub> receptor inhibitors.<sup>4</sup>

The recommendation for ≥12 months of DAPT after PCI with DES has received scrutiny by several randomised controlled trials, which proved non-superiority compared with three to six months of DAPT.<sup>5-9</sup> Furthermore, shorter durations, as opposed to longer durations of DAPT, were associated with lower rates of all cause mortality as a result of lower rates of bleeding-related deaths.<sup>10</sup> Nevertheless, the wide non-inferiority margins of up to six months of DAPT from

## WHAT IS ALREADY KNOWN ON THIS TOPIC

A longer duration of dual antiplatelet therapy (DAPT) for patients receiving DAPT after drug-eluting stent (DES) implantation is associated with an increased risk of bleeding, and a shorter duration of DAPT is associated with an increased risk of ischemia

Pairwise meta-analyses are limited to two durations of DAPT (short term and long term) and network meta-analyses are inclined to evaluate inappropriate arms

## WHAT THIS STUDY ADDS

Short term DAPT (<6 months) is recommended for patients implanted with DES and treated with clopidogrel, in both the general population of patients with coronary artery disease and subgroups of patients with newer-generation DES or acute coronary syndrome

Long term DAPT (>12 months) resulted in more death and bleeding-related events  
Standard term DAPT (12 months) showed similar efficacy and safety compared with short term DAPT

single randomised controlled trials have prevented researchers from concluding that short term DAPT could replace the conventional standard duration. Additionally, a recent individual patient data meta-analysis of six randomised controlled trials suggested that three months of DAPT was associated with an increased risk of ischemia in patients with ACS.<sup>11</sup>

Coronary artery disease is a leading cause of reduced health globally, as well as in each world region.<sup>12</sup> A cost effectiveness analysis of different durations of DAPT after PCI with DES showed that three to six months of DAPT was better than  $\geq 12$  months of DAPT.<sup>13</sup> Moreover, DAPT disruption owing to non-compliance or bleeding, which is more frequent with longer durations of DAPT, increases the risk of adverse events.<sup>14</sup> Thus, shortening the recommended duration of DAPT might relieve the global health burden. However, previous studies have focused on comparing two arms representing longer or shorter durations of DAPT when investigating the efficacy and safety of the discontinuation of DAPT after PCI with DES.<sup>15-18</sup> Without more quantified criteria for various durations, it would be unlikely to make a strong inference regarding rationality of up to six months of DAPT based on the current evidence. Additionally, the limited head-to-head trials might weaken the conclusiveness of pairwise meta-analysis and network meta-analysis results with small sample sizes or unsuitable arms.

Therefore, we performed this network meta-analysis to better quantify durations of DAPT and make full use of direct and indirect evidence to provide a more comprehensive evaluation with more precise results.<sup>19</sup> Here, we concentrated on both the general population of coronary artery disease and subgroups (eg, patients with ACS) to increase the universality of the conclusions.

## Methods

The detailed protocol, which followed the template of a Cochrane review for multiple interventions is available in the PROSPERO registry (CRD42018099519).<sup>20</sup> This systematic review was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and the PRISMA extension statement for network meta-analysis.<sup>21 22</sup>

### Search strategy and selection criteria

We conducted a systematic search of the literature in April 2018. The databases included Medline, Embase, Cochrane Library for clinical trials, PubMed, and Web of Science. We also searched ClinicalTrials.gov and Clinicaltrialsregister.eu. The MeSH search terms included the following: drug eluting stents, percutaneous coronary intervention, platelet aggregation inhibitors, antiplatelet therapy, and aspirin. Our search strategy was tailored to each database (appendix 1).

We included randomised controlled trials that met the following criteria: participants were adults (aged  $\geq 18$ ) who received DAPT after PCI with DES; the interventions were candidate durations of DAPT (that

is, short term ( $\leq 6$  months), standard term (12 months), and long term ( $> 12$  months) DAPT); comparisons with another candidate duration were made; or the outcomes included death, myocardial infarction, stroke, and bleeding.

We excluded studies that met the following criteria:  $\leq 1$  month of DAPT, analyses of non-randomised trials, cross-sectional studies, case reports or case series, ongoing trials, or insufficient data from original studies.

The prespecified efficacy endpoints included all cause mortality, cardiac death, non-cardiac death, myocardial infarction, stroke, definite or probable stent thrombosis, and net adverse clinical events. The safety endpoint included major bleeding and any bleeding. The endpoint definitions applied in each trial (table B in appendix 3) were incorporated.

### Data extraction and risk of bias assessment

For each eligible randomised controlled trial, we extracted the study characteristics (eg, trial registration number, year of publication, first author, arms and treatment regimens, follow-up time, number of intention-to-treat patients, region), patient characteristics (eg, proportions of patients with ACS or diabetes, mean age), and outcome measures (table B in appendix 3). The reviewers independently screened the titles and abstracts of the retrieved studies in pairs (SHLY, PX, BW, HY) to exclude any that did not research the question of interest. Pairs of reviewers (SHLY, PX, BW, HY) then independently screened full texts of the remaining articles to identify studies that met all of the criteria for inclusion in the quantitative synthesis. We manually checked the reference list of each acquired article for relevant studies. For qualified trials, the data were extracted independently by pairs of reviewers (SHLY, PX, BW, HY), and the discrepancies were resolved by a third reviewer.

The quality of the included studies was assessed according to the Cochrane Collaboration's tool for assessing the risk of bias.<sup>23</sup> Any discrepancies were resolved by consensus, referring to the original articles and consulting with a third reviewer.

### Data synthesis and statistical analysis

We applied odds ratios and 95% confidence intervals to summary statistics to quantify the effects of different durations. Odds ratios greater than one represented an efficacy or safety benefit favouring the control duration. Two sided  $P < 0.05$  was considered significant.

We used a frequentist approach to conduct network meta-analyses, because of the complete graphical tools that depict the network geometry. We assumed a common heterogeneity variance across all pairwise comparisons and used the between studies variance  $\tau^2$  to present heterogeneity across the network. Estimates of  $\tau^2$  of approximately 0.04, 0.16, and 0.36 are considered to represent a low, moderate, and high degree of heterogeneity, respectively.<sup>24</sup> We statistically evaluated inconsistency between direct and indirect sources of evidence globally (by fitting

the inconsistency model) and locally (by calculating differences between direct and indirect estimates in closed loops),<sup>25</sup> and provided P values in table C of appendix 3. We used forest plots to present the results of odds ratios and 95% confidence intervals. We presented the treatment hierarchy (fig C in appendix 2) of all endpoints according to cumulative rank probabilities.<sup>26</sup> We assessed small study effects and potential publication bias with comparison-adjusted funnel plot symmetry.<sup>25</sup> We also conducted a pairwise meta-analysis with both a random-effects model of DerSimonian and Laird's method and a fixed effect model of Mantel and Haenszel's method, providing the direct estimates (fig A in appendix 2). Analyses were performed in STATA version 14.0 (StataCorp).

To validate the robustness of the findings, we performed a sensitivity analysis by restricting long term DAPT to  $\geq 18$  months of DAPT, as well as applying a random effects Bayesian network meta-analysis to account for methodological and clinical heterogeneity across studies.<sup>27</sup> We used Markov chain Monte Carlo methods with the GeMTC package (version 0.8-2) in R (version 3.4.4) to calculate odds ratios and 95% credible intervals. Three Markov chains were run simultaneously with 100 000 simulated draws after a burn-in of 50 000 iterations. Trace plots and the Brooks-Gelman-Rubin statistic were assessed to ensure convergence.<sup>28</sup> We evaluated consistency with a node-splitting technique that compares the direct and indirect estimates for each comparison.<sup>29</sup> Model fit was evaluated with the total residual deviance, which indicated good fit, if it approximated the number of data points (table D in appendix 3).

To further consider the effects of clinical presentations and stent technologies, we conducted subgroup analyses in the frequentist framework for patients with ACS and patients implanted with newer generation DES, by using published subpopulation data of the included trials.

### Quality of evidence

Additionally, we assessed the quality of evidence using the GRADE framework with GRADEpro GDT,<sup>30</sup> which characterises the quality of a body of evidence based on the study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations, for each outcome.<sup>31 32</sup> The GRADE approach rates the evidence as high, moderate, low, and very low quality. We also calculated the absolute effects in each comparison for all endpoints.<sup>33</sup>

### Patient and public involvement

No patients or the public were involved in setting the research question or designing the study, nor were they involved in the outcome measures or implementation of the study. No patients were asked to advise on the interpretation or writing of the results. There were no plans to disseminate the results of the research to the study participants or relevant patient communities. It was not evaluated whether the studies included in the review had any patient involvement. It was not

evaluated whether the studies included in the review had any patient involvement.

## Results

### Characteristics of included studies and bias assessment

Figure 1 shows that overall, 10 803 citations met the search criteria, and the full text of 59 potentially eligible articles was scrutinized. All available studies from trial registries were included in the database search, resulting in 17 studies of 18 parallel randomised controlled trials from 2010 to 2018 and including 46 864 participants (range 1259-9961 in each study).<sup>5-9 34-45</sup> The shortest duration of DAPT was three months and the longest duration was 48 months. Overall, 13 234 participants were randomly assigned to short term DAPT, 18 473 to standard term DAPT, and 15 157 to long term DAPT. All randomised controlled trials reported full clinical and demographic characteristics (table 1 and table A in appendix 3).

The risk of bias assessment was performed for each randomised controlled trial and summarised (table A in appendix 3). Most of the studies were in the lowest categories for risk of bias, random sequence generation (16/17, 94%), selective reporting (16/17, 94%), incomplete outcome data (15/17, 88%), and allocation concealment (13/17, 76%). A few studies were in the highest categories for risk of bias, blinding of participants and personnel (2/17, 12%), blinding of outcome assessment (4/17, 24%), and other bias (6/17, 35%). The category of unclear risk contained the most studies for other bias (10/17, 59%), blinding of participants and personnel (9/17, 53%), as well as blinding of outcome assessment (8/17, 47%).

### Outcomes of network meta-analysis

#### *All cause mortality, cardiac death, and non-cardiac death*

We evaluated all studies reporting all cause mortality and 11 studies with a total of 32 826 participants reporting cardiac death. Table 1 shows that we also deduced non-cardiac death from all cause mortality and cardiac death.

Although long term DAPT ( $>12$  months) resulted in more non-cardiac death than short term ( $\leq 6$  months) DAPT (odds ratio 1.63, 95% confidence interval 1.03 to 2.59,  $\tau^2=0.02$ ), all cause mortality and cardiac death showed no significant differences (1.18, 0.93 to 1.49, 0; 1.28, 0.88 to 1.86, 0). Figure 2 shows that standard term DAPT showed rates similar to those of short term DAPT for the three endpoints.

#### *Ischaemic and haemorrhagic endpoints*

Table 1 shows that all studies reported myocardial infarction, definite or probable stent thrombosis, and major bleeding, and 11 studies with 31 194 participants reported any bleeding.

Compared with short term DAPT, long term DAPT decreased the risk of ischemia, myocardial infarction, and definite or probable stent thrombosis. Simultaneously, the risk of major bleeding and any

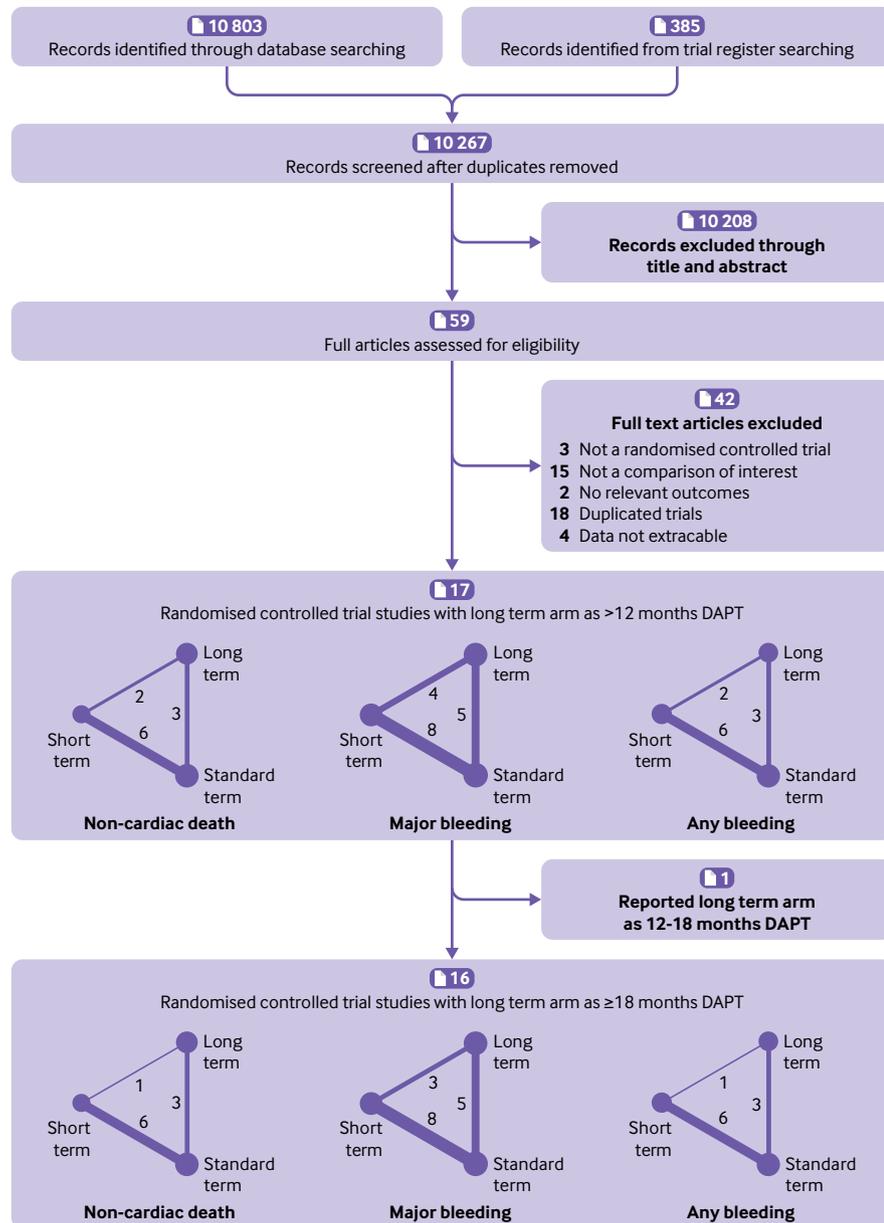


Fig 1 | Flowchart and network showing the procedure for identifying the relevant publications. Circular nodes show each treatment with the circle size indicating the total number of patients. The weight of the line and number on the line indicate the number of direct treatment comparisons within the same study

bleeding (odds ratio 0.63, 95% confidence interval 0.46 to 0.86,  $\tau^2=0.17$ ; 0.57, 0.34 to 0.95, 0.27; 1.78, 1.27 to 2.49, 0; 2.13, 1.46 to 3.10, 0.29) was increased. Standard term DAPT resulted in higher any bleeding than short term DAPT (1.39, 1.01 to 1.92, 0.29). Figure 2 shows that similar rates of myocardial infarction and definite or probable stent thrombosis were noted between standard term and short term DAPT.

#### Stroke and net adverse clinical events

Table 1 shows that all studies reported stroke and nine studies, with a total of 22 927 participants, reported net adverse clinical events. We noted that the three durations presented similar rates of these two outcomes.

#### Sensitivity analysis

The SMART-DATE trial compared short term versus long term DAPT, which might weaken the discrimination among three arms.<sup>44</sup> Thus, we excluded it to restrict the long term arm to ≥18 months of DAPT and generated a group of 16 studies with 44 152 patients. Figure 3 shows the results with more obvious differences, under both frequentist and Bayesian frameworks. Compared with short term DAPT, ≥18 months of DAPT resulted in higher rates of non-cardiac death (frequentist odds ratio 2.28, 95% confidence interval 1.35 to 3.86; Bayesian 2.34, 1.25 to 4.44), major bleeding (frequentist 1.79, 1.26 to 2.56; Bayesian 1.95, 1.28 to 3.39), and any bleeding (frequentist 2.46, 1.61 to 3.77; Bayesian 2.54, 1.48 to 4.63).

Table 1 | Effects of treatment on outcomes in 17 studies

| Months of DAPT                            | Participants | All cause mortality | Cardiac death | Non-cardiac death | Myocardial infarction | Definite or probable stent thrombosis | Stroke | Net adverse clinical events | Major bleeding | Any bleeding |
|---|--------------|---------------------|---------------|-------------------|-----------------------|---------------------------------------|--------|-----------------------------|----------------|--------------|
| <b>OPTIMA-C (Lee, 2018)</b>               |              |                     |               |                   |                       |                                       |        |                             |                |              |
| 6   | 683          | 2                   | 1             | 1                 | 1                     | 0                                     | 0      | NA                          | 1              | NA           |
| 12  | 684          | 3                   | 2             | 1                 | 1                     | 1                                     | 2      | NA                          | 1              | NA           |
| <b>I-LOVE-IT 2 (Han, 2016)</b>            |              |                     |               |                   |                       |                                       |        |                             |                |              |
| 6   | 909          | 11                  | 6             | 5                 | 41                    | 5                                     | 11     | 66                          | 11             | 50           |
| 12  | 920          | 14                  | 7             | 7                 | 36                    | 2                                     | 13     | 60                          | 6              | 52           |
| <b>IVUS-XPL study (Hong, 2016)</b>        |              |                     |               |                   |                       |                                       |        |                             |                |              |
| 6   | 699          | 5                   | 3             | 2                 | 1                     | 2                                     | 6      | 15                          | 5              | NA           |
| 12  | 701          | 10                  | 5             | 5                 | 0                     | 2                                     | 3      | 14                          | 7              | NA           |
| <b>ISAR-SAFE (Schulz-Schupke, 2015)</b>   |              |                     |               |                   |                       |                                       |        |                             |                |              |
| 6   | 1997         | 8                   | NA            | NA                | 13                    | 5                                     | 7      | 29                          | 2              | 27           |
| 12  | 2003         | 12                  | NA            | NA                | 14                    | 4                                     | 5      | 32                          | 8              | 55           |
| <b>SECURITY (Colombo, 2014)</b>           |              |                     |               |                   |                       |                                       |        |                             |                |              |
| 6   | 682          | 8                   | 5             | 3                 | 16                    | 2                                     | 6      | 31                          | 4              | 5            |
| 12  | 717          | 8                   | 3             | 5                 | 15                    | 3                                     | 2      | 27                          | 8              | 8            |
| <b>OPTIMIZE (Feres, 2013)</b>             |              |                     |               |                   |                       |                                       |        |                             |                |              |
| 3   | 1563         | 43                  | 29            | 14                | 49                    | 13                                    | 5      | 93                          | 10             | 35           |
| 12  | 1556         | 45                  | 32            | 13                | 42                    | 12                                    | 5      | 90                          | 14             | 45           |
| <b>EXCELLENT (Gwon, 2012)</b>             |              |                     |               |                   |                       |                                       |        |                             |                |              |
| 6   | 722          | 4                   | 2             | 2                 | 13                    | 6                                     | 3      | 24                          | 2              | 4            |
| 12  | 721          | 7                   | 3             | 4                 | 7                     | 1                                     | 5      | 21                          | 4              | 10           |
| <b>RESET (Kim, 2012)</b>                  |              |                     |               |                   |                       |                                       |        |                             |                |              |
| 3   | 1059         | 5                   | NA            | NA                | 2                     | 2                                     | 6      | NA                          | 2              | 5            |
| 12  | 1058         | 8                   | NA            | NA                | 4                     | 3                                     | 6      | NA                          | 6              | 10           |
| <b>SMART-DATE (Hahn, 2018)</b>            |              |                     |               |                   |                       |                                       |        |                             |                |              |
| 6   | 1357         | 35                  | 18            | 17                | 24                    | 15                                    | 11     | NA                          | 6              | 35           |
| 12.6 to 18                                | 1355         | 39                  | 24            | 15                | 10                    | 10                                    | 12     | NA                          | 10             | 51           |
| <b>NIPPON (Nakamura, 2017)</b>            |              |                     |               |                   |                       |                                       |        |                             |                |              |
| 6   | 1654         | 16                  | NA            | NA                | 4                     | 2                                     | 7      | 34                          | 11             | NA           |
| 18  | 1653         | 7                   | NA            | NA                | 1                     | 1                                     | 6      | 24                          | 12             | NA           |
| <b>ITALIC (Didier, 2017)</b>              |              |                     |               |                   |                       |                                       |        |                             |                |              |
| 6   | 926          | 11                  | 5             | 6                 | 12                    | 6                                     | 6      | NA                          | 0              | NA           |
| 24  | 924          | 20                  | 5             | 15                | 9                     | 3                                     | 7      | NA                          | 4              | NA           |
| <b>PRODIGY (Valgimigli, 2012)</b>         |              |                     |               |                   |                       |                                       |        |                             |                |              |
| 6   | 983          | 65                  | NA            | NA                | 41                    | 15                                    | 14     | NA                          | 6              | 34           |
| 24  | 987          | 65                  | NA            | NA                | 39                    | 13                                    | 21     | NA                          | 16             | 73           |
| <b>OPTIDUAL (Helft, 2015)</b>             |              |                     |               |                   |                       |                                       |        |                             |                |              |
| 12  | 690          | 24                  | NA            | NA                | 16                    | 1                                     | 7      | 52                          | 4              | 20           |
| 48  | 695          | 16                  | NA            | NA                | 11                    | 3                                     | 5      | 40                          | 4              | 18           |
| <b>DAPT Study (Mauri, 2014)</b>           |              |                     |               |                   |                       |                                       |        |                             |                |              |
| 12  | 4941         | 74                  | 47            | 27                | 198                   | 65                                    | 43     | NA                          | 26             | 137          |
| 30  | 5020         | 98                  | 45            | 53                | 99                    | 19                                    | 37     | NA                          | 38             | 263          |
| <b>DES LATE (Lee, 2014)</b>               |              |                     |               |                   |                       |                                       |        |                             |                |              |
| 12  | 2514         | 32                  | 19            | 13                | 27                    | 11                                    | 21     | 74                          | 24             | NA           |
| 36  | 2531         | 46                  | 28            | 18                | 19                    | 7                                     | 21     | 89                          | 34             | NA           |
| <b>ARCTIC-Interruption (Collet, 2014)</b> |              |                     |               |                   |                       |                                       |        |                             |                |              |
| 12  | 624          | 9                   | NA            | NA                | 9                     | 3                                     | 4      | NA                          | 1              | 3            |
| 18 to 30                                  | 635          | 7                   | NA            | NA                | 9                     | 0                                     | 6      | NA                          | 7              | 12           |
| <b>REAL-ZEST LATE (Park, 2010)</b>        |              |                     |               |                   |                       |                                       |        |                             |                |              |
| 12  | 1344         | 13                  | 8             | 5                 | 7                     | 4                                     | 4      | NA                          | 1              | NA           |
| 36  | 1357         | 20                  | 13            | 7                 | 10                    | 5                                     | 9      | NA                          | 3              | NA           |

DAPT=dual antiplatelet therapy; NA=not available

According to fig B2 in appendix 2, differences also presented between  $\geq 18$  months versus standard term DAPT in non-cardiac death (frequentist odds ratio 1.74, 95% confidence interval 1.23 to 2.47; Bayesian 1.71, 1.05 to 2.76), any bleeding (frequentist 1.68, 1.15 to 2.47; Bayesian 1.74, 1.02 to 2.82), and major bleeding (frequentist 1.39, 1.03 to 1.88; Bayesian 1.43, 0.99 to 2.27). These results indicated that the risk of non-cardiac death and bleeding increased synchronously when the duration of DAPT was increased.

Other endpoints presented similar efficacy and heterogeneity as the 17 studies group (fig 3, table C2 in appendix 3).

#### Subgroup analyses based on stent type and patient health

Newer-generation DES improve mortality and ischaemic outcomes compared with first-generation DES,<sup>46 47</sup> and patients with ACS have higher ischaemic risks than patients with stable coronary artery disease.<sup>48 49</sup> Thus, we regarded the patients with the

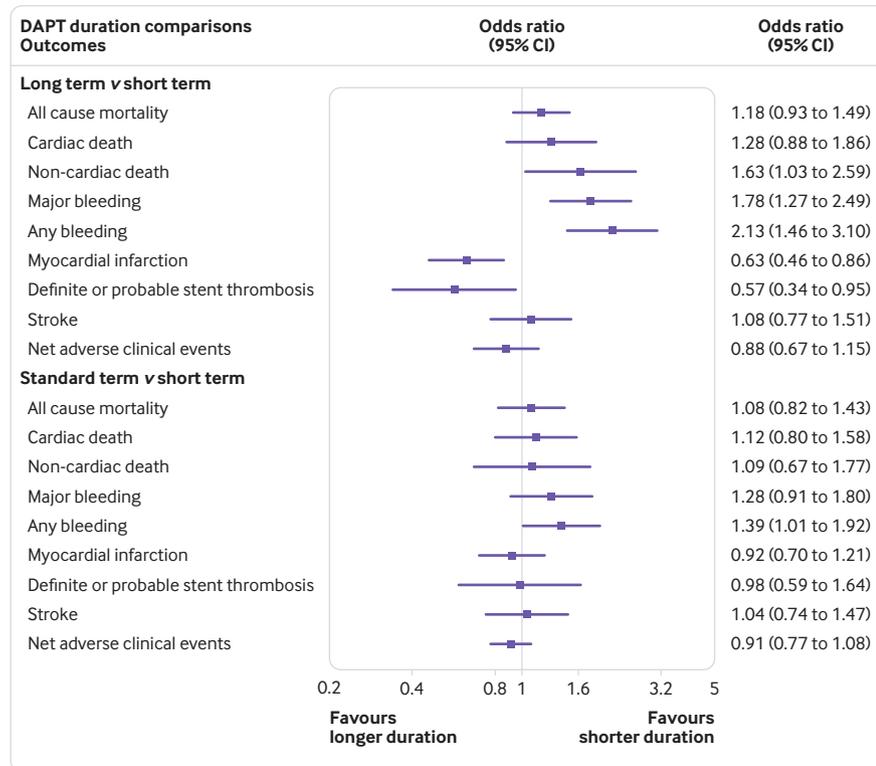


Fig 2 | Network meta-analysis results of all endpoints between two pairs of duration of DAPT

two conditions derived from subgroup or pooled analyses of pertinent randomised controlled trials respectively.

Table 2 shows that 11 trials reported endpoints of newer-generation DES subgroup with 23 753 participants, and eight trials reported endpoints of ACS subgroup with 12 376 participants. In long term DAPT, higher risks of all cause mortality (odds ratio 1.99, 95% confidence interval 1.04 to 3.81), major bleeding (1.88, 1.03 to 3.45), and any bleeding (1.79, 1.28 to 2.50) were observed when compared with short term DAPT in the newer-generation DES subgroup, and merely an increased risk of any bleeding (1.73, 1.11 to 2.69) was noted in the ACS subgroup. Figure 4 shows that no significant difference was obtained for all endpoints between standard term and short term DAPT, in both subgroups.

Therefore, long term DAPT might be associated with increased all cause mortality in patients implanted with newer-generation DES, and short term DAPT might be non-inferior to standard term DAPT independent of DES generation and clinical presentation.

#### Network coherence and quality of evidence

There was no noticeable difference between direct and indirect estimates in closed loops that allowed the assessment of network coherence in all endpoints (table C in appendix 3). The total residual deviance for the outcomes of all endpoints (table D in appendix 3) suggested a good model fit in the sensitivity analysis under the Bayesian framework. We verified the convergence of chains visually in the trace plots and

by inspecting the Brooks-Gelman-Rubin diagnostic statistic with values of approximately one.<sup>28</sup>

A summary of the quality assessment of endpoints by the GRADE criteria was presented in table E in appendix 3. The quality of endpoints was determined to be moderate and high for most of the comparisons. Non-cardiac death and major bleeding were rated high.

#### Discussion

##### Principal findings

In our meta-analysis, which included 17 studies and 46 864 patients, we analysed the comparative efficacy and safety of three durations of DAPT after PCI with DES. We applied frequentist and Bayesian frameworks in intention-to-treat populations to increase confidence in our findings.

In patients with all clinical presentations, firstly, long term DAPT led to a higher risk of non-cardiac death and major bleeding than short term DAPT in patients, and the discrimination was more noticeable when restricting long term DAPT to  $\geq 18$  months. Secondly, myocardial infarction and stent thrombosis showed no obvious difference between short term and standard term DAPT, and standard term DAPT increased the risk of any bleeding. Thirdly, the risk of non-cardiac death and bleeding increased synchronously with increasing durations of DAPT. Fourthly, all cause mortality, cardiac death, stroke, and net adverse clinical events presented similar risks for the three durations.

In both subgroups of newer-generation DES and patients with ACS, long term DAPT was associated with higher bleeding events than short term DAPT, and

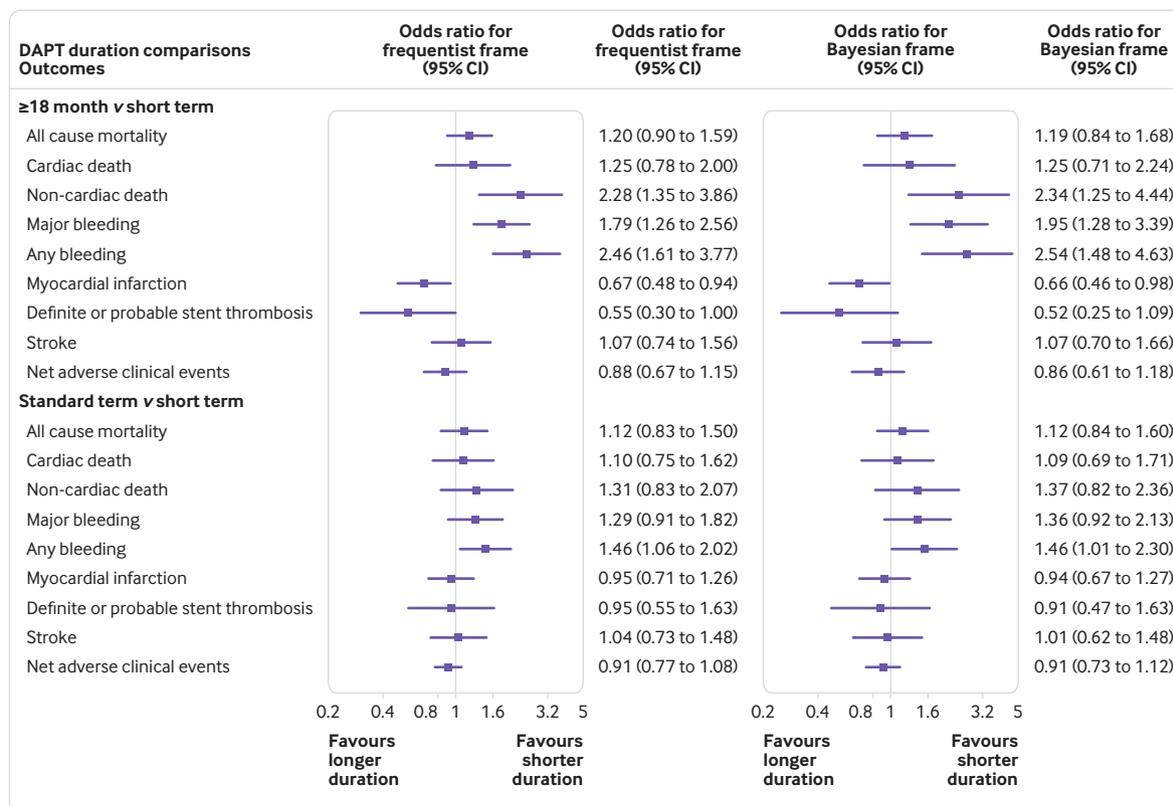


Fig 3 | Network meta-analysis results of all endpoints between two pairs of duration of DAPT

short term DAPT showed similar efficacy and safety to standard term DAPT. Long term DAPT resulted in increased all cause mortality compared with short term DAPT in the newer-generation DES subgroup.

#### Comparison with other studies

Previous trials and pairwise meta-analyses, which were limited to two durations of DAPT as extended term or short term, failed to find disparate risks of mortality for different durations.<sup>56 57</sup> Palmerini and colleagues conducted an individual patient data study showing variant ischaemic risks of three months of DAPT between patients with ACS and stable coronary artery diseases.<sup>11</sup> However, the population of patients with ACS was 4758, which might affect the confidence in the conclusion. Another network meta-analysis studying the impacts of stent types and duration of DAPT, might be limited in clinical practice, owing to too many arms introduced.<sup>58</sup>

In our pooled analysis, we studied short term, standard term, and long term DAPT in both the general population of coronary artery disease and subgroups of patients with newer-generation DES or ACS to evaluate durations of DAPT in a succinct way.

#### Short term versus long term DAPT

NIPPON investigators reported that 18 months of DAPT seemed to incur less all cause mortality than six months of DAPT (7/1653 v 16/1654).<sup>9</sup> However, a meta-analysis based on 10 randomised controlled trials concluded that a DAPT duration of more than one

year was associated with increased mortality because of an increased risk of non-cardiovascular mortality.<sup>59</sup> Another systematic review of 11 randomised controlled trials concluded that 18 to 48 months of DAPT showed no difference in all cause mortality compared with six to 12 months of DAPT.<sup>60</sup>

Our results support that non-cardiac death, instead of non-cardiovascular death, occurred less frequently with short term DAPT than with long term DAPT, and this effect was more apparent when long term DAPT was restricted to ≥18 months. This finding indicates that vascular death (such as death caused by cerebrovascular disease, dissecting aneurysm, or other vascular diseases)<sup>61</sup> might play a role in long term DAPT. We also found that the risks of non-cardiac death and bleeding increased synchronously with prolonged duration of DAPT; this finding is supported by a study that reported shorter durations of DAPT were associated with a lower risk of bleeding-related death than longer durations of DAPT.<sup>10</sup> Additionally, long term DAPT was related to a higher risk of all cause mortality in patients implanted with newer-generation DES, compared with short term DAPT.

#### Short term versus standard term DAPT

Randomised controlled trials have always concluded that short term DAPT was non-inferior to standard term DAPT.<sup>5-8 35 37 40 42 44 62</sup> Piccolo's analysis of 38919 patients reported that long term DAPT exposure showed increased major adverse cardiac and cerebrovascular events (MACCE) through 90 days after

Table 2 | Effects of treatments on outcomes in subgroups of patients

| Original study                   | Subgroup characteristic                           | Subgroup reference             | Months of DAPT treatment | Total | All cause mortality | Myocardial infarction | Definite or probable stent thrombosis | Major bleeding | Any bleeding |
|----------------------------------|---|--------------------------------|--------------------------|-------|---------------------|-----------------------|---------------------------------------|----------------|--------------|
| <b>Newer-generation DES</b>      |   |                                |                          |       |                     |                       |                                       |                |              |
| OPTIMA-C (Lee, 2018)             | BES/ZES   | Lee, 2018 <sup>7</sup>         | 6                        | 683   | 2                   | 1                     | 0                                     | 1              | NA           |
|                                  |   |                                | 12                       | 684   | 3                   | 1                     | 1                                     | 1              | NA           |
| I-LOVE-IT 2 (Han, 2016)          | BP-SES  | Han, 2016 <sup>8</sup>         | 6                        | 909   | 11                  | 41                    | 5                                     | 11             | 50           |
|                                  |   |                                | 12                       | 920   | 14                  | 36                    | 2                                     | 6              | 52           |
| IVUS-XPL study (Hong, 2016)      | EES   | Hong, 2016 <sup>42</sup>       | 6                        | 699   | 5                   | 1                     | 2                                     | 5              | NA           |
|                                  |   |                                | 12                       | 701   | 10                  | 0                     | 2                                     | 7              | NA           |
| SECURITY (Colombo, 2014)         | ZES/BES/EES                                       | Colombo, 2014 <sup>37</sup>    | 6                        | 682   | 8                   | 16                    | 2                                     | 4              | 5            |
|                                  |   |                                | 12                       | 717   | 8                   | 15                    | 3                                     | 8              | 8            |
| OPTIMIZE (Feres, 2013)           | ZES   | Feres, 2013 <sup>35</sup>      | 3                        | 1563  | 43                  | 49                    | 13                                    | 10             | 35           |
|                                  |   |                                | 12                       | 1556  | 45                  | 42                    | 12                                    | 14             | 45           |
| EXCELLENT (Gwon, 2012)           | EES   | Gwon, 2012 <sup>5</sup>        | 6                        | 540   | 3                   | 9                     | 3                                     | 2              | 3            |
|                                  |   |                                | 12                       | 539   | 4                   | 6                     | 1                                     | 3              | 9            |
| SMART-DATE (Hahn, 2018)          | EES/ZES/BES                                       | Hahn, 2018 <sup>44</sup>       | 6                        | 1357  | 35                  | 24                    | 15                                    | 6              | 35           |
|                                  |   |                                | 12.6 to 18               | 1355  | 39                  | 10                    | 10                                    | 10             | 51           |
| NIPPON (Nakamura, 2017)          | BES   | Nakamura, 2017 <sup>9</sup>    | 6                        | 1654  | 16                  | 4                     | 2                                     | 11             | NA           |
|                                  |   |                                | 18                       | 1653  | 7                   | 1                     | 1                                     | 12             | NA           |
| ITALIC (Didier, 2017)            | EES   | Didier, 2017 <sup>43</sup>     | 6                        | 926   | 11                  | 12                    | 6                                     | 0              | NA           |
|                                  |   |                                | 24                       | 924   | 20                  | 9                     | 3                                     | 4              | NA           |
| PRODIGY (Valgimigli, 2012)       | ZES/EES   | Valgimigli, 2013 <sup>50</sup> | 6                        | 492   | 25                  | 12                    | 1                                     | 25             | NA           |
|                                  |   |                                | 24                       | 496   | 30                  | 16                    | 4                                     | 30             | NA           |
| DAPT Study (Mauri, 2014)         | EES   | Hermiller, 2016 <sup>51</sup>  | 12                       | 2358  | 26                  | 72                    | 16                                    | 7              | 30           |
|                                  |   |                                | 30                       | 2345  | 49                  | 48                    | 6                                     | 21             | 57           |
| <b>Patient health</b>            |   |                                |                          |       |                     |                       |                                       |                |              |
| ISAR-SAFE (Schulz-Schupke, 2015) | Acute coronary syndrome                           | Lohaus, 2016 <sup>52</sup>     | 6                        | 794   | 5                   | 6                     | 2                                     | 1              | 3            |
|                                  |   |                                | 12                       | 807   | 7                   | 8                     | 2                                     | 2              | 5            |
| IVUS-XPL study (Hong, 2016)      | Acute coronary syndrome with 2nd generation stent | Jang, 2018 <sup>53</sup>       | 3 to 6                   | 1119  | 9                   | 7                     | 6                                     | 4              | 9            |
|                                  |   |                                | 12                       | 1097  | 11                  | 9                     | 4                                     | 6              | 14           |
| RESET (Kim, 2012)                |   |                                |                          |       |                     |                       |                                       |                |              |
| SMART-DATE (Hahn, 2018)          | Acute coronary syndrome                           | Hahn, 2018 <sup>44</sup>       | 6                        | 1357  | 15                  | 24                    | 15                                    | 6              | 35           |
|                                  |   |                                | 12.6 to 18 months        | 1355  | 10                  | 10                    | 10                                    | 10             | 51           |
| ITALIC (Didier, 2017)            | Acute coronary syndrome                           | Didier, 2017 <sup>43</sup>     | 6                        | 400   | 4                   | 7                     | 5                                     | 0              | NA           |
|                                  |   |                                | 24                       | 406   | 9                   | 6                     | 3                                     | 2              | NA           |
| PRODIGY (Valgimigli, 2012)       | Acute coronary syndrome                           | Costa, 2015 <sup>54</sup>      | 6                        | 733   | 56                  | 39                    | 5                                     | 6              | 3            |
|                                  |   |                                | 24                       | 732   | 52                  | 33                    | 10                                    | 9              | 18           |
| DAPT Study (Mauri, 2014)         | Acute myocardial infarction                       | Yeh, 2015 <sup>55</sup>        | 12                       | 1711  | 27                  | 88                    | 32                                    | 9              | 35           |
|                                  |   |                                | 30                       | 1805  | 24                  | 39                    | 9                                     | 13             | 76           |

DAPT=dual antiplatelet therapy; NA=not available

DAPT continuation which was not observed in <12 months of DAPT.<sup>63</sup> However, several studies showed that long term DAPT was associated with similar major adverse cardiac events and a higher risk of bleeding after PCI with DES compared with short term DAPT, regardless of diabetes diagnosis or sex.<sup>18 57 64</sup>

We extracted data regarding net adverse clinical events, a pooled outcome including MACCE and major bleeding, and found no difference among the three durations, which is supported by Palmerini's individual patient data meta-analysis.<sup>11</sup> In our analysis, the risk of bleeding was higher in standard term DAPT than in short term DAPT, and other endpoints (including ischemia-related and death-related endpoints) were noted with similar rates. Thus, compared with standard term DAPT, short term DAPT might present superiority with higher safety and similar efficacy in the general population of coronary artery disease. However, in subgroups of patients with newer-generation DES or ACS we did not observe a noticeable difference between short term and standard term DAPT for all endpoints.

### Strengths and limitations of this study

The main strength of our study is that we divided the durations of DAPT into three categories with short term ( $\leq 6$  months) DAPT as a control. With a combination of direct and indirect comparisons, network meta-analysis often leads to substantially more precise summary results.<sup>19</sup> The frequentist results were confirmed in in Bayesian framework. Thus, these findings have robust statistical consistency. Furthermore, although the reviewed randomised controlled trials covered the past years of research, heterogeneity was low across trials. We tried our best to extract original data from each study and performed post hoc subgroup analyses according to these data.

This study has several limitations. Firstly, we primarily evaluated durations of DAPT based on clopidogrel, so the conclusion might vary when applying other P2Y<sub>12</sub> inhibitors such as prasugrel and ticagrelor. Secondly, we performed analyses of outcomes from different trials with pooled definitions. Thirdly, several endpoints were not reported by a few

trials, like cardiac death (RESET, OPTIDUAL, and NIPPON trial reported cardiovascular death only), which might partly explain the slight divergence between results under the frequentist and Bayesian frameworks.

### Policy implications

Standard term (12 months) DAPT was the recommended duration for most patients in guidelines published between 2011 and 2014. However, some factors are important in determining the duration of DAPT, such as whether a patient has ACS, type of DES, and bleeding and ischaemic risks.<sup>3 65</sup> Therefore, the current American College of Cardiology/American Heart Association guideline presented critical questions to choose among three to six months, 12 months, and more than 12 months of DAPT according to variant factors.<sup>3</sup>

According to our analysis, three to six months of DAPT with clopidogrel presented similar efficacy and safety to 12 months of DAPT in patients treated with newer-generation DES and patients with ACS, without considering personal haemorrhagic profiles. Though the guidelines recommended six months of DAPT to patients with ACS only when high bleeding risks were considered.<sup>23</sup> Moreover, in a broader spectrum including patients with ACS and stable coronary artery disease, three to six months of DAPT was associated with higher safety than 12 months of DAPT. The present findings suggest additional benefit of three to six months of DAPT.

Additionally, compared with three to six months, long term DAPT was associated with higher all cause mortality in patients implanted with newer-generation DES, as well as higher non-cardiac death in the general population of patients with coronary artery disease. Therefore, it might be reasonable to apply long term DAPT to a narrower spectrum of patients.

### Conclusion

Our comprehensive network meta-analysis provides evidence that short term DAPT (with clopidogrel) could be considered for most patients after PCI with DES. Long term DAPT resulted in more death and bleeding-related events, and standard term DAPT presented similar efficacy and safety. Further studies, such as prespecified randomised controlled trials of patients with newer-generation DES and ACS are required to validate the rationality of short term DAPT after PCI with DES.

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submission. QYW, MLZ, and JRW contributed equally to the work. SHLY, HY, JJC, and XS participated in the formal revision, including data processing, statistical analysis, generating figures and tables, and text modification. All authors had full access to the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. HY is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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**Supplementary materials:** Search strategy  
**Supplementary materials:** Supplementary figures  
**Supplementary materials:** Supplementary tables