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Optimum duration of dual antiplatelet therapy followed by monotherapy for diabetes after percutaneous coronary intervention with drug-eluting stent implantation: a Bayesian network meta-analysis

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Short title: Duration of dual antiplatelet therapy for diabetes after PCI with DES

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Key words: diabetes; drug-eluting stent; dual antiplatelet therapy; network meta-analysis; percutaneous coronary intervention
**What’s new?**

What is the optimum duration of dual antiplatelet therapy (DAPT) for diabetes patients with a drug-eluting stent implantation that is associated with the lowest risk of complications? This network meta-analysis included 18 studies comparing DAPT of four different durations and found that short-term (≤3 months) DAPT was associated with the best treatment response and lowest complication risk. The findings of this study suggest that short-term DAPT is the most beneficial for diabetes patients who have undergone percutaneous coronary intervention with drug-eluting stent implantation.
Abstract

Introduction: The standard 12-month dual antiplatelet therapy (DAPT) following percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation that is recommend for the general population may not be suitable for diabetes patients.

Objectives: To evaluate the efficacy and safety of short-term (≤3 months), midterm (6 months), standard-term (12 months), and extended-term (>12 months) DAPT in diabetes patients with DES implantation. To compare discontinuation of DAPT followed by monotherapy with aspirin versus P2Y12 inhibitor.

Patients and Methods: Randomized controlled trials were searched using PubMed, Web of Science, Embase, Cochrane library, and clinicaltrials.gov up to October 10, 2020. A Bayesian network meta-analysis was conducted with a random-effects model. A total of 18 randomized trials including 20,536 diabetes patients were included.

Results: The network analysis showed that short-term DAPT was the best for reducing the primary endpoint and was superior to extended-term DAPT (odds ratio [OR] 0.48, 95% CI: 0.25–0.85). Standard-term DAPT was also associated with a reduced primary endpoint in comparison with extended-term DAPT (OR 0.56, 95% CI: 0.32–0.90). There was no noticeable difference with respect to the primary endpoint between short-term DAPT followed by aspirin monotherapy and P2Y12 inhibitor monotherapy. No significant differences were observed in secondary endpoints, including all-cause mortality, cardiac mortality, myocardial infarction, stroke, target vessel revascularization, definite or probable stent thrombosis, and major bleeding event.

Conclusions: Short-term DAPT was associated with better primary endpoint benefit for patients with diabetes after PCI with DES than extended-term DAPT.
Introduction

Diabetes mellitus patients have a high risk of developing severe coronary artery disease, and the incidence of postoperative adverse clinical events is higher in this population than that in the general population[1, 2]. Dual antiplatelet therapy (DAPT) involves administration of aspirin and a P2Y12 inhibitor, and DAPT is the main treatment to prevent stent thrombosis and reduce ischemic events after percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation[3, 4]. DAPT is associated with hemorrhage as an adverse effect; therefore, it is important to determine the optimum duration of DAPT to achieve maximum protection against ischemia without the risk of hemorrhage[5]. Standard DAPT following DES implantation involves administration of clopidogrel for 6–12 months, and diabetes patients are typically administered hypoglycemic and hypolipemic drugs that could cause platelet inhibition, such as statins, which are also metabolized in the liver by the same cytochrome P450 isoenzyme 3A4 pathway as clopidogrel. Combined with impaired glucose metabolism in diabetes patients and the risk of glucose fluctuation, current clinical practice guidelines do not recommend this DAPT regimen for diabetes patients[6].

Furthermore, there is no consensus on the duration of DAPT in diabetes [7, 8]. Multiple randomized clinical trials (RCTs) and observational studies have reported contradictory results regarding the duration of DAPT for diabetes patients[9, 10, 11]. A previous meta-analysis study showed no significant difference between extended and short-term DAPT regimens in adverse clinical outcomes among diabetes mellitus patients, except that the extended DAPT regimen resulted in increased bleeding[12, 13]. Yet the importance of considering preexisting diabetes in determining the optimal duration of DAPT remains unclear. It is not established whether discontinuing DAPT and switching to monotherapy with
aspirin or a P2Y12 inhibitor increase safety and efficacy outcomes, and currently no head-to-head RCTs have been conducted to verify this point[14]. Therefore, we conducted this trial-level network meta-analysis (NMA) on studies that employed various DAPT durations to identify the optimum duration of DAPT and to study whether discontinuation of DAPT followed by appropriate monotherapy is beneficial for diabetes patients.

1. Patients and methods

The protocol was registered on PROSPERO (CRD42021231387).

2.1 Search strategy and data sources

An electronic search was conducted systematically for literature published from inception up to October 10, 2020 on PubMed, Embase, Web of Science, clinicaltrials.gov, and the Cochrane Library databases. References of related articles were also searched to ensure the integrity of the data as far as possible. The following search terms were used: “dual antiplatelet,” “drug-eluting stent,” “percutaneous coronary intervention,” and “randomized controlled trial.” The detailed search strategy is provided in Supplementary material, Table S1.

2.2 Inclusion and exclusion criteria

Retrieved articles were screened based on the following predefined inclusion criteria: (1) studies were clinical RCTs; (2) participants were adults with diabetes mellitus who received DAPT after PCI with DES; (3) multiple durations of DAPT, such as short-term (≤6 months), standard-term (12 months), and extended-term (>12 months) regimens, were tested; (4) outcomes reported were primary endpoint, all-cause mortality, cardiac mortality, myocardial
infarction (MI), stroke, target vessel revascularization (TVR), stent thrombosis, and bleeding events; (5) the study included a follow-up of at least 12 months.

Studies that met the following criteria were excluded: (1) a pharmacokinetic or pharmacodynamic study, meta-analysis, observational research, case study, or editorial; (2) patients involved did not have diabetes mellitus; (3) the study did not set adverse events as a clinical endpoint; (4) the study involved identical or reduplicate trials.

2.3 Data extraction and quality evaluation

Two independent investigators (KA and PG) assessed the published articles, adjudicated the data, and reviewed the methodological quality of each eligible study. Any disagreement during the data extraction process was resolved by discussion with a third researcher (SHW). Data on trial name, year of publication, sample size, treatment and control groups, outcomes, clinical events reported in the diabetes group, and follow-up period were obtained. Risk of bias among the trials was assessed by Risk of Bias 2 according to the Cochrane Collaboration’s tool[15], which contains preliminary considerations, signaling questions, and five domains plus overall risk of bias: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result, and ‘Overall risk of bias.’ Articles were categorized as having low risk, some concerns, or high risk of bias.

2.4 Statistical analysis

We performed Bayesian NMA with a random effects model using the Markov chain Monte Carlo (MCMC) method. The Gemtc package was run in R to call the JAGS software to achieve the Bayesian NMA. The effects of different durations of DAPT were analyzed by the odds ratio (OR) and 95% confidence interval (CI) to produce summary statistics.
non-informative uniform and normal prior distributions[16], the initial values were set for four different chains, and 100,000 interactions with 50,000 burn-in samples were produced to obtain the model parameters from the posterior distributions, and one thinning rate was adopted for each chain. Convergence was assessed using trace plots and the Brooks-Gelman-Rubin method to check if the error was <5% of the standard deviation of the effect estimates and between-study variance[17]. The estimates of Bayesian NMA were reported as rank probabilities to identify the relative rankings of DAPT duration based on the surface under the cumulative ranking curve (SUCRA), ranging from 0% (statistically certain to be the worst treatment) to 100% (statistically certain to be the best treatment)[18, 19, 20].

Heterogeneity was examined with the Cochrane’s Q statistic and quantified with the inconsistency statistic (I²), which was considered as low, moderate, or high for I² values under 25%, between 25% and 50%, and over 50%, respectively[21]. A value of P less than 0.05 was considered to indicate statistical significance.

Inconsistency was analyzed by the Gemtc package in R, comparing the deviance residuals and deviance information criterion statistics in fitted consistency and inconsistency models to identify any loops in the treatment network where inconsistency existed[22]. The node splitting approach was also used to assess the inconsistency of the model, in which direct and indirect evidence was separately contrasted for a particular comparison. To validate the robustness of the findings, sensitivity analyses were conducted on the stratification of monotherapy after short-term DAPT, exclusion of trials with high risks of bias, type of P2Y12 inhibitor, and trials with a large number of patients that may limit the generalizability of the achieved results were excluded. The 95% CI that does not cross 1 was considered as statistically significant. All statistical analyses were performed using R 3.6.3 (R Foundation
2.5 Outcome variables

Outcomes consisted of primary and secondary outcomes. We incorporated definitions of the primary outcome as applied in each trial. The secondary outcomes were the individual components of the primary outcome, containing all-cause mortality, cardiac mortality, MI, stroke, TVR, definite or probable stent thrombosis, and major bleeding. Stent thrombosis was defined according to criteria from the academic research consortium[23]. The other outcomes are defined in Supplementary material, Table S2 and S3.

2.6 Ethics

This network meta-analysis does not require the approval by the ethics committee or an appropriate institutional review board.

2. Results

3.1 Search results and study characteristic

Of 3506 articles, 652 were excluded after removing duplicates, 2830 were excluded after reviewing the title and abstract, and additional six studies were excluded because they contained unpublished data, were observational trials, or could not be grouped appropriately [24, 25, 26, 27, 28, 29] (Figure 1). Eighteen trials were ultimately included with a total of 20536 diabetes patients randomly assigned to receive either short-term (≤3 months), midterm (6 months), standard-term (12 months), or extended-term (>12 months) DAPT regimens [10, 11, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45]. Besides, the outcomes of short-term DAPT followed by aspirin monotherapy in comparison with P2Y12 monotherapy
were compared. The characteristics of included RCTs for the NMA are shown in Table 1. Detailed inclusion and exclusion criteria of trials are presented in Supplementary material, Table S4.

3.2 Quality of evidence

Detailed risk of bias assessments are summarized in Supplementary material, Figure S1. The overall heterogeneity assessment of the results showed that the heterogeneity varied from low to moderate for cardiac mortality ($I^2 = 0\%$), stroke ($I^2 = 0\%$), TVR ($I^2 = 6.27\%$), major bleeding ($I^2 = 0\%$), primary endpoint ($I^2 = 28.75\%$), all-cause mortality ($I^2 = 28.19\%$), MI ($I^2 = 25.51\%$). High heterogeneity was detected in comparisons of stent thrombosis (definite or probable) ($I^2 = 64.76\%$), although the 95% CIs showed that this heterogeneity was not statistically significant. Feasible pairwise comparisons with heterogeneity estimates were generated and are shown in Supplementary material, Table S5.

The fit of the consistency model was similar to or better than that of the inconsistency model (Supplementary material, Table S6). Inconsistency between the direct and indirect estimates of the node splitting analysis did not show significant differences in each comparison (Supplementary material, Table S7). The convergence diagnosis model could be used to effectively predict the data. We evaluated the convergence of iterations by visual inspection of the chains to establish homogenous parameter estimates and to comply with the Brooks–Gelman–Rubin diagnostic standard (Supplementary material, Figure S2).

3.3 NMA

3.3.1 Efficacy and safety

Network plots for different outcomes were generated to illustrate the geometries to clarify which treatments were compared directly or indirectly in the included studies[46]. The
network evidence plot of the primary endpoint is shown in Figure 2, and that of short-term DAPT followed by P2Y12 inhibitor or aspirin monotherapy and secondary outcomes is shown in Supplementary material, Figure S3. Results pertaining to NMA of the primary endpoint using the random-effects model are summarized in Table 2. Results of the NMA of other clinical events are shown in Supplementary material, Table S8.

3.3.2 Primary endpoint

Short-term DAPT and standard-term DAPT were associated with a lower risk of primary endpoint (OR 0.48, 0.25–0.85 and 0.56, 0.32–0.9, respectively) than extended-term DAPT, whereas midterm DAPT showed no significant difference (OR 0.62, 0.33–1.06). Furthermore, short-term DAPT followed by aspirin monotherapy did not significantly differ from short-term DAPT followed by P2Y12 inhibitor monotherapy in terms of primary endpoint (OR 1.12, 0.66–1.84). According to the accumulative rankings by SUCRA, we found that the possible best treatment with an improved primary endpoint was short-term DAPT, while the effect was consistent with midterm and standard-term DAPT. The worst treatment was the extended-term DAPT.

3.3.3 Secondary outcomes

All-cause mortality was similar for all four DAPT durations. No noticeable difference was also observed in terms of cardiac mortality. MI or stroke incidence with standard-term DAPT was also not significantly different from that with extended-term DAPT, midterm DAPT, and short-term DAPT. Similarly, the number of cases of definite or probable stent thrombosis with standard-term DAPT was not significantly different from that with extended-term DAPT, midterm DAPT, and short-term DAPT. A similar trend was also observed for TVR. Major bleeding incidence also did not significantly differ between the different DAPT regimens.
3.3.4 Ranking probabilities

Figure 3 shows the ranking probabilities for all treatments included (the detailed ranking results for other outcomes are summarized in Supplementary material, Table S9 and Figure S4). For the treatment effect of ameliorating the primary endpoint, short-term DAPT and standard-term DAPT ranked first with the highest probability (72.18% and 63.55%, respectively), whereas midterm and extended-term DAPT ranked last (62.84% and 95.32%, respectively). For the effect of reducing all-cause mortality, midterm DAPT ranked first with the highest probability (37.59%), whereas extended-term DAPT ranked last (53.43%). Regarding incidence of less cardiac mortality and MI, short-term DAPT ranked first with the highest probability (42.98% and 64.05%, respectively), whereas midterm DAPT ranked last (52.57% and 54.27%, respectively). According to the analysis of stroke and TVR, midterm DAPT (76.61%) and standard-term DAPT (44.92%) had the highest probability of achieving a good prognosis, whereas short-term and midterm DAPT had the lowest probability (46.15% and 43.52%, respectively). Short-term DAPT was the most appropriate treatment strategy ranking first in the effect of delaying the progression of definite or probable stent thrombosis (52.67%), whereas midterm DAPT ranked last (81.18%). Midterm DAPT was the most favorable treatment for postponing major bleeding events in diabetes patients (59.08%), whereas extended-term DAPT achieved the worst outcome (89.32%).

3.4 Sensitivity analyses

Sensitivity analyses did not indicate any influence of the estimates in terms of primary endpoint, all-cause mortality, cardiac mortality and myocardial infarction (Table S10 and S11). Regarding the effect of improving the primary endpoint, all-cause mortality, cardiac mortality, myocardial infarction, and definite or probable stent thrombosis, short-term DAPT
followed by P2Y12 inhibitor monotherapy still ranked first with the highest probability. One-month DAPT followed by P2Y12 inhibitor monotherapy (50.2%) was potentially associated with better primary endpoint than other durations of DAPT. Although the effect was not consistent between midterm DAPT and extended-term DAPT in terms of stroke, sensitivity analyses did not indicate any significant statistical difference.

3. Discussion

In this NMA, which included 18 randomized trials covering 20,536 patients, we comprehensively summarized and analyzed the comparative efficacy and safety of various durations of DAPT for diabetes patients who have undergone PCI with DES. The results showed that short-term DAPT had the highest cumulative probability of ranking first in improving the primary endpoint. Analysis of primary endpoint data showed that short-term DAPT and standard-term DAPT were significantly better than extended-term DAPT. In addition, short-term DAPT followed by P2Y12 inhibitor monotherapy had a potential advantage over short-term DAPT followed by aspirin monotherapy regarding primary endpoint. There was no obvious statistical difference in secondary outcomes between the treatment regimens. In terms of cardiac mortality, MI, and definite or probable stent thrombosis, short-term DAPT had the greatest probability of ranking first (lowest cardiac mortality, lowest MI, and lowest definite or probable stent thrombosis), and midterm DAPT had the greatest probability of ranking last (highest cardiac mortality, highest MI, and highest definite or probable stent thrombosis). According to the evaluation of all-cause mortality, stroke, and major bleeding among diabetes patients, we found that midterm DAPT had the highest probability of achieving a good prognosis. Regarding TVR, standard-term DAPT had
the highest probability. These results were consistent with the results of the sensitivity analysis regarding primary endpoint, all-cause mortality, cardiac mortality, myocardial infarction, and definite or probable stent thrombosis. Our findings suggest the prognostic significance of optimal DAPT duration in diabetes patients who have undergone PCI with DES.

Our current study indicated that short-term DAPT was associated with better primary endpoint and that there was no difference with respect to stent thrombosis or major bleeding events between short-term and extended-term DAPT, which disregards the traditional notion that diabetes patients, as a high-risk population, should receive DAPT for a prolonged period to reduce the risk of revascularization and to achieve better prognosis. Our results were consistent with those of RCTs indicating that diabetes patients do not gain extra benefit from prolonged DAPT [31, 38], whereas a large-scale trial favored extended-term DAPT owing to the lower rates of MI [33]. Furthermore, an observational study showed that diabetes patients who received prolonged DAPT had a lower risk of death or MI [9].

The finding could be explained based on several points as mentioned below. Firstly, although diabetes patients are reported to response poorly to clopidogrel [47], our previous meta-analysis showed that statins do not influence platelet activation and aggregation in patients receiving clopidogrel[43]. Furthermore, with refinements in DES technologies and the application of new degradable stents, it has become possible to shorten the duration of DAPT rather than reduce the risk of thrombosis at the expense of increasing bleeding risk in high-risk diabetes patients[48].

A number of recent clinical trials have explored the efficacy and safety of long-term monotherapy with P2Y12 inhibitors after short-term DAPT (≤3 months) after PCI among the
general population, including STOPDAPT-2 (ShorT and OPtimal duration of Dual AntiPlatelet Therapy-2)[42], TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention)[45], SMART-CHOICE (SMart Angioplasty Research Team: Comparison between P2Y12 antagonist monotherapy and dual antiplatelet therapy in patients undergoing implantation of coronary drug-eluting stents)[43]. Such reports make clinicians consider the possibility of stopping aspirin when DAPT is converted to monotherapy. The mentioned studies, which were based on the comparison of P2Y12 inhibitor monotherapy and long-term DAPT (12–15 months), do not provide a direct answer as to monotherapy with which agent is better, aspirin or P2Y12 receptor inhibitor, for PCI patients who have previously received DAPT. A recent NMA, which included 17 RCTs with a total of 54,625 patients, also reported the absence of any significant differences in the incidence of all-cause death, MI, stent thrombosis, stroke, or bleeding events between aspirin and P2Y12 inhibitors (clopidogrel) when DAPT was converted to monotherapy in the short-term (<6 months) among the general population[49]. Our present results focused on the population of diabetes patients and reveal a similar trend that the efficacy and safety of long-term monotherapy with P2Y12 inhibitors are not better than those of aspirin considering the composite primary endpoint.

Our study was consistent with a recent NMA that suggested that DAPT for <6 months may be considered for most patients after PCI with DES[7]; another NMA reported similarly that among general patients, <6-month DAPT followed by P2Y12 inhibitor monotherapy reduces major bleeding events and extended-term DAPT reduces MI at the expense of a higher bleeding risk[8]. We also found that even among high-risk diabetes patients, short-term DAPT remains the first choice to improve the composite primary endpoint.
Although traditional meta-analysis studies have been conducted in diabetes patients, there is currently no NMA that compares various DAPT of various durations. We hope that our NMA would fill this gap and provide directions for future clinical research on diabetes patients. While previous NMA studies have been mostly focused on the general population, our NMA is the first to focus on the population of diabetes patients. In addition, we classified the DAPT duration into four categories with the standard-term DAPT of 12 months as control. The classification allows us to better understand the clinical significance of a short-term DAPT in diabetes patients. NMA studies often yield substantially accurate summary results by combining direct and indirect comparisons[50].

There remain some limitations to this study. Firstly, the NMA source data were based on the collection of published clinical studies, which are bound to include confounding factors. Despite the use of a random-effects model, heterogeneity in the included studies persisted and it could not be fully explained by a single related factor. The relatively small number of trials and categories of P2Y12 inhibitors may have contributed to the heterogeneity. Different therapeutic durations of DAPT, as well as different follow up periods, may have also contributed to the heterogeneity. In addition, data from diabetes patients with both low and high risk clinical profiles were included, and this also could have influenced the heterogeneity. Although all studies included in this NMA are officially published RCTs, the consistency and translational potential of the data should still be considered while interpreting the results. Secondly, we performed a quantitative NMA based mostly on trial-level data, which could have led to inaccurate results owing to the lack of original individual patient data. Finally, we analyzed some outcomes with pooled definitions which may have resulted in heterogeneity.
4. Conclusions

We found that short-term DAPT associates with better primary endpoint for diabetes patients after PCI with DES than extended-term DAPT. Although the optimal duration should be decided based on the risk-benefit ratio for an individual considering ischemic and bleeding events, this study suggested that short-term DAPT followed by monotherapy with P2Y12 inhibitors may be the optimal strategy for most diabetes patients who have undergone PCI with DES.

**Contribution statement:** KA and PG selected relevant studies and researched data. KA, PG, SQ, WZ, WC and JS contributed to the methods. KA wrote the manuscript. SW revised the manuscript. All authors read and approved the manuscript.

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| Trial                        | Year | Sample size | DAPT groups               | Endpoints for diabetes                                                                 | Mean follow-up (month) |
|-----------------------------|------|-------------|---------------------------|----------------------------------------------------------------------------------------|------------------------|
| REAL/ZEST-LATE              | 2010 | 704         | 12-month vs 36-month      | Primary endpoint, death from any cause, MI, stroke, definite ST, repeat revascularization, TIMI major bleeding | 19.7                   |
| RESET                       | 2012 | 292         | 3-month vs 12-month       | Primary endpoint, death from cardiovascular cause, MI, TVR, definite or probable ST, major or minor bleeding | 12                     |
| EXCELLENT                   | 2012 | 550         | 6-month vs 12-month       | Primary endpoint, total death, cardiac death, MI, death/MI, cerebrovascular accident, target-lesion revascularization, TVR, any revascularization, ST, any bleeding, TIMI major bleeding, MACCE | 12                     |
| OPTIMIZE                    | 2013 | 1103        | 3-month vs 12-month       | Primary endpoint, definite/probable ST                                                 | 12                     |
| ARCTIC-Interruption         | 2014 | 420         | 12-month vs 30-month      | Primary endpoint,                                                                        | 17                     |
| DAPT                        | 2014 | 3391        | 12-month vs               | Definite ST, probable ST, cardiac death, vascular death, non-                         | 17                     |
| Study       | Year | N   | Follow-up | Endpoint                                                                 |
|------------|------|------|-----------|--------------------------------------------------------------------------|
| DES LATE   | 2014 | 1418 | 30-month  | 12-month vs 36-month cardiovascular death, MI, stroke, BARC type 2 bleeding, BARC type 3 bleeding, BARC type 5 bleeding, GUSTO severe bleeding, GUSTO moderate bleeding, |
| ISAR-SAFE  | 2015 | 979  | 6-month   | 12-month Primary endpoint                                              |
| ITALIC     | 2015 | 685  | 6-month   | 12-month Primary endpoint, all-cause death, cardiac death, MI, TVR, minimal bleeding, minor bleeding |
| OPTIDUAL   | 2015 | 435  | 12-month  | 12-month All-cause mortality, cardiac mortality, MI, stroke, TVR, definite or probable ST, TIMI major bleeding |
| SECURITY   | 2016 | 429  | 6-month   | 12-month Primary endpoint, all-cause mortality, cardiac mortality, MI, definite or probable ST, TVR, stroke, type 3 or 5 BARC bleeding |
| I-LOVE-IT 2| 2016 | 414  | 6-month   | 12-month Primary endpoint, TLF, cardiac death, MI, TLR, all-cause death, BARC 3 or 5 major bleeding |
| IVUS-XPL   | 2016 | 506  | 6-month   | Primary endpoint                                                         |
| Study           | Year | N    | Time Period   | Primary Endpoint                                                                 | Duration |
|----------------|------|------|---------------|----------------------------------------------------------------------------------|----------|
| GLOBAL LEADERS | 2018 | 4038 | 1-month vs 12-month | Primary endpoint, BARC 3 or 5 bleeding                                           | 24       |
| STOPDAPT-2     | 2019 | 1159 | 1-month vs 12-month | Primary endpoint                                                                  | 12       |
| SMART-CHOICE   | 2019 | 1122 | 3-month vs 12-month | Primary endpoint, BARC 2,3 or 5 bleeding                                          | 12       |
| REDUCE         | 2019 | 298  | 3-month vs 12-month | Primary endpoint                                                                  | 24       |
| TWILIGHT       | 2020 | 2620 | 3-month vs 12-month | BARC 2,3 or 5 bleeding, BARC 3 or 5 bleeding, TIMI major or minor bleeding, GUSTO moderate or severe bleeding, ISTH major bleeding, all-cause death, cardiovascular death, MI, stroke, definite or probable ST, NACE | 15       |

Abbreviations: MI: myocardial infarction; ST: stent thrombosis; TVR: target vessel revascularization; TLR: target lesion revascularization
Table 2. Estimate results according to the network meta-analysis on primary endpoint

|                          | Short-term DAPT | 0.77 (0.46, 1.32) | Midterm DAPT | 0.85 (0.62, 1.19) | 1.1 (0.73, 1.66) | Standard-term DAPT | 0.62 (0.33, 1.06) | 0.56 (0.32, 0.9) | Extended-term DAPT |
|--------------------------|-----------------|-------------------|--------------|-------------------|------------------|---------------------|-------------------|------------------|-------------------|
Figure 1. Flow diagram

3506 reports identified with PubMed (n=361), Web of Science (n=895), Embase (n=1679), Cochrane Library (n=489), and ClinicalTrials.gov (n=82)

- Duplicated articles excluded (n=652)

- Articles remained after excluding duplicates (n=2854)
  - Articles excluded after title/abstract review (n=2830)
    - not related on the main topic
    - review/meta-analysis/commentary/protocol
    - objects are not diabetes mellitus

- Full-text articles assessed for eligibility (n=24)
  -Articles excluded after full-text review (n=6)
    - unpublished data not available (n=4)
    - not randomized controlled study (n=1)
    - cannot be grouped (n=1)

- Articles included in the network meta-analysis (n=18)
Figure 2. Network evidence plot for primary endpoint

Figure 3. Ranking and cumulative ranking curve of primary endpoint