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Abstract:

Objectives:

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 between the 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 33458 patients, the longest duration of follow up was 48 months while the shortest was 3 m. Network meta analysis results demonstrated that compared with 12 months, longer DAPT therapy of 30 months reduced the hazard ratio (HR) of stent thrombosis (HR: 0.29, 95% CrI = 0.17 to 0.49). There was no difference in mortality between short and longer durations of DAPT except for 30 vs 48 months (HR 0.48, 95% CrI 0.23 to 0.98). Compared with 12 months, longer DAPT therapy of 30 months reduced the risk of myocardial infarction (HR: 0.47, 95% CrI = 0.37 to 0.61). Results also demonstrated that compared with 12 months, a shorter term DAPT therapy reduced the risk of major bleeding (6 months: HR 0.53: 95% CrI = 0.29-0.98) while longer DAPT therapy increased major bleeding (30 months: HR: 1.61, 95% CrI = 1.21 - 2.15).

Conclusion:

As expected bleeding is less in the shorter duration regimens while the ischemic outcomes are better on the longer duration.

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) while 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, whilst preserving randomization of included trials. This allows 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 identified and analyzed. We restricted our analyses to

randomized controlled trials. The present NMA review was done according to PRISMA guidance for performing Network meta-analysis(11).

Search Strategy

The authors performed data collection from 4 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 "Dual Antiplatelet Therapy," "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, myocardial infarction, stent thrombosis 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, major bleeding, or stent thrombosis. 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) non randomized 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, myocardial Infarction and stent thrombosis. All end points were evaluated according to per protocol and individual study definitions (**Table 1**).

Statistical Analysis

A Bayesian NMA, using non-informative priors, was conducted on the hazard ratio scale to account for the varying follow-up times across studies. Relative effect estimates are presented as median hazard ratios 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 is 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 results. Between-studies heterogeneity estimates from random effects models are presented as median and 95% CrI.

12 months DAPT duration 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 the relative effects calculated using direct and indirect evidence differ.

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 (17) using code adapted from the Dias et al (18-20). Non-informative priors were used for all relative treatment effects and heterogeneity parameters. Three independent chains were run and checks for convergence and auto-correlation were carried out using the Brooks-Gelman-Rubin tools and by inspecting trace and autocorrelation plots. All results are based on post-convergence 150,000 iterations (50,000 on each of 3 independent chains).

Results

Using the keyword search, 18467 reports were identified of which 1122 relevant publications were selected by screening at the abstract and title level (**Figure 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 its meeting appropriate criteria. These 11 unique trials included a total of 33458 patients. The longest duration of follow up was 48 months (m) while the shortest was 3 m. Majority of the dual antiplatelet agents were Aspirin or Acetylsalicylic acid and Clopidogrel, while Prasugrel was used sparingly. All the included trials reported end points including Stent thrombosis, Myocardial

infarction, Mortality and Bleeding. The main study details and clinical characteristics of enrolled patients are shown in **Tables 2a & 2b**.

There were 2 studies that compared 3 months vs. 12 months, 3 studies that compared 6 months vs. 12 months, 2 studies compared 6 months vs. 24 months, 3 studies compared 12 vs. 30 months (DES LATE which compared 12 vs 36m was included for ease of comparison) and 1 study compared 12 vs. 48 months of DAPT after drug eluting stent 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 (stent thrombosis) 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 & interpretations using the GRADE recommendations. **(Table 3a & 3b). The probabilities and numbers needed to treat based on our network analysis are provided in Tables 4 & 5.**

Stent Thrombosis: (Figure 4)

Network meta analysis results demonstrated that compared with 12 months, longer DAPT therapy of 30 months reduced the hazard ratio (HR) of stent thrombosis (HR: 0.29, 95% CrI = 0.17 to 0.49). Similarly 30 months of DAPT was better than 3 months of DAPT to prevent stent thrombosis (HR: 0.29, 95% CrI = 0.12 to 0.70). The probability that 30 months of DAPT is the best of the durations compared at reducing stent thrombosis is 96%. There was no difference in stent thrombosis between 3 months vs. 12 months or 6 months or 24 months or 48 months, 6 months vs. 12 months or 24 months or 30 months or 48 months, 24 months vs. 48 months and 30 months vs 48 months. The number needed to prevent one stent thrombosis with 30 months of DAPT compared to 12 months was 327 (95 % CrI of 116 – 939) vs 816 (287 – 2346).

Mortality: (Figure 5)

Network meta analysis results demonstrated that there was no difference in mortality between short and longer durations of DAPT except for 30months vs 48 months (HR 0.48, 95% CrI 0.23 to 0.98) indicating that 48 months duration reduces mortality, compared to 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 to 12 months was 84 (95 % CrI 619-165) vs 325 (2409-640). There was no significant effect noted when 30 months was compared to 12 months.

Myocardial Infarction: (Figure 6)

Network meta analysis results demonstrated that compared with 12 months, longer DAPT therapy of 30 months reduced the hazard risk (HR) of myocardial infarction (HR: 0.47, 95% CrI = 0.37 to 0.61). Similarly 30 months of DAPT was better than 3 months (HR: 0.42, 95% CrI = 0.26 to 0.68), 6 months (HR: 0.47, 95% CrI = 0.30 to 0.72) or 24 months (HR: 0.54, 95% CrI = 0.34 to 0.86) of DAPT to prevent myocardial infarction. There was no difference in myocardial infarction between 30 and 48 months of DAPT (HR: 1.42, 95% CrI = 0.63 to 3.21). There was no difference in myocardial infarction between the other durations of DAPT. The probability that 30 months of DAPT is the best of the durations compared at preventing myocardial infarction is 80%. The number needed to prevent one myocardial infarction with 30 months of DAPT compared to 12 months was 91 (95 % CrI of 51 – 165) vs 225 (126 – 411).

Bleeding: (Figure 7)

Network meta analysis results demonstrated that compared with 12 months shorter DAPT therapy reduced the risk of major bleeding (6 months: HR 0.53: 95% CrI = 0.29-0.98) while longer DAPT therapy increased the hazard risk (HR) of major bleeding (30 months: HR: 1.61, 95% CrI = 1.21 to 2.15). Similarly

3 months of DAPT was better than 24 months (HR: 2.50, 95% CrI = 1.08 to 5.85) and 30 months (HR: 2.66, 95% CrI = 1.25 to 5.72). 6 months therapy was also better than 24 months (HR: 2.85, 95% CrI = 1.48 to 5.44) and 30 months (HR: 3.02, 95% CrI = 1.54 to 6.00) of DAPT to prevent major bleeding. 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 major bleeding event with 30 months of DAPT compared to 12 months was 139 (95 % CrI 434-64) vs 343 (1076-157).

Discussion

DAPT after PCI has been a cornerstone as it has been shown to be beneficial in reducing complications including stent thrombosis. It is a class I A recommendation from major societies including ACC (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, 48 months).We have performed a NMA comparing different durations of DAPT duration on studies incorporating nearly 30,000 patients undergoing PCI with drug eluting stent 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 stent thrombosis and myocardial infarction. We also found no difference in mortality between shorter or longer duration DAPT. However, we were able to delve further into the data and show that (1) significantly reduced risks of stent thrombosis and MI are only seen with durations of DAPT greater than 24 months and (2) in preventing one myocardial infarction and one stent thrombosis with 30 months of DAPT, ≈ 3 and 11 patients, respectively, developed one major bleeding complication.

As shown by the majority of previous studies, incidence of stent thrombosis tended to decrease as DAPT duration increased (21 – 23). However, our analysis showed that stent thrombosis rates were significantly lower only when DAPT was continued for 30 months when compared to any duration up to and including 24 months. It would seem the advantage is highest when compared to durations of 3, 6 or 12 months. Comparisons of differing DAPT durations up to 24 months did not have any statistical benefit. It may be that continuing 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 as compared to 2nd generation DES, it can be speculated that the continuation of therapy 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 stent thrombosis after the first year and up to the third year to be 0.4% with EES and 0.70% with PES. 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 stent thrombosis by prolonging DAPT to 30 months as opposed to standard therapy was 327. Whether prolonged DAPT duration has clinical significance in preventing stent thrombosis post 2nd generation DES is therefore debatable.

Similar to stent thrombosis, Myocardial infarction 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 myocardial infarction by prolonging DAPT to 30 months as opposed to standard therapy was 91. In the PEGASUS trial (25) patients who were 1-3 years post-MI and had specific high-risk characteristics (age 65 years or older, diabetes mellitus, second prior spontaneous MI, multi-vessel CAD, 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 myocardial infarction (HR 0.83, 95% CrI 0.72 to 0.95) over the study period compared to Aspirin alone. However, reduction in

myocardial infarction came at the price of increased major bleeding (1.85% vs. 1.09%; RR 1.73; 95% CrI 1.19-2.50; p=0.004; NNH = 132). In our analysis prevention of one myocardial infarction with prolonged DAPT was estimated to occur at the expense of three major bleeds.

As expected, longer duration of DAPT increased the risk of major bleeding. Bleeding during 3 months or 6 months of DAPT was less than at 12, 24 or 30 month durations. 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 therapy. Recent analysis by Palmerini et al(26), concluded that at 1 y, bleeding was lower with shorter duration (less than 6 months) as compared to one 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 as opposed to 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 duration of therapy. This reinforces the findings by Palmerini et al. albeit over a longer term. Another recent analysis by Giustino et al (22), showed that longer duration DAPT correlated to lower risk of ST, MI and longer term increased the bleeding risk.

In the DAPT trial (10) prolonged DAPT was however associated with an increased risk of non-cardiac death. Similarly in the meta analysis by Palmerini et al prolonged DAPT was associated with increased mortality. Our meta-analysis incorporates the OPTIDUAL study published by Helft et al, which randomized 1385 patients to DAPT with clopidogrel for 12 months versus 48 months (27). They found a trend towards 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 when compared to shorter duration. Though stent thrombosis and MI rates are reduced with longer duration DAPT this did not lend itself to a mortality benefit. This could be due to

higher bleeding risk negating any mortality benefit of reduced stent thrombosis and MI rates. One aspect of note was that compared to 30 months, 48 months therapy seemed to reduce mortality but the risk of Stent thrombosis, Bleeding or Myocardial infarction was no different. Its unclear if this pertains to only cardiac deaths or combined mortality. Prior analysis seems to suggest while longer DAPT therapy lowers many complications, some risks seem to plateau over time including very late Stent Thrombosis.(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 anti-platelet agents (Clopidogrel vs. Ticagrelor vs. Prasugrel). We were also unable to assess the effect of stent generation on patient outcomes and risk of stent thrombosis 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 the NMA on the hazard ratio 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 network analysis of randomized trials comparing different durations of DAPT after DES implantation, we found there probably is no benefit in extending DAPT beyond 12 months. The lower frequency of myocardial infarction and stent thrombosis likely comes at the price of increased major

bleeding. 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 risk of MI or ST. DAPT therapy following

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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Tables Legend:

1. Definitions/Criteria of Primary end point, Major Bleeding & Stent Thrombosis

2a, 2b. Study characteristics of the randomized trials

3a. GRADE Assessment

3b. GRADE Assessment Scoring System

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