Safety of short-term dual antiplatelet therapy after drug-eluting stents: an updated meta-analysis with direct and adjusted indirect comparison of randomized control trials.

Short title: Duration of dual antiplatelet after coronary intervention

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Abstract

Background: Duration of dual antiplatelet therapy (DAPT) following drug-eluting stents (DES) remains controversial and is a topic of ongoing research.

Methods: Direct and adjusted indirect comparisons of all the recent randomized control trials (RCTs) were performed to evaluate the safety of short-term versus long-term DAPT following DES.

Results: 8 RCTs were identified and 7 (16 318 subjects) were included. 4 groups of 3 vs 12 months, 6 vs 12 months, 6 vs 24 months and 12 vs 24 months of DAPT were used for direct comparison. There was no significant difference in stent thrombosis, myocardial infarction (MI), stroke and revascularization, cardiovascular and all-cause mortality between the different durations in all 4 groups. Pooling trials of 3 - 6 months of DAPT against 12 months, we found a significant reduction in the risk of total bleeding (RR 0.61, 95% CI 0.43 – 0.87). Adjusted indirect comparison between 3 vs 6 months, 3 vs 24 months and 6 vs 24 months duration of DAPT showed no significant differences in risk of death or MI, or revascularization between 3 or 6 months and 24 months. However, 24 months of DAPT was associated with significantly more bleeding than 3 or 6 months.

Conclusions: 3 to 6 months of DAPT following second generation DES and above is safe with no increased risk of thrombotic complications and mortality and lower bleeding risk. However a tailored approach may be more appropriate for high-risk patients.

Key words: Percutaneous coronary intervention; drug-eluting stent; acute coronary syndrome; dual antiplatelet treatment; duration of therapy

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is the mainstay treatment after drug-eluting stent (DES) implantation and has been shown to reduce stent thrombosis[1-3]. However, with the emergence of newer generation DES, late and very late stent thrombosis have reduced significantly[4]. Prolonged treatment with DAPT is associated with a higher bleeding risk[5-7], can be costly and can delay elective and semi-elective operations. Therefore, the optimal duration of DAPT after DES remains a topic of ongoing debate and research.

North American and European recommendations differ and are largely based on observational studies[1, 8, 9]. The American Heart Association (AHA)/American College of Cardiology (ACC) recommend at least 12 months of aspirin and clopidogrel after DES implantation for patients at low risk of bleeding [10] whereas the European Society of Cardiology (ESC) recommends 6 to 12 months of DAPT for patients following elective DES implantation and 12 months in the context of acute coronary syndromes[11] .

We recently published a meta-analysis [12] on 4 RCTs and found no cardiovascular or mortality benefits associated with prolonged duration of DAPT. Moreover, shorter periods of DAPT resulted in a lower risk of major bleeding as compared to longer periods. At that time, we noted that there were a number of other ongoing trials, and we have now become aware of recent RCTs[13-16] published on this topic. The availability of additional new trial data in an up-to-date meta-analysis would help us overcome previous limitations of lack of power and generalizability, and also enable us to conduct an adjusted indirect comparison between treatment durations that had not been directly compared in existing trials.

Methods

Eligibility criteria

RCTs comparing different durations of dual antiplatelet therapy (aspirin plus any one of the P2Y12 inhibitors: ticlopidine, clopidogrel, prasugrel and ticagrelor) following percutaneous coronary intervention (PCI) were included. We focused on RCTs using only DES or a mixture of predominantly DES and some bare metal stents (BMS). Trials comparing different stents, or different antiplatelet agents rather than different durations of DAPT after PCI were excluded.

Search strategy

MEDLINE and EMBASE through OvidSP using the Haynes optimized search strategy (Health Information Research Unit, McMaster University) [17] were searched. Conference Proceedings (from August 2013 to October 2014) of the AHA, ACC, ESC and the Transcatheter Cardiovascular Therapeutics (TCT) were searched manually. The exact search strategy is shown in Appendix 1. We also checked the references of included RCTs for any relevant studies. In addition, we used the PubMed automated updates for new articles up to October 2014.

Study selection and data abstraction

Two reviewers (HB and CSK) independently and in duplicate assessed trial eligibility based on titles and abstracts. The reviewers then went on to screen the full-text articles of potentially suitable RCTs for detailed evaluation against the eligibility criteria.

Following discussion and full agreement, the two reviewers independently extracted data from the selected studies. The data extraction was then checked by the other authors (YKL and ADR) and any discrepancies were resolved by consensus.

We evaluated individual endpoints of myocardial infarction, stroke, cardiovascular death, all-cause mortality, stent thrombosis and need for revascularization. In addition, we considered a composite endpoint of death or myocardial infarction to be of clinical relevance within our analysis.

We aimed to evaluate adverse events including total number of bleeds, major bleeding, as well as specific subcategories of gastrointestinal bleeding and intracranial hemorrhage where reported.

Study characteristics and quality assessment

As reported in our previous meta-analysis [12], two reviewers (HB and CSK) extracted data on study characteristics, which was then checked by the other reviewers (AR and YKL). We recorded the study design, duration of DAPT exposure, number of participants, duration of follow up, outcomes evaluated, outcome events, PCI procedural data, angiogram results, patient selection criteria, compliance with medication and doses of antiplatelet used in the RCTs.

Quality assessment was conducted based on the recommendations of the Cochrane handbook of systematic reviews [18] which included consideration of randomization sequence generation, allocation concealment, blinding of participants, personnel and outcome, incomplete or

selective outcome reporting and publication bias. We aimed to produce a funnel plot if there were >10 included studies with no evidence of statistical heterogeneity.

Quantitative data synthesis

RevMan 5.2 (Nordic Cochrane Center) was used to conduct fixed-effect meta-analysis for the pooled Relative Risks (RR), with 95% confidence intervals for dichotomous outcomes. The main analysis was on an intention to treat basis, and all reported P values are two-sided, with significance set at p less than 0.05. Statistical heterogeneity was assessed using I^2 statistic, with I^2 values of 30-60% representing a moderate level of heterogeneity [19].

We aimed to perform pre-specified subgroup analysis based on nature and duration of antiplatelet therapy, type of stent, and on specific patient populations such as the elderly, or those with diabetes mellitus. Risk ratios were pooled using the inverse variance method for specific patient subgroups in the trials.

Adjusted Indirect Comparison

We used the summary estimates of treatment effect from the meta-analysis in adjusted indirect comparison (AIC) (Bucher's method[20]) through ITC software[21]. The AIC technique compares the size of the treatment effect between two treatment regimens judged in relation to a common comparator, which works as a link between the two regimens. A large survey has demonstrated that AIC can yield effect estimates similar to those derived from direct or head-to-head trials[22]. At present, AIC is considered to be the most established method for indirect comparisons, with acceptance by pharmaceutical reimbursement agencies such as Australian Pharmaceutical Benefits Advisory Committee, the UK National Institute for

Health and Clinical Excellence, and the Canadian Agency for Drug and Technologies in Health[23].

Here, the treatment effects from two different antiplatelet regimens could be compared indirectly through a common control DAPT duration. For instance, if the outcomes data were available for 3 months vs. 12 months DAPT, and 6 months vs. 12 months DAPT, we aimed to compare 3 months vs. 6 months through AIC based on the 12 months common control arm. In order to check the validity of the AIC, we aimed to evaluate the results obtained through AIC against that of any head-to-head data where available.

Results

Study selection, design and methodology

Our previous search up to August 2013 yielded 20 potentially relevant studies and a total of 5 were included in our recent study[12]. From August 2013 to October 2014 3 new studies were identified via MEDLINE and EMBASE through OvidSP. The article by Lee et al [14] actually consists of two trials as it included all the participants from REAL-LATE and ZEST-LATE previously published by Park et al [24] and therefore the latter was excluded from our analysis. The process of study selection is shown in Appendix 1. The study design, definition of short and long duration of therapy, number of participants, follow-up time and outcomes evaluated is shown in Table 1. The duration of short- and long-term antiplatelet therapy varied from 3 months to 12 months for the short duration and 12 to 24 months for the long duration. The number of participants ranged from 182 to 3,119 with a total of 16,534 participants across all eight studies. The follow up time for outcome evaluation ranged from 1 year to 3 years after PCI. The studies evaluated composite cardiovascular events and mortality as their primary outcome and secondary individual cardiovascular events and mortality outcomes. The participant selection criteria, patient demographics, clinical presentation, procedural

information for PCI, angiography results, study outcomes, compliance with medications are shown in Appendix Table 2-6.

Quality assessment

The quality of studies is shown in Appendix 7. Randomization was considered adequate for six out of eight trials, but some degree of loss to follow up was noted in the same six trials. Although the majority of the studies were open-label, blinded observers independently adjudicated the adverse events in five of them. We did not test for publication bias as there were too few trials.

Pooled analysis of thrombotic events for shorter as compared to longer duration of DAPT

The number of thrombotic events in the shorter and longer duration of DAPT is shown in Appendix 8. A total of seven articles (reporting on eight trials) were included which evaluated 3 vs 12 months, 6 vs 12 months, 6 vs 24 months and 12 vs 24 months and there was no significant difference in stent thrombosis, myocardial infarction, stroke and revascularization with shorter or longer duration of DAPT (Figure 1).

Pooled analysis of mortality events for shorter as compared to longer duration of DAPT

The composite of death or myocardial infarction was available from all the included trials and similarly there was no significant difference with shorter and longer duration of DAPT (Figure 2). For all-cause mortality, meta-analysis of all the included trials showed a non-significant trend towards slightly less events with shorter duration of DAPT (Figure 2).

Pooled analysis of risk of bleeding for shorter as compared to longer duration of DAPT

All the studies were included in the analysis of major bleeding (Appendix 9, Figure 3). For the four different time comparisons (3 vs 12 months, 6 vs 12 months , 6 vs 24 months and 12

vs 24 months) there was a non-significant trend towards fewer bleeding events with 3 vs 12 months, 6 vs 12 months and 12 vs 24 months and significantly fewer events with 6 vs 24 months (RR 0.38, 95% CI 0.15-0.96). For total bleeding, significant differences in events was observed for 12 vs 24 months (RR 0.25, 95% CI 0.07-0.90), but no significant difference was observed for the comparison of 3 vs 12 months (RR 0.72, 95% CI 0.48-1.08), 6 vs 12 months (RR 0.42, 95% CI 0.15-1.19) and 6 vs 24 months (RR 0.56, 95% CI 0.30-1.04) (Figure 3).

Risk of adverse outcomes with specified subgroup with continued and discontinued antiplatelet therapy

We considered different categories of participants as an additional analysis (Figure 4). There was no significant difference with shorter and longer duration of DAPT for the subgroups of age <65-years/ age> 65 years, diabetes/no diabetes and acute coronary syndrome/ stable disease.

One study by Hu et al [25] was not included in the pooled analysis due to insufficient information for detailed quantitative analysis but its findings are consistent with our meta-analysis. This trial randomized 182 Chinese patients who were event-free at 12 months post left main stem PCI to 12 months or ≥36 months of dual antiplatelet therapy and found that there was no difference between the groups for mortality, myocardial infarction, stent thrombosis or composite outcomes.

Adjusted Indirect Comparison of different treatment durations

In order to maximize statistical power in the AIC, we chose outcomes that were reported most frequently in the entire dataset of all eight trials i.e. death or MI, revascularization, and

major bleeding. Results for the AIC are shown in Table 2. There were no significant differences in risk of death or MI, or revascularization when comparing patients receiving 3 or 6 months DAPT to those treated for 24 months. However, 24 months of DAPT was associated with a significant excess of major bleeding compared to 3 or 6 months. We did not identify significant differences when comparing 3 months DAPT to 6 months DAPT for any of the outcomes.

We were able to check the validity of the AIC estimate (for 6 vs. 24 months) by evaluating it against Valgimigli's trial involving a direct head-to-head comparison of 6 months vs. 24 months. For Death or MI, the adjusted indirect estimate of RR 1.12 (95% CI 0.62 – 2.03) was very similar to that seen in the direct comparison RR 1.07 (95% CI 0.81 – 1.41). The analysis of major bleeding for 6 vs. 24 months showed an adjusted indirect RR of 0.32 (95% CI 0.11-0.98), which again was very similar to the direct RR estimate of 0.38 (95% CI 0.15 – 0.96) from Valgimigli's trial[26].

Evaluation of 3 or 6 months against longer durations

As part of a sensitivity analysis, we also pooled the data from the 3 month and 6 month trials to enable a comparison of 3 to 6 months versus 12 months. This showed no significant difference between the two aforementioned durations with regards to death/MI (RR 1.06, 95% CI 0.82 – 1.38), or revascularization (RR 1.12, 95% CI 0.89 – 1.42), but a significant reduction in risk of total bleeds (RR 0.61, 95% CI 0.43 – 0.87) and a non-significant reduction in major bleeds (RR 0.57, 95% CI 0.32 – 1.01).

We also conducted a sensitivity analysis involving pooled estimates from the three trials where 6 months duration was compared to 12-24 months. This showed no significant difference between the shorter and longer duration with regards to death /MI (RR 1.08, 95%

CI 0.85 – 1.37), but the 6 months arm was associated with significant reductions in risk of major bleeds (RR 0.44, 95% CI 0.22 – 0.86) and total bleeds (RR 0.52, 95% CI 0.30 – 0.88).

Discussion

DES is currently the stent of choice in patients undergoing PCI due to its lower risk of restenosis and target lesion revascularization[27]. However, this is offset by the risk of late and very late stent thrombosis. Although stent thrombosis is becoming less frequent with newer generation DES[4, 28, 29], mortality can be as high as 45%[1]. On the other hand, DAPT has been shown to significantly increase the risk of bleeding[5-7]. Therefore it is important to prescribe the optimal duration of DAPTs to patients to balance their thrombotic and hemorrhagic risks. Our up-to-date analysis of randomized data of 16 318 participants demonstrates that extending the period of DAPT does not significantly reduce the risk of thrombotic complications and mortality when compared to shorter durations but the risk of bleeding is clearly increased when compared with shorter duration DAPT. Overall 3-6 months of DAPT is associated with the lowest risk of harm from bleeding, with direct supporting evidence from the pooled comparison of 3-6 months vs. 12 months, and 6 months vs. 12-24 months, as well as adjusted indirect evidence of 3-6 months vs. 24 months treatment. This was mainly driven by significantly less bleeding with shorter duration treatment and there was no added benefit from death or MI and revascularization when treatment was extended to 24 months.

The absence of cardiovascular harm with shorter durations of DAPT was consistently noted in different subgroups stratified by duration of DAPT, individual endpoints, or patient characteristics. Although Gwon et al [30] suggested that patients with diabetes mellitus were at significantly higher risk of myocardial infarction and target vessel revascularization in the short DAPT group, this was not the case with OPTIMIZE [13] and our subgroup analysis did

not demonstrate any impact of age, presence of diabetes mellitus and acute coronary syndrome (ACS) on the adverse primary outcomes in both short and long DAPT groups. Our results build upon the findings of our previous meta-analysis [12] but with a much larger sample size and stronger statistical power overall and provide the strongest evidence to date on this topic. Shorter duration of DAPT seems a safe option; especially in low risk patients having second generation stents but the cohort of patients that would benefit from longer duration of DAPT remains unanswered.

Late stent thrombosis is thought to be the result of delayed arterial healing after DES [31] and can be due to a combination of various factors such as comorbidities of the patient and lesion-specific and stent-specific characteristics [32]. However, premature DAPT cessation is considered to be the main cause of stent thrombosis[1]. Therefore it is likely that we would never find a simple answer for the optimal duration of DAPT that would apply to all patients. This is also compounded by the fact that newer stents are constantly being designed and newer antiplatelet agents are increasingly being used in clinical practice. These make the conduct of a large-scale RCT that could potential stratify for all confounding factors very difficult and the result of such a trial may become obsolete once it is finally published because of the constant evolution in technology and pharmacology. Therefore, in an attempt to update the current evidence on this topic, there have been a number of meta-analyses[12, 26, 33-35] conducted over the last few years. Our meta-analysis, to our knowledge, is the most up-to-date and summarizes all the relevant RCTs to date.

Our study has several strengths. First of all we included high quality RCTs only, totaling > 16000 patients, which has more power that previous meta-analyses of RCTs only conducted on this topic [12, 26, 34, 35]. Secondly, our previous work [12] had patients from South Korea and

Italy only but now includes more patients from Europe and includes patients from the South American continent. The current work also includes a proportion of patients on prasugrel (8.5% of patients in the ARTIC-INTERRUPTION trial), which is being used more frequently in clinical practice and may be more representative.

However, our study also has several limitations. First of all, the RCTs included were comparing different durations of DAPT, which made pooling of the different time points difficult. We had to conduct an adjusted indirect comparison of durations of DAPT not directly compared in the RCTs, but our consistency check was reassuring in that the AIC for 6 vs. 24 months yielded very similar findings to the direct comparison. Secondly, the time of randomization differed in these 7 studies with randomization performed at index PCI in EXCELLENT [30], RESET [36], OPTIMIZE [13] and SECURITY [16] trials and at 1 month after index PCI in PRODIGY [37]. In the study by Lee et al [14] and ARTIC-INTERRUPTION [15], randomization was performed at a year post the index PCI. As a result, patients developing early adverse events (within 30 days and within 12 months respectively) in the later 3 studies were excluded. Therefore it was not possible to analyze events within 30 days and within 12 months in these patients. The SECURITY trial did reported on numbers of cardiovascular events at different time-points of follow-up and no consistent differences were reported. EXCELLENT [30], RESET [36] and OPTIMIZE [13] trials provided Kaplan-Meier plots, which individually did not show significant differences in cardiovascular outcomes during follow-up. Furthermore, in the former 3 studies, EXCELLENT [30] excluded patients with myocardial infarction within 72 hours, RESET [36] and SECURITY [16] excluded patients with acute ST-elevation myocardial infarction within 48 hours and OPTIMIZE [13] also excluded patients with acute ST-elevation myocardial infarction. PRODIGY [37] on the other hand included patients with acute coronary syndrome including non ST-elevation and ST-elevation

myocardial infarction, which accounted for around 74% of patients. Lastly, different generations of DES and a small proportion of BMS (25% of patients in PRODIGY[37]) were used in the trials included in this analysis. Although the majority of the trials used second-generation stents (61% in SECURITY, 63% in ARCTIC-INTERRUPTION, 75% in EXCELLENT, 86 % in RESET, 100% in OPTIMIZE) except in Lee et al (30%) and PRODIGY (50%), we were not able to extract the required data to perform a sensitivity analysis pertaining to the stent type. The Endeavor Zotarolimus-Eluting Stent (ZES) used in RESET [36] in 50% of the cohort and in the OPTIMIZE [13] has now been superseded by the Resolute ZES which has a new durable polymer coating with improved drug-release kinetics. However, in this rapidly evolving field, it is inevitable that the stent platform with continue to change in the current ongoing and future trials.

A retrospective study by Silber et al [38] recently found that patients with the Resolute ZES who interrupted DAPT after at least one month was safe which supports the notion that 3 months of DAPT following DES with the newer generation DES in low risk patients is safe. On the other hand, a recent meta-analysis of almost 50,000 patients by D'Ascenzo et al [39] showed that ACS patients undergoing PCI suffered more adverse events compared to ACS patients treated medically if they stopped DAPT after a year. Although they concluded that this result was hypothesis generating, it supports the fact that high-risk patients would need a tailored approach to the duration of DAPT.

Several other RCTs on this topic are currently being undertaken (DAPT trial [40], ISAR-SAFE [41], OPTIDUAL [42], Nobori DAPT (NCT01514227), EDUCATE (NCT01069003), DAPT-STEMI (NCT01459627), SMART-DATE (NCT1701453)). All of these trials are comparing between 6 to 12 months of DAPT against 12 to 30 months and looking at different clinical presentations and stent platforms. Therefore it is likely that we would be able to identify

patients who would benefit from longer duration of DAPT in a near future. GLOBAL LEADERS (NCT01813435) is the largest RCT involving DES designed so far, aiming to recruit 16 000 participants. This trial is currently looking at all-comers post PCI (Biomatrix Flex^{TM}: DES and an abluminally coated biodegradable polymer) on DAPT with aspirin and ticagrelor for one month, then randomized to either ticagrelor monotherapy for 23 months or standard therapy (12 months of either clopidogrel or ticagrelor with aspirin) and so we would have more data on ticagrelor use post PCI.

Conclusions

3 to 6 months of DAPT following second generation DES and above is safe with no increased risk of stent thrombosis, myocardial infarction, stroke, revascularization and death and the added benefit of minimizing the risk of bleeding. A tailored approach may be appropriate for high-risk patients.

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