Article details: 2021-0119
Title: Extended dual antiplatelet therapy following percutaneous coronary intervention in clinically important patient subgroups: a systematic review and meta-analysis
Authors: Jesse Elliott PhD, Shannon E. Kelly MSc, Zemin Bai MSc, Becky Skidmore MLS, Michel Boucher BPharm MSc, Derek So MD, George A Wells PhD

Reviewer 1: Natalia Pinilla Echeverri
Institution: Medicine, McMaster University Faculty of Health Sciences
General comments (author response in bold)

Systematic review that assessed the benefits and harms of extending DAPT beyond one year after the target event. Great initiative as optimal duration of DAPT therapy remains uncertain in some situations. Methodology was followed accordingly, and limitations are well described. The most important limitations are lack of considering high risk subgroups in the initial randomization, potentially leading to imbalance; and also, high risk subgroups may have been excluded based on eligibility criteria. All of this, elucidates the need to include RCT that consider high risk subgroups that might benefit for longer term DAPT.

A better description of "no DM" as a high-risk subgroup should be included, as there might be some bias in inclusion criteria for the studies that were considered for the review, and DM has been identified in the past as a risk marker. It remains unclear how the investigators defined “no DM” as the biological plausibility for this finding is questionable.
We thank Reviewer 1 for this comment. We agree that the inclusion and exclusion of the included studies is an important consideration; indeed, this is a relevant comment for all systematic reviews. We would like to clarify that the “no DM” subgroup was as defined by the included studies. To facilitate comparison across studies, we have added a table to the supplementary file (as part of Appendix 3), which includes the definition of diabetes as specified by each included RCT. For each, the “no DM” subgroup was comprised of participants not classified as having diabetes as per these definitions.

Reviewer 2: Bobby Yanagawa
Institution: Division of Cardiac Surgery, University of Toronto
General comments (author response in bold)

This is a SR and MA comparing conventional DAPT vs extended DAPT for patients with PCI. The authors found 9 RCTs that fit the study criteria. They report that patients with extended DAPT had lower risk of MI and (probable) stent thrombosis but higher risk of bleeding. Patients with a history of ACS, age<75yo and non-diabetics deprived the most benefit from extended DAPT post-PCI. There were no differences in death, stroke, stent thrombosis, repeat revasc and MACCE. This is a question of great clinical interest. The results are not too surprising overall. There is considerable variation in studies with respect to type of stent, definitions of outcomes and duration of DAPT therapy which makes the results difficult to interpret. Overall, this study does not present much new data and these results do not really move the dial in terms of duration of DAPT post-PCI.

I have a few questions.
We thank Reviewer 2 for these comments. Author responses have been included for each question, listed below:

1. Of the 9 studies, how many were found by the systematic search and how many by other sources? If there a significant number for the latter, a wider search may be indicated.
All studies were located through the systematic search.

2. A sensitivity analysis only looking at DES may be helpful.
We agree that sensitivity analyses by DES status could add additional information. In our earlier work (www.cadth.ca/sites/default/files/pdf/HT0001_DAPT_Post_PCI_.pdf), we found limited subgroup data specific to patients with drug-eluting vs bare-metal stents, and we did not include type of stent in our a priori protocol for the current systematic review.

3. Forest plots are quite helpful to display the results. I would consider this for the major outcomes of interest. The tables are a bit complicated and difficult to follow. They can be included in the supplement.
The forest plot for each outcome has been added to the supplemental file (Appendix 8).

Reviewer 3: Michael Yamashita
Institution: Surgery, St Boniface General Hospital
General comments (author response in bold)

I read with interest the manuscript submitted by Dr. Elliot and colleagues. They present a systematic review and meta-analysis examining the outcomes of extended DAPT vs 6-12 months of DAPT in patients undergoing PCI. They have identified that patients with previous MI, ACS at presentation, no diabetes and younger than 75 years benefit the most from extended DAPT. I congratulate the authors on a well performed study on a timely topic. The manuscript is well written and comprehensive with the inclusion of their search strategy. The statistical analysis is also robust. I have a few comments and questions for the authors to improve their paper prior to publication.
We thank Reviewer 2 for these comments. Author responses have been included for each question, listed below:

1. In the PRISMA flow diagram, how did the authors go from 55 records included to 7 RCTs included in the qualitative analysis? More detail is required for this last step.
As noted in the footnote for Figure 1, the 55 records (58 after the search was updated in 2022) all pertain to the included RCTs (16), of which 9 RCTs reported outcome data and 7 were sufficiently similar for pooling. For example, the DAPT study was represented by 17 records (primary publication, plus companion records). As such, the number of included records exceeds the number of included RCTs.

2. Why did the authors choose to only perform publication bias analysis for outcomes with data from at least 10 studies. This led to no analysis of publication bias being performed for this meta-analysis. While I understand that a publication bias analysis is only meaningful when there is a significant amount of studies available, I would suggest at least performing a funnel plot for the outcome with the largest amount of studies to investigate whether publication bias may have played a role here.
We followed the Cochrane guidelines for testing for publication bias via funnel plot asymmetry: "As a rule of thumb, tests for funnel plot asymmetry should be

used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry."

3. Why was I^2>75% considered to represent substantial statistical heterogeneity? There is a p-value that accompanies the I2 statistic which could be used.
We followed the Cochrane guidelines for interpreting heterogeneity by use of the I2 statistics rather than p value; p values may be misleading when there are small sample sizes or few included studies, and a non-significant result should not be taken as evidence of no heterogeneity. We considered that important heterogeneity was present when the I2 value was at least 75% and did not pool studies above this threshold. However, we do present Forest plots for all analyses (including those with I2 above 75%; Supplementary appendix).

4. There are no forest plots in this manuscript. Forest plots are a visually appealing method of displaying meta-analysis results for outcomes that come from multiple studies as they provide a visual display of the size/weight of each study, the size of the confidence intervals for each outcome, the amount of heterogeneity among study results etc... I would suggest the authors include at least a few forest plots, particularly for the most important outcomes.
Forest plots for all outcomes have been included in the supplementary file.

5. Due to the large number of outcomes and several different subgroup analyses, it is at times a bit difficult to follow the results of the paper. The authors may wish to consider breaking up the data into different manuscripts or excluding some of the less significant outcomes.
While we agree that there are a large number of outcomes and subgroups. These were all defined a priori on the basis of clinical expert input, and it would be inappropriate to exclude results with "less significant outcomes". While splitting the data into different manuscripts would reduce the size of the manuscript, we feel that this would not be ideal as it would make accessing and using the findings more difficult for knowledge users.

6. The studies used both BMS and DES as well as different P2Y12 inhibitors. Did the authors perform any subgroup analyses to determine if the type of stent or P2Y12 inhibitor made a difference?
As noted above, we did not include stent type as a variable of interest in our a priori protocol. While we did intend to evaluate outcomes via P2Y12 inhibitor type as per our protocol, there were insufficient data available to support such analyses.

7. It seems a bit counterintuitive to me that patients without diabetes benefitted from extended DAPT compared to diabetics. Do the authors have an explanation for this finding?
The prevalence of diabetes among the included studies ranged from 24-38%. While we have summarized the findings among patients with or without diabetes, as reported in the included RCTs, it is possible that patients with diabetes have additional and complicating comorbidities that we are unable to account for with the current study design. The take-away, however, is that, diabetes is a confounding factor in the duration of DAPT, and that, for patients with diabetes,

clinicians should be cognisant that these patients may derive less benefit from extended DAPT.