Author’s response to reviews

Title: Perioperative management of antiplatelet therapy in patients undergoing non-cardiac surgery following coronary stent placement: A systematic review

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David Moher, PhD
Editor-In-Chief, Systematic Reviews

Dear Dr. Moher
We are pleased to resubmit our manuscript entitled, “Perioperative management of antiplatelet therapy in patients undergoing non-cardiac surgery following coronary stent placement: A systematic review” for consideration as a Research Article in Systematic Reviews.

We greatly appreciate the thoughtful and constructive comments of the reviewers. Below we detail each editor/reviewer comment, and how we have responded.

Overarching comment: The search is nearly two years old and is therefore older than is recommended for publication within Systematic Reviews.

We have updated the search through October 11th, 2017. The search identified an additional 814 articles. Only 3 met our inclusion criteria and have been added to the review. One was a randomized trial. However, this study only included 43 cases and had significant methodologic limitations. We also added 2 observational studies – one focused on “bridging” therapy, and the other, a case-control study. Our conclusions have not changed substantially as a result of these additions. The manuscript has been extensively revised, however, to include these additional studies.

REVIEWER 1

Major Points

1. I’m concerned about the appropriateness of the included studies. This review includes several studies without a control group. I think this is a major limitation and would need to be addressed to ensure that the final results are accurate. Ideally, the authors will exclude uncontrolled studies, cross-sectional studies and case control studies.

We agree with the reviewer that the included studies are of low to very low quality and were not ideal for answering our question(s). The updated search included one randomized trial, but this trial was very small (39 patients, 43 cases), and had additional limitations. If we had limited our review to only studies that compared two or more strategies, with sufficient APT management, we would have been left with 4 studies. None of these 4 studies compared the same 2 strategies and only 1 of these studies used multivariate adjustment for sample differences. Further, excluding case-control designs would have eliminated perhaps the most informative study (Hawn et al.). This was the only one that matched patients across a variety of relevant clinical variables and meticulously described pre and perioperative APT strategies. Given these limitations, we felt it was important to describe the literature that does exist and hope that a critical review of the weaknesses will help guide future research in this area. We have expanded our limitations to reflect the reviewer’s concerns:

This systematic review is limited primarily by the quality and quantity of the available evidence. Only one RCT evaluated the management of APT in patients undergoing NCS, but this study was very small (<40 patients) and included almost 30% of patients without a history of coronary stent. Observational studies in this space are insufficient to make up for the paucity of randomized evidence. Many of the included observational studies lacked a control group
rendering comparisons impossible. The few studies that did include a control group did not address sample imbalances. Case control studies are not directly comparable to cohort studies as they do not provide actual event rates. Further, patients within and across studies were heterogeneous along multiple domains including time since stent implantation, indication for procedure, and type of surgery. APT management within a given study was similarly heterogeneous using multiple APT strategies, inconsistent timing of discontinuation and restarting therapy, as well as the use of bridging.

2. I think that the authors should be more specific about their inclusion/exclusion criteria and the comparisons that are being made e.g. trials were included if they compared stopping antiplatelet drugs to continuing one or more drugs; and/or trials were included if they compared bridging to no bridging. Was there any restriction on the type of surgery e.g. could both major vascular surgery and skin biopsies be considered?

We have significantly expanded our methods section to address this concern. Our revised inclusion/exclusion criteria are as follows:

After initial title and abstract screen, full text articles presenting original data were included based on the following PICOT criteria:

(1) Patients were status post PCI with stent placement, on APT, undergoing elective NCS. Studies that combined cardiac and non-cardiac surgery were excluded unless outcomes were sufficiently stratified, or the proportion of cardiac surgery was small (<10%). Surgery was broadly defined and included major and minor procedures as well as endoscopy.

(2) Interventions considered included any combination of preoperative and perioperative APT management, including bridging. Preoperative strategies included DAPT or single APT (aspirin, P2Y12). For each preoperative strategy, multiple permutations of perioperative management were considered such as: DAPT, continue both agents; DAPT, hold one agent; or DAPT, hold both agents. Bridging strategies were also considered.

(3) Comparisons included alternative APT or bridging strategies, as well as stratification by time from PCI, type of surgical procedure, and by drug.

(4) Outcomes included bleeding and/or Major Adverse Cardiac Events (MACE) either as a composite or independently (i.e. in-stent thrombosis rates).

(5) There was no restriction on timing.

3. I found the tables and figures difficult to interpret. In tables 2 and 3 I find it difficult to understand what has been compared. If space is a problem, I don't think it is necessary to include the last two columns, because these can be summarised in the figures. Could the "stent" and "time since stent" boxes be combined to make it more readable?
We have included a lot of data in the tables and admit that it has been challenging to condense them into a readable, yet comprehensive, format. The complexity and “messiness” of the included studies at least partially contributes as studies used different designs (RCT vs. observational, cohort versus case-control), and numerous APT strategies. As a part of updating the search we added 3 additional studies and have revised the tables. We have alphabetized the studies within each table, standardized the order of operations included, merged the stent type and time since stent boxes, and expanded the headers to be more descriptive. We unfortunately cannot remove the outcome event rates (last two columns) in lieu of the figures as several studies (Assali, Bolad, as well as the case-control studies) are not included in the figures; this is mentioned in the text:

Each study included one or more APT strategy, with or without bridging. For two studies we were unable to determine preoperative APT. Details of these two are included in the tables but are not in the figures or our analysis. Similarly, the case-control studies did not have event rate. We therefore had 12 studies with both pre and perioperative APT strategies with sufficient data to calculate outcome rates. Because studies could describe more than one strategy, there was a total of 17 MACE data points and 17 bleeding data points.

4. Figures - I think the results should be presented in forest plots with an appropriate summary statistic e.g. odds ratios and 95% confidence interval. I can't see comparisons within these figures and I think that stopping antiplatelet drugs should be compared to continuing them (or standard of care versus other strategies).

We agree with the reviewer that this would be the ideal format for presenting comparative data. As mentioned in response to major point #1, the included studies made this very challenging. First, there is no standard of care when it comes to APT management in patients with coronary stents. Perhaps as a result of this, very few studies framed their protocol in a traditional comparative fashion (i.e. here is the base strategy and here is our “new” strategy). Most studies only described outcome rates for a single strategy. In the end, six different APT pre/perioperative strategies were described with no more than 3 data points within each strategy. Bridging added an additional layer of complexity. Due to this variety, our analytic strategy was to extract event rates for each strategy (when possible) and graphically portray these next to each other to assess visual relationships. We have expanded our methods section to reflect this:

Data were too heterogeneous for statistical pooling. Further, most studies only described one APT strategy without a comparison group. Of the studies that did compare two or more strategies, none compared the same two strategies. We were therefore unable to graph outcome rates in the traditional fashion (forest plots) but instead elected to plot MACE and bleeding outcomes stratified by pre and perioperative APT management. This allowed visual assessment of the relationship between multiple APT strategies and event rates. Studies were further stratified across multiple variables including bridging, timing of APT discontinuation, surgical procedure (major versus minor), and duration of time between stent placement and surgery.

Minor points
1. Please explain role of bridging in the background to make it clear how this fits with your questions about stopping/starting.

We have added the following to the bottom of the introduction:

Bridging therapy – the act of discontinuing oral antiplatelet agents and substituting short acting anticoagulants or intravenous antiplatelet agents - is sometimes considered in lieu of holding APT in its entirety. Despite ACC/AHA guidelines finding no evidence to support this strategy, a 2011 survey indicated that as many as half of interventional cardiologists would endorse it.

2. Search strategy 20 months old at time of review and would benefit from an update.

We have updated the search through October 11th, 2017. The search identified an additional 814 articles. Only 3 met our inclusion criteria and have been added to the review. One was a randomized trial. However, this study only included 43 cases and had significant methodologic limitations. We also added 2 observational studies – one focused on “bridging” therapy, and the other, a case-control study. Our conclusions have not changed substantially as a result of these additions. The manuscript has been extensively revised, however, to include these additional studies.

3. Devereaux et al. N Engl J Med 2014;370(16):1494-503 included a subgroup of 470 participants who would have been eligible for this review. While it is not essential these patients are included in this review, it significantly weakens it. Please would the authors justify why the original authors of trials such as the one above were not contacted for randomised subgroup data. It is likely that this will be the highest quality data available.

Attempts were made throughout the review to contact authors when the information provided would have been beneficial to our study. For example, two of the included studies did not have quite enough detail to ascertain preoperative APT management. Attempts were made to contact these authors several times without success. This is included in our methods section:

When preoperative and perioperative APT strategies were unclear, attempts were made to contact the corresponding authors for clarification.

The study by Devereaux and colleagues was identified in our literature search but we did not reach out for subgroup data for several reasons. First, over half of the patients in this study were not on antiplatelet therapy prior to study enrollment and were started on aspirin for the surgical procedure. Second, patients of interest to our question were explicitly excluded including those with DES < 1 year prior to surgery and those on P2Y12 inhibitors. Finally, the management of ASA alone in the perioperative setting was not considered as meaningful to the surgeons in our group compared to the management of P2Y12 inhibitors or DAPT.
4. The authors conclude: "perioperative APT management likely has a small impact on MACE and bleeding events relative to other clinical factors". I think this conclusion is too strong. I don't think there is enough evidence to assess this one way or the other.

We respectfully disagree with this concern for the following reasons. The evidence shows 5 to 10-fold differences in the rates of MACE or bleeding between the included studies. Some clinical factors must be responsible for these differences. Relative risks of 5 or greater are large effects, and if APT had that kind of effect than there should have been more of a signal of association between APT strategy and MACE or bleeding. Since we didn’t observe any signal at all, we can conclude that the RR for APT management strategy is probably less than 5, which means it is smaller than the other clinical factors, since there are up to 10-fold differences.

However, your point is well taken and we have softened the language, specifically in the conclusion of the abstract, to the following:

Evidence regarding perioperative APT management in patients with cardiac stents undergoing NCS is insufficient to guide clinical practice. Other clinical factors may have a greater impact that perioperative APT management on MACE and bleeding events.

5. Page 6: please expand on the definition of significant bleeding (this can be added to an appendix if necessary)

We have expanded the methods section as follows:

Hemorrhagic outcomes were heterogeneous. We included clinically significant bleeding events as decided by consensus of surgeon members of the study team (CC, MMG, JU, IM). Definitions of bleeding for each study were extracted and included in data tables. Examples of clinically relevant bleeding included need for blood transfusion, re-operation, escalation of care, or escalation of care. Some studies used standardized criteria, such as Bleeding Academic Research Consortia (BARC), but no two studies used the same criteria. Minor bleeding events (i.e. wound hematomas) were not included.

Further, we have added the individual studies definition of major bleeding to Tables 2 and 3 in the footnotes.

6. Page 6: numbers in "description of studies identified by the literature search" don’t match the PRISMA flow diagram - please amend

Thank you for noticing this. The number of studies has been reconciled between the text and the flow diagram.

7. Pre-perioperative is often used - I assume the authors mean pre-operative?
Our goal was to generate outcome rates for all possible combinations of preoperative and perioperative therapy. For example, a patient who presents to clinic on DAPT has at least 4 options – continue DAPT, hold ASA alone, hold the P2Y12 inhibitor alone, or hold both. We felt it was insufficient to assess outcome rates using the perioperative management (i.e. hold therapy) alone as the cardiac risk is presumably different between a patient on DAPT holding therapy versus a patient on ASA alone, holding therapy. We have tried to clean this language up throughout the text and have expanded the methods with the following:

Interventions considered included any combination of preoperative and perioperative APT management, including bridging. Preoperative strategies included DAPT or single APT (aspirin, P2Y12). For each preoperative strategy, multiple permutations of perioperative management were considered such as: DAPT, continue both agents; DAPT, hold one agent; or DAPT, hold both agents. Bridging strategies were also considered.

And then later…

Outcomes assessed included MACE and bleeding events. We attempted to extract MACE and/or bleeding rates for each combination of pre and perioperative APT (e.g. DAPT, hold both).

8. Please would the authors provide an overall assessment of the quality of the data. I suspect it is of very low quality, which will mean that the results should be considered to be very uncertain.

We have added a quality assessment of the one randomized trial as well as an overall assessment of quality using GRADE criteria. Our revised results now include:

The included RCT did not blind participants/personnel and had unclear allocation concealment and blinding of outcome assessment (Table 1a). The quality of cohort studies was variable; while most studies included a representative sample and abstracted data from medical records, methods used for assessing and adjusting differences in clinical variables were very heterogeneous (Table 1b).

And then later…

Grading the Quality of Evidence

We judged the overall quality of evidence as very low, based on serious limitations in study design, consistency of results, and precision of the estimates.

REVIEWER 2

1. The authors acknowledge this manuscript is a condensed version of a report prepared for the Veterans Affairs (VA) that is publicly available in reference 6. Could you please clarify if this VA report is cataloged in PubMed (available for free)? Perhaps, the authors should state in the
Abstract/Methods (or Funding) section some of this (e.g. This article presents a condensed version of the report published by the Department of Veterans Affairs).

The full report is available online for free, through the link in the citation. These reports do eventually get indexed in PubMed. We have updated the funding section as follows:

Funding/Support: The publication is based on a systematic review conducted by the Evidence-based Synthesis program funded by the Department of Veterans Affairs (VA). The full report is publically available online at:
https://www.hsrd.research.va.gov/publications/esp/AntiplateletTherapy.cfm

2. Page 6 line 137. Methods. The authors state: "The quality of cohort studies were evaluated based on design (retrospective versus prospective), representativeness of the enrolled subjects, balancing for sampling differences, follow-up rates, and statistical methods." Could you please clarify whether a specific risk of bias/quality assessment tool was used for epidemiological studies (including any reference)? Did you evaluate the quality of the case-control study(ies)?

We adapted items from the Quality in Prognosis Studies tool (Hayden JA, et al Ann Intern Med 2013;158:280-86) which has 6 domains: study participation (study sample adequately represents the population of interest), study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting. The domains we used, and their QUIPS equivalents, were: representativeness of the enrolled subject/study participation, follow-up rates/study attrition, balancing for sample differences/study confounding, and statistical methods/statistical analysis and reporting. The QUIPS domains of prognostic factor measurement and outcome measurement were handled separately in our assessment of reporting of perioperative APT management and in our assessment of MACE and bleeding. This reference has been added to the methods section.

3. Page 10 lines 239-244. Discussion. Perhaps the terms "strong signal of effect", and "lack of signal" could be reworded in line with the conclusion (e.g. Evidence regarding (...) is insufficient to guide clinical practice).

Thank you for this recommendation. We have revised the first paragraph of our discussion to mirror the conclusion more closely:

The principle conclusion from our systematic review is that the available literature is insufficient to guide perioperative APT management in patients with coronary stents undergoing NCS. Further, the results suggest that clinical factors other than APT management may be more responsible for MACE and bleeding rates such as indication and urgency of operation, timing since stent placement, invasiveness of the procedure, preoperative cardiac optimization, and functional status.
We again thank the reviewers and editors for their time. We hope this revision has sufficiently addressed their concerns, but please let us know if there is anything else we can edit or elaborate on further.

Sincerely,

Christopher Childers, MD