APPENDIX A. SEARCH STRATEGIES

Database searched and time period covered:
PubMed – From inception to 10/18/2016

Language:
English

Search strategy:
platelet aggregation inhibitors[mh] OR antiplatelet therap* OR anti-platelet therap*
AND
surgery OR surgical
AND
elective

Limited to English
## APPENDIX B. PEER REVIEW COMMENTS/AUTHOR RESPONSES

<table>
<thead>
<tr>
<th>Comment</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>I found one typo, there is no space between “13studies”. It is throughout the manuscript. Search and replace on “13studies” and make it “13 studies”.</td>
<td>The change has been made from “13studies” to “13 studies”.</td>
</tr>
<tr>
<td>I am disappointed that nothing could be concluded. The management of anti-platelet therapy is a major concern. We spend a lot of thought on it and finding that the evidence for our approaches is non-existent is disappointing. We must be doing something approximately correct as we seem to have reduced the number of catastrophes from APT management choices and surgery, but the evidence for our approaches is clearly non-existent. The review was straightforward and understandable, though of course limited due to lack of available literature to address the questions posed. That said, it articulated the issues (and lack of evidence) well. I found one typo on page 18, line 15: lacks” should be “lack”. Otherwise I have no comments.</td>
<td>The change has been made from “lacks” to “lack”.</td>
</tr>
</tbody>
</table>
| This will be an important publication and clearly outlines a large gap in our understanding of how best to manage high-risk patients with vascular disease. Minor points for revision: 1. Should key question 1 be changed from, “undergoing elective non-cardiac surgical procedures” to “undergoing elective non-cardiac surgery”? Or, should the title be changed to end in ‘Surgical Procedures” rather than “Surgery.” 2. Line 10: procedures in its first instance is misspelled 3. Would consider replacing phrase, “cerebrovascular accident” with, “Ischemic stroke.” 4. Under ‘Data Synthesis and Analysis,’ Methods section: Consider placing either eg, or ie, in the phrase, “setting (academic, community, Veterans Affairs)” | Unfortunately we are unable to change the title or key questions at this point; however, we did find an inconsistency in the language between the abstract and main body of the text that has been resolved. Thank you for the other recommendations. We have changed “cerebrovascular accident” to “ischemic stroke” throughout the report, and we have added “eg.” in the phrase, “setting (academic, community, Veterans Affairs)”.
| There is clearly a lack of reported data on the management of perioperative APT with peripheral stents. Clinicians generally manage APT based on the type of stents and the duration after implantation. Most vascular surgeons will operate on ASA alone as a bridging agent. Stent thrombosis is antecdotally low in this circumstance. Validation of these guidelines could be accomplished by retrospective reporting of outcomes based on these clinical guidelines. The VA is an ideal environment for such reporting, although clinical interest is relatively low. A randomized trial of this research question would require a large sample size (as mentioned) and has a low clinical impact. | This is a good point that we have incorporated into our research gaps/future research discussion. Given the size and quality of studies that currently exist, even a well-constructed observational study would have significant merit and may be more pragmatic in the event an RCT is never considered. |
## APPENDIX C. EVIDENCE TABLES

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Setting, # of Sites</th>
<th>Country</th>
<th>Sample Size</th>
<th>Surgical Field</th>
<th>Indications for APT</th>
<th>Perioperative Management</th>
<th>Major Bleeding</th>
<th>Thrombotic Outcomes</th>
<th>Other Outcomes</th>
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</thead>
<tbody>
<tr>
<td>Hussain, 2007</td>
<td>Retrospective, Case-Control (Case = post ERCP major bleeding)</td>
<td>Academic, Multi Site</td>
<td>Canada</td>
<td>126</td>
<td>Endoscopy</td>
<td>NR</td>
<td>Created variable for APT exposure within 10 days of procedure including ASA, NSAIDs, COX2 inhibitors and P2Y12 inhibitors</td>
<td>Exposure to APT not significantly associated with post procedural bleeding</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Jacob, 2014</td>
<td>Retrospective</td>
<td>Academic, Single Site</td>
<td>United States</td>
<td>142</td>
<td>Orthopedics</td>
<td>NR</td>
<td>Clopidogrel (n=142) Compared those that received dose within 7 days (n=24) to those that held &gt; 7 days (n=118)</td>
<td>NR</td>
<td>Transfusions: 29% vs 10% for intra-operative; 32 vs 8% within 24 hours; 37 vs 15% for entire hospitalization</td>
<td>MACE: Not statistically different</td>
</tr>
<tr>
<td>MacKinnon, 2008</td>
<td>Retrospective</td>
<td>Academic, Multi Site</td>
<td>United Kingdom</td>
<td>135</td>
<td>Renal Biopsy</td>
<td>NR</td>
<td>ASA (n=122), clopidogrel (n=9), dipyridamole (n=4) Continued (n=75), held (n=60)</td>
<td>NA</td>
<td>No difference in major bleeding</td>
<td>NR</td>
</tr>
<tr>
<td>McCunniff, 2016</td>
<td>Retrospective</td>
<td>Academic, Single Site</td>
<td>United States</td>
<td>454</td>
<td>Orthopedics</td>
<td>NR</td>
<td>Clopidogrel (n=13), ASA (n=72), No APT (n=369) All held</td>
<td>No difference in transfusions</td>
<td>MI, IS, DVT/PE: No events</td>
<td>NR</td>
</tr>
<tr>
<td>Radovanovic, 2012</td>
<td>Retrospective</td>
<td>Academic, Single Site</td>
<td>Ireland</td>
<td>60</td>
<td>Orthopedics</td>
<td>Atrial Fibrillation (n=12), DVT (n=4), NR (n=14) Coumadin (n=20), clopidogrel (n=10), control (n=30)</td>
<td>Coumadin 3-5 days until INR &lt;1.4; clopidogrel &gt;=5 days</td>
<td>Transfusions: Warfarin 40% vs 13% control; No difference clopidogrel vs control</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study Design</td>
<td>Setting, # of Sites</td>
<td>Country</td>
<td>Sample Size</td>
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<td>Indications for APT</td>
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<td>Thrombotic Outcomes</td>
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<tr>
<td>Ryan, 2013</td>
<td>Prospective</td>
<td>Academic, Multi Site</td>
<td>Ireland</td>
<td>85</td>
<td>Optho</td>
<td>CAD (n=38), Cerebro-vascular disease (n=11), Atrial Fibrillation (n=13), PVD (n=3), Thrombo-embolic Disease (n=4), Other (n=11)</td>
<td>DAPT (n=11), Plavix (n=8), ASA (n=77), Warfarin (n=11)</td>
<td>Continue</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Strosberg, 2016</td>
<td>Retrospective</td>
<td>Academic, Single Site</td>
<td>United States</td>
<td>200</td>
<td>General, Thoracic, Vascular</td>
<td>Coronary stent (n=75), peripheral stent (n=58), IS (n=34)</td>
<td>Clopidogrel (n=200), 143 of those on DAPT</td>
<td>Compared those that received clopidogrel within 5 days (n=88) to those that held &gt; 5 days (n=112)</td>
<td>NR</td>
<td>No difference in perioperative transfusion</td>
</tr>
<tr>
<td>Toepfer, 2013</td>
<td>Retrospective</td>
<td>Academic, Single Site</td>
<td>United States</td>
<td>624</td>
<td>Minor Urology</td>
<td>MI (n=39), IS (n=9), Afb (n=6), PE/DVT (n=7)</td>
<td>DAPT (n=13), clopidogrel (n=4), ASA (n=137), Controls (n=470)</td>
<td>Compared patients who received APT within 2 days of surgery to patients not on APT or on APT but discontinued &gt;5 days; patients who received dose between 2-5 days were excluded</td>
<td>NR</td>
<td>No difference in urinary clot retention</td>
</tr>
</tbody>
</table>

ALI = Acute limb ischemia, ASA = Aspirin; APT = Antiplatelet; CABG = Coronary Artery Bypass Graft; DVT = Deep Vein Thrombosis; ERCP = Endoscopic Retrograde Cholangio-Pancreatography; IS = Ischemic Stroke; MACE = Major Adverse Cardiac Event; MI = Myocardial Infarction; NSAID = Non-steroidal anti-inflammatory; Optho = Ophthalmology; PCI = Percutaneous Coronary Intervention; PE = Pulmonary Embolus | NA = Not applicable; NR = Not Recorded
APPENDIX D. CITATIONS FOR EXCLUDED STUDIES

Less than 70% on DAPT (n=11)


**Non Systematic Review (n=14)**


Not measuring outcome of interest (n=5)


Coronary stents (n=2)


Letter/commentary (n=4)


No original data (n=3)


Not population of interest (n=2)


Study protocol (n=1)


Case report (n=1)