

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

Comment	Response
<p>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".</p> <p>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.</p>	<p>The change has been made from "13studies" to "13 studies".</p>
<p>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</p>	<p>The change has been made from "lacks" to "lack".</p>
<p>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.</p> <p>Minor points for revision:</p> <ol style="list-style-type: none"> 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 <i>eg</i>, or <i>ie</i>, in the phrase, "setting (academic, community, Veterans Affairs) 	<p>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.</p> <p>Thank you for the other recommendations. We have changed "cerebrovascular accident" to "ischemic stroke" throughout the report, and we have added "<i>eg</i>," in the phrase, "setting (academic, community, Veterans Affairs)".</p>
<p>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 anecdotally 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.</p>	<p>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.</p>

APPENDIX C. EVIDENCE TABLES

Author, Year	Study Design	Setting, # of Sites	Country	Sample Size	Surgical Field	Indications for APT	Perioperative Management				Major Bleeding	Thrombotic Outcomes	Other Outcomes
							Preop	Periop	>5d?	Postop			
Hussain, 2007	Retro-spective, Case-Control (Case = post ERCP major bleeding)	Academic, Multi Site	Canada	126	Endoscopy	NR	Created variable for APT exposure within 10 days of procedure including ASA, NSAIDs, COX2 inhibitors and P2Y12 inhibitors				Exposure to APT not significantly associated with post procedural bleeding	NR	NR
Jacob, 2014	Retro-spective	Academic, Single Site	United States	142	Orthopedics	NR	Clopidogrel (n=142)	Compared those that received dose within 7 days (n=24) to those that held > 7 days (n=118)		NR	Transfusions: 29% vs 10% for intra-operative; 32 vs 8% within 24 hours; 37 vs 15% for entire hospitalization	MACE: Not statistically different	No difference in readmission or reoperation between groups
Mackinnon, 2008	Retro-spective	Academic, Multi Site	United Kingdom	135	Renal Biopsy	NR	ASA (n=122), clopidogrel (n=9), dipyridamole (n=4)	Continued (n=75), held (n=60)	Yes	NA	No difference in major bleeding	NR	NR
McCunniff, 2016	Retro-spective	Academic, Single Site	United States	454	Orthopedics	NR	Clopidogrel (n=13), ASA (n=72), No APT (n=369)	All held	Yes	NR	No difference in transfusions	MI, IS, DVT/PE: No events	NR
Radovanovic, 2012	Retro-spective	Academic, Single Site	Ireland	60	Orthopedics	Atrial Fibrillation (n=12), DVT (n=4), NR (n=14)	Coumadin (n=20), clopidogrel (n=10), control (n=30)	Stopped	Coumadin 3-5 days until INR <1.4; clopidogrel >=5 days	NR	Transfusions: Warfarin 40% vs 13% control; No difference clopidogrel vs control	NR	NR



Author, Year	Study Design	Setting, # of Sites	Country	Sample Size	Surgical Field	Indications for APT	Perioperative Management				Major Bleeding	Thrombotic Outcomes	Other Outcomes
							Preop	Periop	>5d?	Postop			
Ryan, 2013	Prospective	Academic, Multi Site	Ireland	85	Ophtho	CAD (n=38), Cerebrovascular disease (n=11), Atrial Fibrillation (n=13), PVD (n=3), Thromboembolic Disease (n=4), Other (n=11)	DAPT (n=11), Plavix (n=8), ASA (n=77), Warfarin (n=11)	Continue	NA	NA	Type of APT or anticoagulant not a significant risk factor for intraoperative or postoperative bleeding	NR	NR
Strosberg, 2016	Retro-spective	Academic, Single Site	United States	200	General, Thoracic, Vascular	Coronary stent (n=75), peripheral stent (n=58), IS (n=34)	Clopidogrel (n=200), 143 of those on DAPT	Compared those that received clopidogrel within 5 days (n=88) to those that held > 5 days (n=112)		NR	No difference in perioperative transfusion	No difference in MI, IS, ALI, visceral ischemia	No difference in 30 day mortality
Toepfer, 2013	Retro-spective	Academic, Single Site	United States	624	Minor Urology	MI (n=39), IS (n=9), Afib (n=6), PE/DVT (n=7)	DAPT (n=13), clopidogrel (n=4), ASA (n=137), Controls (n=470)	Compared patients who received APT within 2 days of surgery to patients not on APT or on APT but discontinued >5 days; patients who received dose between 2-5 days were excluded		NR	No difference in urinary clot retention	No difference in stroke MI, DVT, PE	No difference in mortality, 30 day readmission, reoperation

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; Ophtho = 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)

1. Rahman M, Donnangelo LL, Neal D, Mogali K, Decker M, Ahmed MM. Effects of Perioperative Acetyl Salicylic Acid on Clinical Outcomes in Patients Undergoing Craniotomy for Brain Tumor. *World neurosurgery*. 2015;84(1):41-47.
2. Alcock RF, Naoum C, Aliprandi-Costa B, Hillis GS, Brieger DB. The peri-operative management of anti-platelet therapy in elective, non-cardiac surgery. *International journal of cardiology*. 2013;167(2):374-377.
3. Antolovic D, Rakow A, Contin P, et al. A randomised controlled pilot trial to evaluate and optimize the use of anti-platelet agents in the perioperative management in patients undergoing general and abdominal surgery--the APAP trial (ISRCTN45810007). *Langenbeck's archives of surgery*. 2012;397(2):297-306.
4. De Martino RR, Beck AW, Hoel AW, et al. Preoperative antiplatelet and statin treatment was not associated with reduced myocardial infarction after high-risk vascular operations in the Vascular Quality Initiative. *Journal of vascular surgery*. 2016;63(1):182-189.e182.
5. De Martino RR, Eldrup-Jorgensen J, Nolan BW, et al. Perioperative management with antiplatelet and statin medication is associated with reduced mortality following vascular surgery. *Journal of vascular surgery*. 2014;59(6):1615-1621, 1621.e1611.
6. De Martino RR, Hoel AW, Beck AW, et al. Participation in the Vascular Quality Initiative is associated with improved perioperative medication use, which is associated with longer patient survival. *Journal of vascular surgery*. 2015;61(4):1010-1019.
7. Dzupa V, Waldauf P, Motovska Z, et al. Risk comparison of bleeding and ischemic perioperative complications after acute and elective orthopedic surgery in patients with cardiovascular disease. *Arch Orthop Trauma Surg*. 2016;136(7):907-911.
8. Hermiz S, Larsen P, Galletly DC, Harding SA. Peri-operative management of anti-platelet agents. *ANZ J Surg*. 2009;79(7-8):521-525.
9. Joo MS, Ahn BM, Kim HJ, et al. Evaluation of feasible timing of elective noncardiac procedure after antiplatelet discontinuation in patients treated with antiplatelet agents. *Journal of investigative medicine : the official publication of the American Federation for Clinical Research*. 2014;62(5):808-812.
10. Ong WL, Koh TL, Fletcher J, Gruen R, Royce P. Perioperative Management of Antiplatelets and Anticoagulants Among Patients Undergoing Elective Transurethral Resection of the Prostate--A Single Institution Experience. *Journal of endourology*. 2015;29(11):1321-1327.

11. Wolf AM, Pucci MJ, Gabale SD, et al. Safety of perioperative aspirin therapy in pancreatic operations. *Surgery*. 2014;155(1):39-46.

Non Systematic Review (n=14)

1. Abdel Samie A, Theilmann L. Endoscopic procedures in patients under clopidogrel/dual antiplatelet therapy: to do or not to do? *Journal of gastrointestinal and liver diseases : JGLD*. 2013;22(1):33-36.
2. Chassot PG, Delabays A, Spahn DR. Perioperative use of anti-platelet drugs. *Best practice & research Clinical anaesthesiology*. 2007;21(2):241-256.
3. Chassot PG, Marcucci C, Delabays A, Spahn DR. Perioperative antiplatelet therapy. *American family physician*. 2010;82(12):1484-1489.
4. Degirmenci SE, Steib A. Peri-operative management of anticoagulation and antiplatelet therapy in gastrointestinal surgery. *Journal of visceral surgery*. 2014;151(2):125-135.
5. Di Minno MN, Prisco D, Ruocco AL, Mastronardi P, Massa S, Di Minno G. Perioperative handling of patients on antiplatelet therapy with need for surgery. *Internal and emergency medicine*. 2009;4(4):279-288.
6. Gandhi S, Narula N, Mosleh W, Marshall JK, Farkouh M. Meta-analysis: colonoscopic post-polypectomy bleeding in patients on continued clopidogrel therapy. *Alimentary pharmacology & therapeutics*. 2013;37(10):947-952.
7. Gerstein NS, Schulman PM, Gerstein WH, Petersen TR, Tawil I. Should more patients continue aspirin therapy perioperatively?: clinical impact of aspirin withdrawal syndrome. *Annals of surgery*. 2012;255(5):811-819.
8. Kiire, C. A., Mukherjee, R., Ruparelia, N., Keeling, D., Prendergast, B., & Norris, J. H. Managing antiplatelet and anticoagulant drugs in patients undergoing elective ophthalmic surgery. *British Journal of Ophthalmology*, bjophthalmol-2014.
9. McKenzie JL, Douglas G, Bazargan A. Perioperative management of anticoagulation in elective surgery. *ANZ J Surg*. 2013.
10. McKenzie JL, Douglas G, Bazargan A. Perioperative management of anticoagulation in elective surgery. *ANZ J Surg*. 2013;83(11):814-820.
11. Mohr TS, Brouse SD. Perioperative management of antiplatelet agents. *Orthopedics*. 2012;35(8):687-691.
12. O'Riordan JM, Margey RJ, Blake G, O'Connell PR. Antiplatelet agents in the perioperative period. *Archives of surgery (Chicago, Ill : 1960)*. 2009;144(1):69-76; discussion 76.
13. Sahebally SM, Healy D, Coffey JC, Walsh SR. Should patients taking aspirin for secondary prevention continue or discontinue the medication prior to elective, abdominal surgery? Best evidence topic (BET). *International journal of surgery (London, England)*. 2014;12(5):16-21.
14. Steele MJ, Fox JS, Fletcher JP, Grigg LE, Bell G. Clopidogrel dilemma for orthopaedic surgeons. *ANZ J Surg*. 2011;81(11):774-784.

Not measuring outcome of interest (n=5)

1. Kim SH, Lee JH, Joo W, et al. Analysis of the risk factors for development of post-operative extradural hematoma after intracranial surgery. *British journal of neurosurgery*. 2015;29(2):243-248.
2. Mantas GK, Antonopoulos CN, Sfyroeras GS, et al. Factors Predisposing to Endograft Limb Occlusion after Endovascular Aortic Repair. *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery*. 2015;49(1):39-44.
3. Okano A, Oya S, Fujisawa N, et al. Analysis of risk factors for chronic subdural haematoma recurrence after burr hole surgery: optimal management of patients on antiplatelet therapy. *British journal of neurosurgery*. 2014;28(2):204-208.
4. Trellopoulos G, Georgiadis GS, Nikolopoulos ES, Kapoulas KC, Georgakarakos EI, Lazarides MK. Antiplatelet treatment and prothrombotic diathesis following endovascular abdominal aortic aneurysm repair. *Angiology*. 2014;65(9):783-787.
5. Wild JB, Dattani N, Stather P, Bown MJ, Sayers RD, Choke E. Effect of anticoagulation and antiplatelet therapy on incidence of endoleaks and sac size expansions after endovascular aneurysm repair. *Ann Vasc Surg*. 2014;28(3):554-559.

Coronary stents (n=2)

1. Abdel Samie A, Stumpf M, Sun R, Theilmann L. Biliary-Pancreatic Endoscopic and Surgical Procedures in Patients under Dual Antiplatelet Therapy: A Single-Center Study. *Clinical endoscopy*. 2013;46(4):395-398.
2. Abdel Samie AA, Sun R, Vohringer U, Theilmann L. Safety of endoscopic sphincterotomy in patients under dual antiplatelet therapy. *Hepato-gastroenterology*. 2013;60(124):659-661.

Letter/commentary (n=4)

1. Belletrutti PJ, Heitman SJ. Management of anticoagulants and antiplatelet agents in elective endoscopy: weighing the risks and benefits. *Canadian journal of gastroenterology = Journal canadien de gastroenterologie*. 2007;21(9):553-555.
2. Al Busafi SA. Management of antiplatelets in elective GI endoscopies: a collaboration between the endoscopist and the cardiologist. *Gastrointestinal endoscopy*. 2009;69(1):185; author reply 185-186.
3. Clevenger B, Jaggar S. Anti-platelet therapy in non-cardiac elective surgery. *British journal of anaesthesia*. 2012;108(4):699; author reply 699.
4. Mukherjee R, Kiire CA, Ruparelia N, Keeling D, Prendergast B, Norris JH. Managing antiplatelet and anticoagulant drugs in patients undergoing elective ophthalmic surgery. Authors' response. *The British journal of ophthalmology*. 2014;98(8):1136-1137.

No original data (n=3)

1. Mitka M. Myocardial infarction risks remain for patients undergoing noncardiac elective surgery. *Jama*. 2014;311(19):1955-1956.

2. Mukerji G, Munasinghe I, Raza A. A survey of the peri-operative management of urological patients on clopidogrel. *Annals of the Royal College of Surgeons of England*. 2009;91(4):313-320.
3. Savage JR, Parmar A, Robinson PJ. Antiplatelet drugs in elective ENT surgery. *The Journal of laryngology and otology*. 2012;126(9):886-892.

Not population of interest (n=2)

1. Arias EJ, Patel B, Cross DT, 3rd, et al. Timing and nature of in-house postoperative events following uncomplicated elective endovascular aneurysm treatment. *Journal of neurosurgery*. 2014;121(5):1063-1070.
2. Kim B, Kim K, Jeon P, et al. Thromboembolic complications in patients with clopidogrel resistance after coil embolization for unruptured intracranial aneurysms. *AJNR American journal of neuroradiology*. 2014;35(9):1786-1792.

Study protocol (n=1)

1. Antolovic D, Reissfelder C, Rakow A, et al. A randomised controlled trial to evaluate and optimize the use of antiplatelet agents in the perioperative management in patients undergoing general and abdominal surgery--the APAP trial (ISRCTN45810007). *BMC surgery*. 2011;11:7.

Case report (n=1)

1. Harris K, Kebbe J. Endobronchial biopsies on aspirin and prasugrel. *Heart, lung & circulation*. 2015;24(6):e68-70.