

A Meta-analysis of the Impact of Aspirin, Clopidogrel, and Dual Antiplatelet Therapy on Bleeding Complications in Noncardiac Surgery

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Objective: The aim of this study was to determine the bleeding risks associated with single (aspirin) and dual (aspirin + clopidogrel) antiplatelet therapy (DAPT) versus placebo or no treatment in adults undergoing noncardiac surgery.

Summary of Background Data: The impact of antiplatelet therapy on bleeding during noncardiac surgery remains controversial. A meta-analysis was performed to examine the risk associated with single and DAPT.

Methods: A systematic review of antiplatelet therapy, noncardiac surgery, and perioperative bleeding was performed. Peer-reviewed sources and meeting abstracts from relevant societies were queried. Studies without a control group, or those that only examined patients with coronary stents, were excluded. Primary endpoints were transfusion and reintervention for bleeding.

Results: Of 11,592 references, 46 studies met inclusion criteria. In a meta-analysis of >30,000 patients, the relative risk (RR) of transfusion versus control was 1.14 [95% confidence interval (CI) 1.03–1.26, $P = 0.009$] for aspirin, and 1.33 (1.15–1.55, $P = 0.001$) for DAPT. Clopidogrel had an elevated risk, but data were too heterogeneous to analyze. The RR of bleeding requiring reintervention was not significantly higher for any agent compared to control [RR 0.96 (0.76–1.22, $P = 0.76$) for aspirin, 1.84 (0.87–3.87, $P = 0.11$) for clopidogrel, and 1.51 (0.92–2.49, $P = 0.1$) for DAPT]. Subanalysis of thoracic and abdominal procedures was similar. There was no difference in RR for myocardial infarction [1.06 (0.79–1.43)], stroke [0.97 (0.71–1.33)], or mortality [0.97 (0.87–1.1)].

Conclusions: Antiplatelet therapy at the time of noncardiac surgery confers minimal bleeding risk with no difference in thrombotic complications. In many cases, it is safe to continue antiplatelet therapy in patients with important indications for their use.

Keywords: antiplatelet therapy, antiplatelet therapy in noncardiac surgery, bleeding in noncardiac surgery, meta-analysis, perioperative bleeding risk for antiplatelet therapy, perioperative management of antiplatelet therapy, systematic review

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Perioperative management of antiplatelet therapy is ubiquitous in contemporary surgical practice.^{1,2} Nearly one-third of the US population older than 40 years uses aspirin.³ Furthermore, although the widespread utilization of alternative and synergistic antiplatelet therapies has fundamentally advanced cardiovascular care in many patients,⁴ it has also simultaneously complicated the medical management among those presenting for surgery.^{5,6} To date, randomized trials have demonstrated that >40% of patients presenting for noncardiac surgery take aspirin regularly,¹ and some observational studies suggest even more prevalent use.² Accordingly, surgeons are regularly confronted with the decision of whether or not to interrupt antiplatelet therapy during the perioperative period.

Medical management strategies remain controversial and hinge on the tradeoff between the potential protective effect of antiplatelet therapy versus the risk of bleeding.^{7,8} These observations are grounded in the findings of increased perioperative cytokine and hormonal changes, which potentially expose vulnerable patients to an increased risk of thrombotic events.^{9–11} Conversely, the possible impaired hemostasis owing to antiplatelet agents may have a more deleterious impact.^{11,12} Data surrounding this topic are mixed. Although some studies have reported a modest increase in bleeding risk, but no difference in myocardial infarction (MI), stroke, or death in patients taking antiplatelet agents,^{1,13} other studies have revealed no difference in significant bleeding events,^{14,15} even among those on dual antiplatelet therapy (DAPT).² Consequently, controversy persists with some surgeons stopping antiplatelet therapy in advance of surgery, whereas others continue therapy perioperatively.

Previous reviews have examined the benefits and risks of antiplatelet therapy in the perioperative period among those undergoing noncardiac surgery; however, many remain fraught with important limitations. Specifically, heterogeneity in outcome reporting has hindered the ability to compare results across studies.¹⁶ In addition, previous studies have focused only on certain agents,¹⁷ restricted populations,¹⁸ specific years,¹⁶ or were published >10 years ago, thereby diminishing their applicability to current practice.¹⁹

To address these concerns, a systematic review and meta-analysis was performed to determine the bleeding risks associated with single and DAPT versus placebo or no treatment in adults undergoing noncardiac surgery. Our hypothesis was that antiplatelet therapy would confer a modest increase in the risk of perioperative bleeding events. These results will further delineate the risk-benefit balance of continuation versus interruption of antiplatelet therapy in the perioperative period.

METHODS

This systematic review and meta-analysis was conducted in accordance with the recommendations set forth by the Transparent Reporting of Systematic Reviews and Meta-analyses²⁰ statement for randomized controlled trials (RCTs), and with the Meta-Analyses

and Systematic Reviews of Observational Studies²¹ guidelines for observational data. The protocol has been registered with PROSPERO (registration number CRD42016053663), and full details are available on their website.²²

Study Eligibility and Outcomes

Study Population

Studies that measured perioperative bleeding events in adult (≥ 18 years) patients taking oral aspirin or contemporary p2y12 inhibitors at the time of noncardiac surgery were included. The protocol allowed RCTs as well as prospective and retrospective observational studies. Studies whose cohorts were made up entirely of patients with coronary stents were excluded,²³ as results for this subgroup of patients are unlikely to be generalizable to the adult population. However, patients with coronary stents are regularly encountered in surgical practice. For this reason, articles that reviewed a broad group of patients, including those with or without previous coronary stents, were included.

Drugs of Interest

The primary focus was on studies examining aspirin (75–500 mg daily)⁷ and clopidogrel (75 mg daily)⁴ or a combination thereof. In addition, studies examining both prasugrel (10 mg daily)⁵ and ticagrelor (90 mg twice daily)⁶ were also queried to assess the potential effect of newer antiplatelet regimens. When observational studies did not report the dose of the aforementioned medications, it was assumed that regimens were in compliance with the usual dosing recommendations above.

Timing of Administration

Although current societal-based guidelines recommend cessation of aspirin 7 to 10 days before elective surgery,²⁴ platelet function is likely to recover earlier than this, and contemporary RCTs have used 72 hours as the period of cessation before surgical intervention.¹ Therefore, patients were considered to be on aspirin therapy if aspirin had been administered within 48 to 72 hours of surgery. Although no societal-based guidelines exist within the United States for clopidogrel, the British National Formulary recommends cessation 7 days before elective surgery.²⁵ Clinical trials have also demonstrated that platelet function returns to the level of placebo after 7 days.²⁶ For this reason, patients who had taken a dose of clopidogrel within 7 days before an operation were considered to be on clopidogrel therapy perioperatively. Platelet function after ticagrelor has been shown to return to the level of placebo after 5 days in experimental trials.²⁶ Therefore, patients were considered to be on ticagrelor if they had taken a dose within 5 days before surgery. No official guidelines exist to direct cessation of prasugrel therapy. Accordingly, a conservative threshold of 7 days' cessation was utilized to be considered off the drug before surgery.²⁷ Studies that evaluated high-dose aspirin (> 500 mg daily), intravenous inhibitors, investigational drugs, drugs no longer in production in the United States (ticlopidine),²⁸ and drugs with other mechanisms of action (eg, vitamin K antagonists or novel oral anticoagulants) were excluded. A control group (placebo or no antiplatelet therapy with cessation times as listed above) with $< 10\%$ contamination of patients taking antiplatelet agents was required for inclusion.

Procedures of Interest

Studies that examined general noncardiac, thoracic, abdominal, major urologic, orthopedic, and vascular operations, were included. Those that focused exclusively on cardiac, neurosurgical, ophthalmologic, dental, cutaneous, percutaneous, or endoscopic procedures were excluded. Studies were also excluded if they did

not report any details on bleeding events. When multiple manuscripts were found utilizing the same registry or database, the study with the largest number of patients was included in the review. The remaining studies were excluded to ensure patients were not counted repeatedly.

Outcome Measures

The primary outcome was perioperative bleeding. All bleeding outcomes reported by the authors of the included studies were considered. For summary estimates, studies were pooled on 2 specific endpoints: 1) the need for red blood cell transfusion and 2) the need for reintervention for bleeding. To allow for a conservative estimate, reintervention for bleeding included reoperation for bleeding, angiographic embolization for bleeding, and conversion from minimally invasive to open surgery. These outcomes were chosen because they are commonly reported and represent discrete, clinically meaningful events. Secondary outcomes included MI, stroke, and all-cause mortality.

Search Strategy

Databases, Search Terms, and Limits

A search was conducted with the assistance of a reference librarian (HJ) to identify relevant studies within MEDLINE (January 1, 1946 to September 12, 2016), Embase (January 1, 1974 to September 13, 2016), the Cochrane Library (inception to September 14, 2016), and Web of Science (inception to September 13, 2016) databases. To identify potentially relevant studies in MEDLINE, exploded MeSH terms and keywords were used to generate sets for the following themes: surgery [MeSH: operative surgical procedures; keywords surg*(tiab)], antiplatelet therapy [MeSH: aspirin, platelet aggregation inhibitors, platelet aggregation inhibitors (pharmacologic action), purinergic P2Y receptor antagonists; keywords aspirin(tiab), acetylsalicylic acid(tiab), antiplatelet(tiab), platelet aggregation inhibitor(tiab), brilinta(tiab), ticagrelor(tiab), clopidogrel(tiab), plavix(tiab), prasugrel(tiab), effient(tiab)], and perioperative bleeding [MeSH: postoperative hemorrhage, blood loss, surgical; keywords bleed*(tiab), blood loss(tiab), hemorrhage(tiab), haemorrhage(tiab)]. The Boolean operator "AND" was used to find the intersection between these themes. No limits were used and no language restrictions were applied. This search approach was modified as necessary to search each electronic database.

Additional Search Methods

To identify additional and unpublished data, subject matter experts were contacted, and references of included studies and ClinicalTrials.gov (inception to September 23, 2016) were reviewed. Furthermore, abstracts were reviewed from the last 5 years of the American Heart Association, the Society for Vascular Surgery, the American College of Surgeons, and the American Society of Hematology annual meetings.

Study Selection

Six reviewers (SB, NC, JC, DL, AL, RS) screened titles and abstracts from the preliminary search results to select studies for full-text review based on the eligibility criteria described above. All relevant articles underwent full-text review. Two independent reviewers (JC, AL) conducted full-text review for all studies passing the screening phase. Each reviewer then classified articles as either meeting or not meeting inclusion criteria based on full-text consideration. Multilingual reviewers (BS, IB) considered articles not written in English.^{29,30} All discrepancies between reviewers were resolved by consensus or by a third-party reviewer if consensus could not be reached.

Data Extraction and Synthesis

Data Collection

Two reviewers (JC, AL) independently extracted data from the included studies using a piloted, standardized data abstraction form. Data were abstracted across multiple domains to include information on study details, intervention type, patient demographics, potential confounding variables, and outcomes determined a priori to our data collection. When data were reported as percentages, they were back-calculated to raw numbers by multiplying the percentages by the number of patients at risk. If numbers could not be reasonably obtained from the manuscript, the data point was noted as “not reported.” When authors stratified results by different surgical procedures, results in this review were likewise reported in a stratified manner. When authors stratified patient groups based on the timing of the last dose of antiplatelet therapy, groups were pooled for this review based on our a priori timing criteria described above. Contact was attempted with corresponding authors for all studies that did not report the primary endpoints in a granular manner to allow for meta-analysis (authors responding are listed in the acknowledgments). All discrepancies among reviewers were resolved by consensus or by a third-party reviewer if consensus could not be reached.

Assessment of Methodological Quality

Two blinded reviewers (NC, RS) independently assessed each of the included studies for bias. Observational cohort studies were assessed with the Newcastle-Ottawa Quality Assessment Scale (NOS).³¹ Using the NOS, each observational study was scored on the domains of case selection (maximum possible 4 stars), comparability (maximum possible 2 stars), and outcome (maximum possible 3 stars) for a total of 9 possible stars. RCTs were assessed with the Cochrane Risk of Bias Tool.³² Using this tool, 6 domains related to randomization, blinding, outcomes, reporting, and other potential sources of bias were assessed. Each of the 6 domains was graded as high, low, or unclear risk of bias. All discrepancies between reviewers were resolved by consensus or by a third-party reviewer if consensus could not be reached. Multilingual reviewers (BS, IB) abstracted data and assessed bias from articles in languages other than English.^{29,30}

Data Synthesis

Results are reported as numbers, percentages, odds ratios (OR), and relative risks (RR), as appropriate. We calculated RRs with 95% confidence intervals (CI) for the predetermined pooled endpoints using RevMan software.³³ To ensure that estimates remained stable, OR and Peto OR were also calculated, with both random- and fixed-effect modeling, for each outcome of interest. Because these sensitivity analyses did not change the results in a meaningful way, results are reported as RR using a random-effects model. A *P* value of <0.05 was considered statistically significant for each pooled effect. Heterogeneity was assessed using Cochran's *Q* and *I*² statistic. Statistically significant and meaningful heterogeneity was defined as an *I*² >50% and a *P* value of <0.1. Prespecified subgroup analyses were conducted based on the type of study design (RCT vs prospective observational vs retrospective observational), and type of procedure (thoracic or abdominal). Sensitivity analyses based on operation type, study design, and risk of bias (low-moderate risk vs high-risk) were conducted to assess the stability of the magnitude, direction, and statistical significance of the summary estimates given each of these criteria. When studies reported no events in one of the study arms, the traditional 0.5 correction for the estimate of that study was applied as is the standard in RevMan.³³ To ensure the stability of these estimates, a sensitivity analysis was performed using the *Metan* command in Stata with a more conservative correction of 0.1.³⁴ When studies reported no

events in either arm, they were excluded from that portion of the analysis. Not all studies provided outcomes of sufficient granularity for meta-analysis, we therefore conducted a qualitative analysis of all included articles. This was performed by review of the main findings of each individual study by 2 independent reviewers (JC, AL) and then consensus for the aggregate effect. Lastly, publication bias was assessed by visual inspection of funnel plots for studies reporting results on both sides of the summary estimate. A minimum of 10 pooled studies was required for this assessment.

Dealing with Confounding

As many patients are on chronic antiplatelet therapy for secondary prevention,^{3,35} these patients are at an elevated baseline risk for MI, stroke, and all-cause mortality.³⁶ Those with more comorbid conditions may also have an increased risk of chronic anemia, and therefore be at higher risk of blood transfusion.³⁷ For this reason, sensitivity analyses were conducted by study design for the primary outcomes. These effects, however, are likely to be most pronounced when considering the risks of MI, stroke, and all-cause mortality. Owing to these factors, data from observational studies were not combined on the secondary endpoints, and meta-analysis of MI, stroke, and all-cause mortality were limited to RCTs.

RESULTS

Search Results

The initial search yielded a total of 10,361 unique references for review (Fig. 1). After screening, a full-text review was conducted on 926 distinct reports. Ultimately, 46 studies were included in the qualitative synthesis (full reference list available in the Supplementary Appendix, <http://links.lww.com/SLA/B222>). Of these 46 studies, 37 provided a granular level of detail for meta-analysis. Table 1 describes the key characteristics and findings of the included studies, which included 8 RCTs, 13 prospective observational studies, and 25 retrospective observational studies. The studies covered a variety of different operations, and sample sizes varied widely (range 43–13,356 patients). The primary antiplatelet agents studied were aspirin, clopidogrel, or DAPT with both agents. No studies that primarily focused on prasugrel or ticagrelor were identified. Among RCTs, the risk of bias was low. Among observational cohort studies, the risk of bias on average was low, with the most common bias being attributed to concerns about the comparability of the drug and control groups. Although RCTs were well-balanced, observational studies tended to include older patients with more comorbid diagnoses and higher American Society of Anesthesiologists (ASA) scores. Exhaustive study details and the risk of bias assessment details are available in the Supplementary Appendix, <http://links.lww.com/SLA/B222>. One ongoing prospective study that may have met inclusion criteria was identified; however, the author was unable to be reached for comment.³⁸

Primary Outcomes: Quantitative Analysis

Reintervention

Of the 46 included studies, 28 provided appropriate data for pooling to evaluate the risk of reintervention. There was no increased risk of reintervention for aspirin (27 studies: RR 0.96, 95% CI 0.76–1.22), clopidogrel (7 studies: RR 1.84, 95% CI 0.87–3.87), or DAPT (5 studies: RR 1.51, 95% CI 0.92–2.49). Heterogeneity was low across the different antiplatelet regimens (Cochran's *Q* = 19.1, *P* = 0.64, *I*² = 0% for aspirin; Cochran's *Q* = 5.73, *P* = 0.57, *I*² = 0% for clopidogrel; and Cochran's *Q* = 4.47, *P* = 0.61, *I*² = 0% for DAPT). Findings were robust to sensitivity analyses performed with respect to bias, study design, type of operation, and the

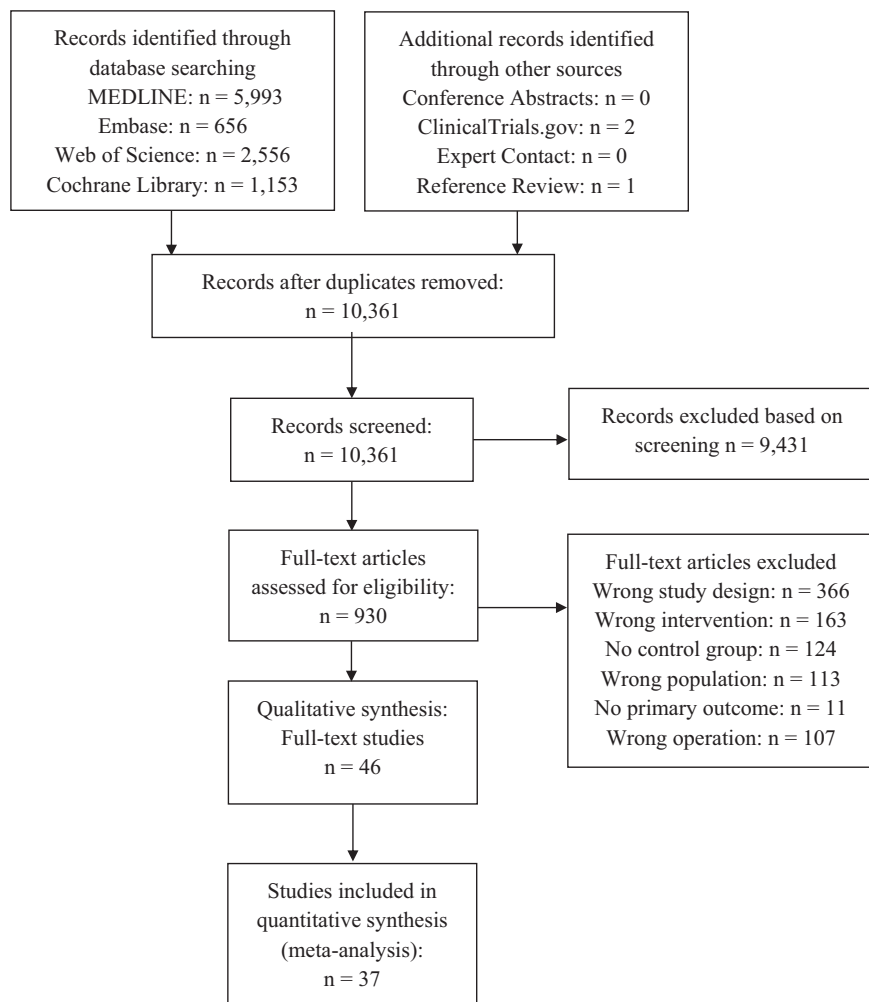


FIGURE 1. Transparent Reporting of Systematic Reviews and Meta-analyses flow diagram outlining the search strategy results from initial search to included studies.

variations on estimate modeling mentioned above (Figs. 2 and 3). The risk of publication bias appeared to be low (Supplementary Appendix, <http://links.lww.com/SLA/B222>).

Blood Transfusion

There were 29 studies that provided appropriate data for pooling to evaluate the risk of blood transfusion in the perioperative period. There was an increased risk of blood transfusion among RCTs and prospective observational studies (10 studies: RR 1.28, 95% CI 1.1–1.5) with minimal heterogeneity (Cochran's $Q = 6.33$, $P = 0.71$, $I^2 = 0\%$) for aspirin versus control. Although the risk estimates were similar for retrospective studies (18 studies: RR 1.22, 95% CI 1.06–1.41), these studies introduced significant heterogeneity (Cochran's $Q = 60.38$, $P = 0.0001$, $I^2 = 57\%$). This heterogeneity was attributed primarily to open abdominal aortic aneurysm repair (low rates of transfusion vs control),² and open prostate surgery (high rates of transfusion vs control).³⁹ After removal of these respective strata, we noted a persistent increased risk of blood transfusion for aspirin versus control among pooled RCTs and observational studies (28 studies: RR 1.14, 95% CI 1.03–1.26) with reduced heterogeneity (Cochran's $Q = 29.15$, $P = 0.21$, $I^2 = 18\%$). There was also significant heterogeneity for the 5 studies examining the risk of transfusion for clopidogrel versus control (Cochran's $Q = 20.83$, $P = 0.0003$, $I^2 = 87\%$). No clear reason for this

heterogeneity was identified, and therefore a pooled estimate was not created. Finally, 3 studies evaluating DAPT reported a significant increase in the risk of transfusion (RR 1.33, 95% CI 1.15–1.55) and had little heterogeneity (Cochran's $Q = 3.26$, $P = 0.52$, $I^2 = 0\%$). These risk estimates for studies reporting on transfusion were robust to sensitivity analyses performed with respect to bias, study design, type of operation, and the variations on estimate modeling mentioned above (Figs. 2 and 3). The risk of publication bias appeared to be low (Supplementary Appendix, <http://links.lww.com/SLA/B222>).

Primary Outcomes: Qualitative Synthesis

As reported by the individual authors, most studies reported no difference in perioperative bleeding with antiplatelet therapy ($n = 31$, Table 1); however, 2 large RCTs documented a mildly increased risk.^{1,13} In a trial of 10,010 patients undergoing noncardiac surgery, Devereaux et al¹ noted an increased risk of bleeding in patients taking aspirin versus placebo (RR 1.23, 95% CI 1.01–1.49, $P = 0.04$). Additionally, in a trial of 13,356 patients undergoing surgery for hip fracture, the Pulmonary Embolism Prevention investigators also reported an increased risk of blood transfusion in those taking aspirin versus placebo (2.9% vs 2.4%, $P = 0.04$).¹³ One active prospective study was identified that is examining the use of aspirin in elective hernia surgery. Although enrollment is ongoing, interim analysis shows no difference in bleeding complications (personal

TABLE 1. Key Characteristics and Bleeding Outcomes of Included Studies

Author, Year	Surgery	n Intervention/n Control	Risk of Bleeding for Antiplatelet Relative to Control*
Randomized controlled trials: aspirin vs placebo			
Lindbald, 1993	CEA	117/115	No difference
PEP Group, 2000	Hip fracture	6679/6677	Transfusion 2.9% vs 2.4%, $P = 0.04$
Oscarsson, 2010	Noncardiac	109/111	No difference
Mantz, 2011	Noncardiac	145/146	No difference
Devereaux, 2014	Noncardiac	4998/5012	Major bleeding [†] RR 1.23 (1.01, 1.49), $P = 0.04$
Aspirin vs no AP			
Antlovic, 2012	Noncardiac	26/26	No difference
Clopidogrel vs placebo			
Ghorbani, 2009	AVF	46/47	No difference
Clopidogrel vs no AP			
Chu, 2016	Abdominal	22/21	No difference
Prospective observational studies: aspirin vs no AP			
Ferraris, 1983	Noncardiac	27/25	No difference
Anekstein, 2004	Hip fracture	39/65	Inc. mean transfusion 0.5 units in aspirin group, $P = 0.007$
Manning, 2004	Hip fracture	24/53	Transfusion 37.5% vs 17.3%, $P < 0.05$
Ono, 2011	Lap cholecystectomy	29/241	No difference
	Lap colorectal cancer	23/195	No difference
Binhas, 2012	Robot/lap prostatectomy	54/569	No difference
Cossetto, 2012	THA TKA	63/76	No difference
Schoenefeld, 2012	CEA	267/273	No difference
Mas-Atance, 2013	Hip fracture	70/105	No difference
Dual AP vs clopidogrel vs aspirin vs no AP			
Thaler, 2010	Hip fracture	3/19/98/342	No difference
Chechik, 2011 [‡]	Hip fracture	15/30/22/25	Inc. EBL in clopidogrel, $P = 0.005$ and dual AP, $P = 0.0003$
Bücking, 2013	Hip fracture	3/6/101/94	No difference
Widimský, 2014	Noncardiac	44/20/638/198	No difference
Retrospective observational studies: aspirin versus no AP			
Kennedy, 2006	Hip fracture	40/58	No difference
Kragh, 2011	Hip fracture	118/137	Transfusion OR 1.8 (1.04, 3.3), $P = 0.04$
Castillo Monsegur, 2012	TKA	30/277	No difference
Parikh, 2012	Robot/lap nephrectomy	14/12	No difference
	Robot/lap prostatectomy	51/44	No difference
Bogani, 2013	Lap EC staging	43/274	Transfusion 5% vs 1%, $P = 0.09$
Mortezavi, 2013	Robot radical prostatectomy	38/76	No difference
Kanzaki, 2014	Lung cancer resection	20/26	No difference
Leyh-Bannurah, 2014	Robot prostatectomy	19/381	No difference
	Open prostatectomy	118/1943	Transfusion 21% vs 8%, $P < 0.001$; Inc. EBL, $P = 0.04$
Wolf, 2014	Pancreatic	289/728	No difference
Joseph, 2015	Lap cholecystectomy	56/56	No difference
Kara, 2016	Robot partial nephrectomy	16/762	Transfusion 18.8% vs 6.4%, $P = 0.04$
Leavitt, 2016	Lap partial nephrectomy	17/84	No difference
Ong, 2016	Lap inguinal hernia	30/27	No difference
	Open inguinal hernia	30/55	No difference
Packiam, 2016	Robot partial nephrectomy	49/165	IR embolization 3% vs 1.2%, $P = 0.07$
Dual AP vs clopidogrel vs aspirin vs no AP			
Chechik, 2011	Appendectomy	0/8/31/140	No difference
Stone, 2011	CEA	708/147/3823/583	No difference
	EVAR	60/17/742/300	No difference
	LEB	207/53/1812/811	No difference
	oAAA	42/12/755/318	No difference
Collinge, 2012	Hip fracture	34/40/253/619	No difference
Hale, 2013	CEA	315/0/639/518	Bleeding [†] OR 5.1 (1.8, 14.2), $P < 0.002$ for dual AP
Noda, 2014	Lap cholecystectomy	0/4/15/162	No difference
Weinrich, 2014	CEA	28/44/287/182	Reoperation OR 6.51 (CI NR), $P = 0.014$ for dual AP
Ginsel, 2015	Hip fracture	0/28/105/167	No difference
Yu, 2015	VATS for lung cancer	11/NR/NR/106	Inc. transfusion, $P = 0.003$; bleeding, $P = 0.005$ for dual AP
Ito, 2016 [‡]	Partial nephrectomy	1030/NR/NR/NR	Inc. EBL, $P = 0.001$; transfusion (rate NR) for clopidogrel/dual AP
Abstracts and active studies—aspirin vs no AP			
Vitello [‡] —active study	Inguinal hernia	Still enrolling	No difference (interim analysis)
Sihoe, 2012—abstract	VATS lobectomy	6/109	Conversion to thoracotomy 33% vs 7% for aspirin, $P = 0.03$
Ichikawa, 2013—abstract	Lap nephrectomy	5/39	No difference

AP indicates antiplatelet; AVF, arteriovenous fistula; CEA, carotid endarterectomy; Dual, combined aspirin and clopidogrel therapy; EBL, estimated blood loss; EC, endometrial cancer; EVAR, endovascular aneurysm repair; IR, interventional radiology; Lap, laparoscopic; LEB, lower extremity bypass; NR, not reported; Inc., increased; OR, odds ratio; oAAA, open abdominal aortic aneurysm repair; RR, relative risk; THA, total hip arthroplasty; TKA, total knee arthroplasty; VATS, video-assisted thoracoscopic surgery.

*As reported by the authors, risk of bleeding reported with 95% confidence intervals (CI) in parentheses where available.

[†]Study-specific endpoint.

[‡]Contains unpublished data.

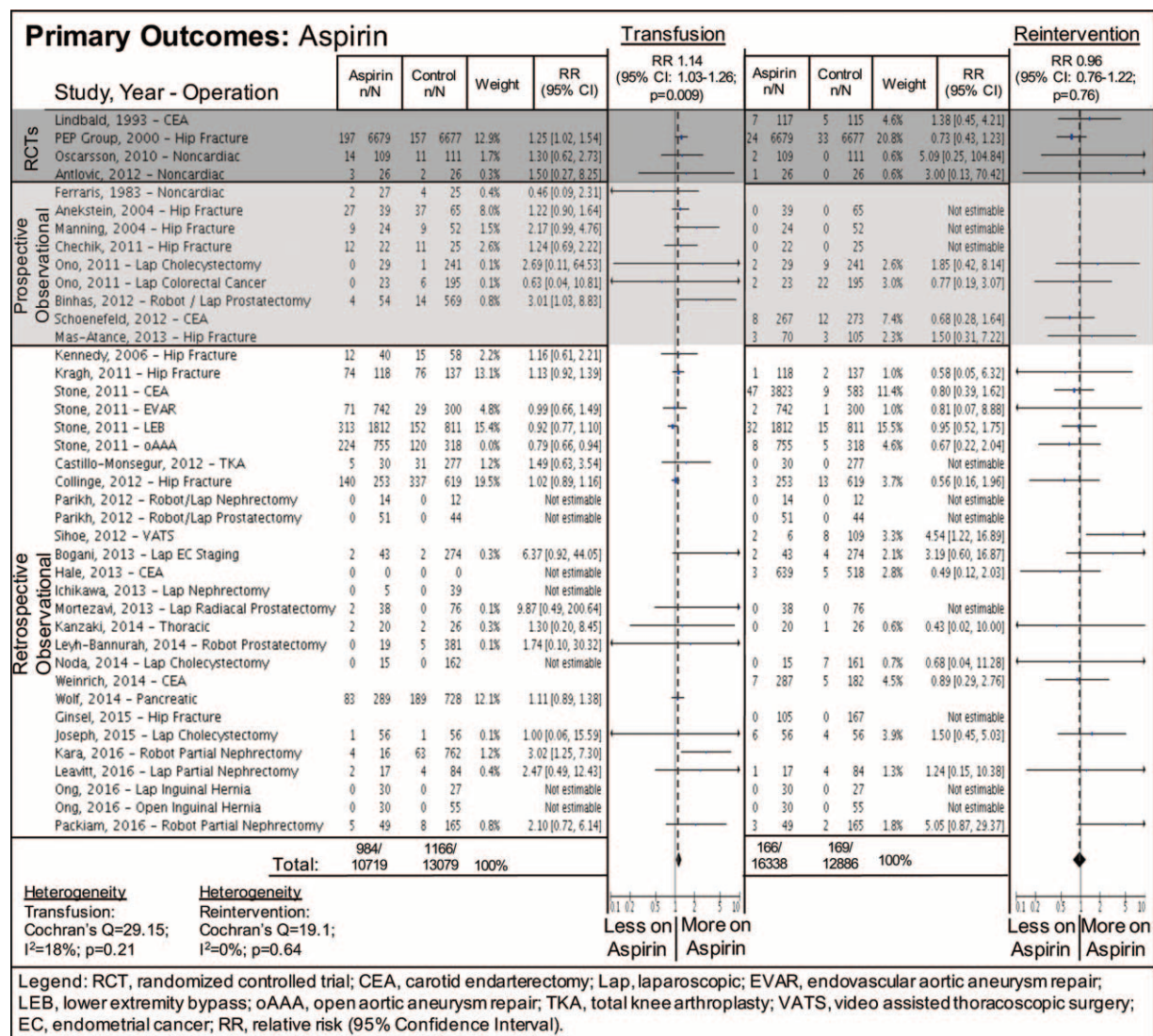


FIGURE 2. Figure demonstrating the summary estimates and meta-analysis details for the risk of transfusion and reintervention for bleeding for adults undergoing noncardiac surgery while on aspirin relative to control. Each line represents an individual study, or study strata when available.

communication).⁴⁰ In aggregate, there was a negligible to mildly increased risk of bleeding associated with antiplatelet therapy use in the perioperative period.

Secondary Outcomes

The secondary outcomes of MI, stroke, and all-cause mortality were routinely reported for RCTs, but less frequently reported for observational studies. Qualitative review noted no difference among RCTs, with regards to either aspirin or clopidogrel versus control. Although observational studies showed a trend toward increased thrombotic outcomes for those on aspirin, these findings were often associated with higher ASA scores, advanced age, and comorbidity profiles (Supplementary Appendix, <http://links.lww.com/SLA/B222>). When RCTs (6 trials) reporting on thrombotic outcomes were pooled, there was no significant increase in MI (RR 1.06, 95% CI 0.79–1.43; heterogeneity: Cochran's Q = 0.04, P = 0.12, I² = 49%), stroke (RR 0.97, 95% CI 0.71–1.33; heterogeneity:

Cochran's Q = 0.00, P = 0.63, I² = 0%), or all-cause mortality (RR 0.97, 95% CI 0.87–1.1; Cochran's Q = 0.00, heterogeneity: P = 0.67, I² = 0%) for aspirin versus control. Risk estimates were robust to sensitivity analyses performed with respect to bias, type of operation, and the variations on estimate modeling mentioned above (Figure 4). There were too few studies to assess for publication bias. Two studies were found that compared thrombotic events with clopidogrel vs. control: one study reported no events (ie, no heart attack, stroke, or death) in either arm,⁴¹ and the other study did not report heart attack or stroke, but did note 2 deaths in each arm.⁴² No RCTs evaluated the effect of DAPT vs. control.

DISCUSSION

In this systematic review and meta-analysis of over 30,000 patients on the effect of antiplatelet therapy and perioperative bleeding during noncardiac surgery, no significant increase in the

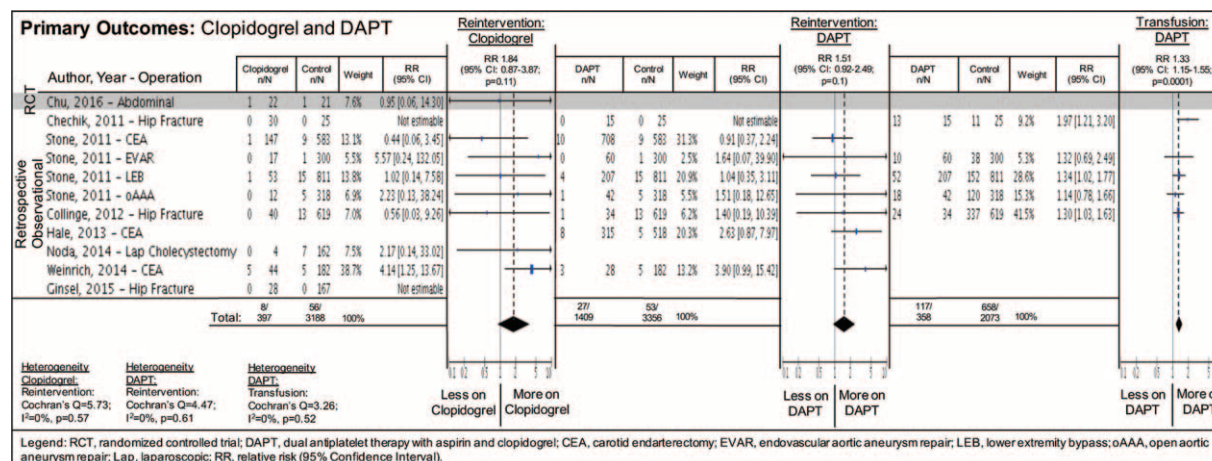


FIGURE 3. Figure demonstrating the summary estimates and meta-analysis details for the risk of transfusion and reintervention for bleeding in adults undergoing noncardiac surgery while on clopidogrel or dual antiplatelet therapy relative to control. Each line represents an individual study, or study strata when available.

risk of reintervention for bleeding was found. The risk of transfusion, however, was noted to be increased for patients taking aspirin, clopidogrel, and DAPT. Moreover, this risk followed a dose-response phenomenon for increasing levels of platelet inhibition (ie, aspirin<clopidogrel<DAPT). These findings were preserved among those undergoing thoracic or abdominal procedures, and were robust to sensitivity analyses with respect to type of procedure, methodological quality, and study design. In addition, there was no increased risk of MI, stroke, or all-cause mortality among included RCTs for aspirin versus control. Our findings demonstrate that although the risk of bleeding requiring blood transfusion is mildly elevated, the risk of reintervention for bleeding and thrombotic outcomes did not differ. Accordingly, these findings should assuage the perception of uniform increased perioperative bleeding risk. Rather, surgeons may be reassured that in many cases, antiplatelet therapy can be safely continued in patients with important indications for their use, such as recent coronary stent implantation.

Heterogeneity in the perioperative management of antiplatelet therapy is likely because of several factors. As noted in this review, although there are abundant data surrounding the bleeding risk for patients taking aspirin, there are fewer studies examining the bleeding risk for patients on clopidogrel, and the potential additive effect of multiple agents. Furthermore, no studies were found documenting the risk associated with newer antiplatelet agents. The intended

pharmacologic effect of antiplatelet therapy is to prevent platelet aggregation, thereby prolonging bleeding time.^{11,12} This prolonged bleeding time may lead to a spectrum of potential sequelae during the perioperative period, ranging from clinically inconsequential to more serious events such as blood transfusion and surgical reintervention. Therefore, these factors may potentially lead to variation in practice based on the perceived risk of perioperative bleeding. Consequently, there may be baseline variation associated with the threshold to reintervene for bleeding or to administer a blood transfusion in the postoperative period.⁴³ This threshold may also be affected by provider- and institutional-level practice pattern variation.⁴⁴ Furthermore, both endpoints may be biased if the attending provider is aware that a patient is taking antiplatelet therapy. However, if these factors were to impact the reported findings, it would be expected that a sensitivity analysis by study design would demonstrate inconsistent findings between randomized and observational data. Rather, this sensitivity analysis demonstrated that the point estimates for reintervention and blood transfusion did not meaningfully change when stratified by study design. Therefore, although variation is present in perioperative decision-making, the findings reported herein add evidence to inform this complex process.

Previous reviews have examined the risks and benefits of antiplatelet therapy in the perioperative period for noncardiac surgery. Di Minno et al¹⁶ found that both continuing and

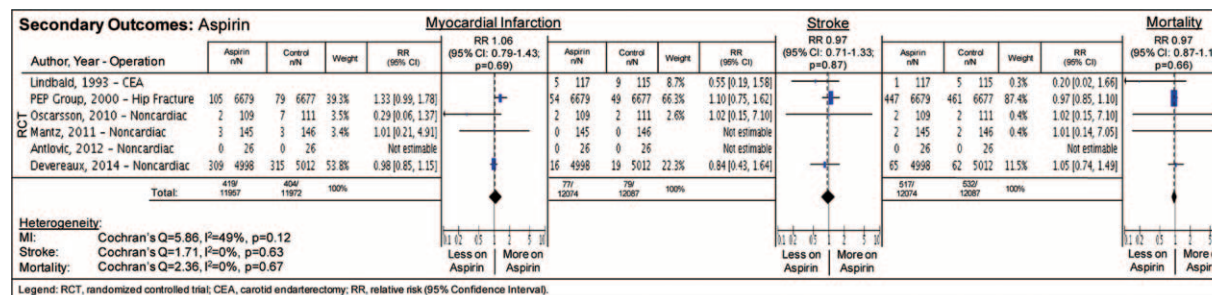


FIGURE 4. Figure demonstrating the summary estimates and meta-analysis details of randomized controlled trials for the secondary outcomes in adults undergoing noncardiac surgery while on aspirin relative to control. Each line represents an individual study.

discontinuing antiplatelet therapy can be associated with significant risks, and that risk stratification is critical to optimizing perioperative approaches to antiplatelet therapy. However, this study was limited to an interval year period, and included only 8 studies—one of which was in a population of patients with existing coronary stents, which may have biased the observed thrombotic outcomes.²³ Furthermore, owing to the heterogeneity of reporting, they were unable to perform a meta-analysis. Contrary to the findings described herein, Siller-Matula et al¹⁷ noted an increased risk of reoperation for bleeding in patients on clopidogrel therapy. Unlike the present study, these authors did not require a clear control group for study inclusion, and most included studies had many patients on concomitant aspirin therapy. This is a possible source of confounding, and may account for the difference from the current observation that reintervention is not increased for patients on any type of antiplatelet agent. More recently, Fang et al¹⁸ performed a review focusing on gastrointestinal procedures. Although the majority of included studies were endoscopic, 6 studies focused on surgical procedures. Although no meta-analysis was performed owing to heterogeneity in bleeding outcome reporting, they concluded that there was no increased risk of bleeding for patients on antiplatelet therapy, findings which are consistent with the present study.

As noted above, heterogeneity in study findings and outcome reporting has been a major limitation in past reviews.^{16,18} In the present analysis, the pooled primary and secondary endpoints allowed for inclusion of 37 studies. This represents one of the only meta-analyses comparing antiplatelet therapy to a control group in this patient population. Moreover, the inclusion requirement of a control group with no antiplatelet therapy or placebo allowed for a true estimate of relative risk. Among the included studies, the risk of bias appeared to be low, likely owing to both strict inclusion criteria and specification of clinically discrete bleeding endpoints. Contact was attempted with all authors of studies that did not report data with sufficient granularity for meta-analysis. No language limits were used, and multilingual reviewers were used for 2 non-English studies.^{29,30} This further ensures inclusion of all relevant data. The examination of thrombotic outcomes provides an estimation of the tradeoff between continuation and interruption of antiplatelet therapy for patients with similar baseline risks.

This study has several intrinsic limitations. First, the risks associated with clopidogrel, other p2y12 agents, or DAPT remain heterogeneous and often lack an appropriate control cohort, which inevitably impacts their inclusion in a systematic review. In addition, the available literature may not reflect the complete spectrum of abdominal, thoracic, or major cavitory operations. Accordingly, case mix may not adequately reflect large magnitude operations with a greater proclivity for bleeding. Therefore, findings should be interpreted with caution, especially when considering complex operations on DAPT. A search strategy was used that specified the intersection between antiplatelet therapy, noncardiac surgery, and perioperative bleeding. The specification of perioperative bleeding may have excluded studies that did not report bleeding or that focused on thrombotic complications. This approach was unlikely to overlook articles as the primary outcome of interest was perioperative bleeding events; however, one additional study was identified on reference review that was not initially picked up by the search strategy. No RCTs of DAPT and only 2 RCTs studying clopidogrel were identified. This likely represents paucity in available literature rather than overlooked data.

Most of the included reports were cohort studies, which are subject to both measured and unmeasured confounding. The decision to administer a blood transfusion or reintervene postoperatively for bleeding is ultimately at the discretion of the operating surgeon. It is not possible to know how antiplatelet therapy may have affected

surgical decision-making. Moreover, there is persistent heterogeneity inherent in surgical decision-making for which a systematic review remains unable to account for at the surgeon level. It is also important to note that certain additional endpoints potentially indicative of a bleeding event remain elusive in this comprehensive review. Specifically, events such as surgical drain placement, platelet transfusion, and hematoma, all may relate to increased bleeding. The extent to which these less common endpoints are reported in the surgical literature remains infrequent, making our ability to glean clinical inference on these endpoints less reliable. Inclusion of observational studies may introduce some bias in the primary endpoints. However, because the current findings were robust to sensitivity analyses of the primary outcomes by study design, it is unlikely that confounding played a meaningful role in the results. Given the higher baseline comorbid conditions for those on established antiplatelet therapy and the potential for confounding, data from cohort studies were not included in summary estimates of MI, stroke, or all-cause mortality. However, because only 2 trials examined the risk of clopidogrel versus control, and no trials evaluated the risk of DAPT versus control, evidence surrounding the thrombotic risk in these patients is not robust. We are therefore unable to draw firm conclusions regarding the risk of MI, stroke, or all-cause mortality in these drug groups. Future research may be directed toward investigating the risk of perioperative bleeding events for clopidogrel and DAPT. We did not include studies that only examined patients with coronary stents. Our findings may therefore be limited in their generalizability to this select group of patients. Lastly, bleeding and thrombotic events may not be mutually exclusive at the patient level, but we are unable to report this granular level of detail in this systematic review.

In summary, although single and DAPT did not confer a significantly increased risk of reintervention for bleeding, there was a stepwise increase in the risk of blood transfusion for aspirin, clopidogrel, and DAPT. This risk was persistent among randomized and observational data. Moreover, these risk estimates were robust to sensitivity analyses. In addition, these findings were preserved among studies that included primarily thoracic and abdominal surgical procedures. The risk of bias appeared to be low among included studies, likely because of the strict inclusion criteria and clinically discrete endpoints. Finally, there was no elevated risk of MI, stroke, or all-cause mortality in patients taking aspirin versus placebo.

CONCLUSIONS

In this meta-analysis of >30,000 patients evaluating the effect of single and DAPT versus placebo or no treatment on the risk of perioperative bleeding in noncardiac surgery, there was a modest, stepwise increase in the risk of blood transfusion with increasing levels of platelet inhibition. However, there was no significant difference in reintervention for any agent, including DAPT. Although it is not possible to account for the potential of surgeon-level variation in this meta-analysis, our findings were robust to sensitivity analyses by study design and therefore this variation was unlikely to meaningfully affect our findings. Furthermore, there was no statistically significant difference in the risk of MI, stroke, or all-cause mortality for aspirin versus control. Although interruption of antiplatelet therapy in those at low risk for thrombotic complications may be considered, surgeons should be aware that these agents can likely be continued safely among patients with important indications for their use.

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