Systematic Review and Meta-Analysis Oral Surgery

Incidence of bleeding after minor oral surgery in patients on dual antiplatelet therapy: a systematic review and meta-analysis

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Abstract. Bleeding is a feared complication of minor oral surgery in patients on treatment with antiplatelet agents and there is no agreed strategy regarding the cessation or not of antiplatelet treatment. The aim of this systematic review was to evaluate bleeding with minor oral surgery in patients on dual antiplatelet therapy (DAPT), single antiplatelet therapy (SAPT), or no antiplatelet therapy (no APT). The PubMed, Embase, Web of Science, and Cochrane Library databases were screened. Sixteen studies were included. DAPT was continued in all studies. The perioperative bleeding risk was significantly higher for DAPT than for SAPT (risk ratio (RR) 10.16, $P = 0.010$; risk difference (RD) 0.35, $P = 0.269$), but not higher compared to no APT (RR 6.50, $P = 0.057$; RD 0.19, $P = 0.060$). The postoperative bleeding risk was significantly elevated for DAPT compared to SAPT (RR 2.61, $P = 0.010$) and no APT (RR 3.63, $P = 0.035$), but only by 1% (RD 0.01, $P = 0.103$) and 1% (RD 0.01, $P = 0.421$), respectively. Clinically, this may be considered quite similar. Additionally, local haemostatic measures could control all reported bleeding and no lethal events occurred. Therefore, DAPT interruption is not advised before minor oral surgery.

Key words: dual antiplatelet therapy; minor oral surgery; bleeding; haemostatic measures.

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The incidence of cardiovascular and cerebrovascular diseases is increasing with the growing aging population. Antithrombotic therapies are constantly evolving and new drugs or new drug combinations brought into practice. About 20 years ago, dual antiplatelet therapy (DAPT) was introduced for patients with coronary artery diseases treated with a stent or bypass graft, or following a heart attack. DAPT comprises acetylsalicylic acid (aspirin) in combination with a P2Y₁₂ inhibitor, such as clopidogrel, ticlopidine, ticagrelor, or prasugrel. All of these drugs inhibit platelet function by different mechanisms. Today, DAPT has proven superior to anticoagulant therapy for patients undergoing percutaneous coronary interventions¹. Accordingly, this therapy has become the first choice for patients with acute or stable coronary disease to prevent thrombotic complications. However, the use of antiplatelet medications increases the risk of bleeding², and this risk is even higher when a combination of antiplatelet medications is taken³. With the trend of an aging population in many countries, there are more elderly people on antiplatelet medications requiring multiple dental extractions and minor oral surgical procedures. The elevated bleeding risk has therefore become a greater concern for oral and maxillofacial surgeons and their patients.

There is no generally accepted strategy for preventing bleeding with minor oral surgery in patients on antiplatelet treatment. Antiplatelet therapy is sometimes discontinued before elective surgery due to the fear of bleeding. However, any interruption of antithrombotic therapy increases the risk of thromboembolic events, which can be life-threatening^{4,5}. The risk of bleeding while continuing antiplatelet therapy and the risk of thromboembolic events while interrupting antiplatelet therapy have to be carefully balanced.

For patients treated with single antiplatelet therapy (SAPT), it seems advisable not to interrupt the antiplatelet drug before minor oral surgery because the risk of non-fatal bleeding does not outweigh the risk of a fatal thromboembolic event⁵. The perioperative management of DAPT remains a clinical challenge, as the bleeding risk may be higher than with SAPT³. Guidelines for the perioperative management of patients on DAPT undergoing minor oral surgery are scarce in the literature. The Scottish Dental Clinical Effectiveness Programme, for instance, advises that patients be treated without interrupting their antiplatelet medication⁶. However,

the guidelines also state that this recommendation is based on low quality evidence. This might be explained by the lack of good evidence in the literature on the risk of bleeding complications after minor oral surgery in patients on DAPT.

The objective of this systematic review and meta-analysis was to evaluate the risk of bleeding complications in patients on DAPT compared to patients on SAPT or no antiplatelet therapy (no APT) in order to develop clinically relevant recommendations for such patients undergoing oral surgery.

Materials and methods

This systematic review was registered with PROSPERO (ID: CRD42018107806) and was conducted according to the Cochrane guidelines⁷ and in accordance with all Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) items⁸.

Search strategy, study selection, and data extraction

All studies investigating complications with minor oral surgery in patients on DAPT treatment were included. The following patients–exposure–comparison–outcome (PECO) search was addressed: (1) patients were those undergoing minor oral surgery; (2) the exposure was dual antiplatelet therapy; (3) the comparison was single or no antiplatelet therapy; (4) the outcome was bleeding complications.

Studies in languages other than English, Dutch, or French were excluded, as were animal studies, in vitro studies, case reports, studies including fewer than 10 patients on DAPT, conference reviews, and letters to the editor.

The PubMed, Embase, Web of Science, and Cochrane Library databases were screened in September 2018 for eligible articles (Supplementary Material, Table S1). In addition, journals within the field of oral and maxillofacial surgery and the reference lists of included articles were screened by hand.

After removing duplicates, two reviewers independently screened all titles and abstracts. In the case of disagreement about inclusion or exclusion, a consensus between the two reviewers was reached. Thereafter, the full-text articles were surveyed in duplicate and the following data were extracted: study design, patient groups, types of minor oral surgery, bleeding, and haemostatic measures applied. Bleeding complications were divided into perioperative bleeding (events during and

immediately after dental surgery) and postoperative bleeding (events occurring after the patient had been discharged from the hospital). Further, haemostatic measures were divided into primary measures applied during surgery and secondary measures applied in the case of bleeding.

Risk of bias

A level of evidence was assigned to each study based on evidence-based medicine standards. Selection bias, performance bias, detection bias, attrition bias, and reporting bias were also assessed for each study⁷. A consensus was reached between the two reviewers in the case of disagreement in the bias assessment. The risk of selection bias was evaluated by determining whether patients in one group could have had a higher bleeding risk than those in the other group. Performance bias was non-existent for the included studies because they were all observational, non-interventional studies. The risk of bias was classified as low, unclear (in the case of a lack of information), or high, and given one point, half a point, or zero points, respectively. Studies with 5 points had the lowest risk of bias, whereas studies with less than five points had a higher risk of bias.

Statistical analysis

The bleeding outcomes of all studies were combined to perform a meta-analysis using the statistical software Stata version 13.1 (StataCorp LP, College Station, TX, USA). Due to the intention of generalization inference and the possible heterogeneity from different studies, a random-effects method was used. The risk ratio (RR) and the risk difference (RD) with corresponding 95% confidence intervals (CI) were calculated. For the RR estimation, in the event that zeros caused computation problems for the standard error, 0.5 would be added to all cells of the study results tables; however, if zeros occurred in both groups, the study would be excluded from the meta-analysis^{9,10}. Substantial heterogeneity between studies was quantified using the χ^2 test with a *P*-value of <0.10 or an *I*² statistic of >50%⁷.

Results

Study selection

In total, 377 articles were identified via the electronic database search and one article in the hand search. After removing duplicates and screening by title and abstract, 18

Fig. 1. PRISMA flow diagram depicting the flow of information through the different phases of the systematic review. After database screening, the hand search of journals and reference lists, and the removal of duplicates, 253 articles were evaluated by title and abstract. Eighteen were included for full-text assessment^{11–28}, of which two were excluded^{27,28}. One article included patients who had undergone orthognathic surgery, which is not considered a minor oral surgical intervention²⁷. The other study was excluded as it compared patients who were being treated with a great variety of antithrombotic regimens, which made it impossible to compare or differentiate between the patient groups²⁸. Thus, 16 articles were included for qualitative and quantitative synthesis^{11–26}.

papers were included for full-text assessment^{11–28}. Two of these were excluded^{27,28} and¹⁶ were included for quantitative and qualitative synthesis^{11–26} (Fig. 1).

Study characteristics and results

Nine studies were prospective controlled cohort studies^{11–12,15–18,20,25–26}, five were retrospective controlled cohort studies^{13–14,21–23}, and two were prospective case-series studies^{19,24}. In total, the studies included 1059 patients on DAPT, 1428 patients on SAPT, 4452 patients not on APT (no APT), and 111 patients on triple antiplatelet therapy (TAPT) or vitamin K antagonists (VKAs). Importantly, all patients on DAPT and SAPT continued their therapy during minor oral surgery.

Four studies included various minor oral procedures such as dental extraction, alveoloplasty, apical surgery, cyst removal, and periodontal treatment^{11–14}. All other studies included solely dental

extractions; 10 included multiple dental extractions^{15–24} and two limited inclusion to the non-surgical extraction of one tooth^{25,26}. Exclusion criteria were similar for all studies, i.e., patients with systemic (such as liver or renal) diseases, congenital bleeding disorders, an abnormal blood count, suffering from alcoholism, or taking medication affecting haemostasis (apart from antiplatelet drugs) were excluded.

Perioperative and postoperative bleeding

Table 1 summarizes perioperative bleeding. Girotra et al.¹¹ studied persistent bleeding (bleeding persisting after 30 minutes of gauze pressure) during minor oral procedures and reported a significantly higher occurrence for DAPT than for SAPT and no APT. Five studies evaluated bleeding during multiple dental extractions. Similar to Girotra et al.¹¹, Lillis et al.¹⁵ showed a significantly higher frequency of events for DAPT compared to

SAPT and no APT. Additionally, Buhatem Medeiros et al.¹⁶ showed a significantly higher volume of blood loss in those on DAPT compared to those on no APT. On the other hand, Park et al.¹⁷ reported no significant difference in blood loss exceeding 30 ml between the DAPT, SAPT, and no APT groups. Further, Dezzi et al.¹⁸ compared the bleeding time between two DAPT regimens: aspirin plus clopidogrel versus aspirin plus prasugrel, and showed a significantly longer bleeding time for the aspirin plus prasugrel regimen. Olmos-Carrasco et al.¹⁹ evaluated persistent bleeding in a case-series of patients treated with DAPT and recorded 16/181 events (8.8%). Lastly, Sadeghi-Ghahrody et al.²⁵ assessed persistent bleeding (persisting after 10 minutes of gauze pressure) after single tooth extraction in DAPT, SAPT, and no APT patients and did not detect a significant difference.

A summary of all studies concerning postoperative bleeding is given in the Supplementary Material (Table S2). Two prospective studies^{11,12} and two retrospective studies^{13,14} evaluated postoperative bleeding after various minor oral procedures. None showed a significant difference between DAPT, SAPT, and no APT. Further, four out of seven studies (two prospective^{15,20} and two retrospective^{22,23}) examining bleeding after multiple dental extractions also did not detect a significant difference between DAPT, SAPT, and no APT. Only the retrospective study of Yanamoto et al. (Table 2) showed a significant increase in postoperative bleeding events for DAPT compared to SAPT²¹. The remaining two of the seven were case-series studies and detected 0/32 (0%) and 4/181 (2.2%) postoperative bleeding events in patients on DAPT^{19,24}. Lastly, Babaji and Rishal²⁶ studied postoperative bleeding after single tooth extraction and did not report any bleeding events with DAPT or no APT.

The link between postoperative bleeding and DAPT in combination with periodontitis is worth mentioning. Three studies indicated a higher postoperative bleeding risk after dental extraction in patients on DAPT having periodontitis than in patients on DAPT not having periodontitis^{15,22,23}.

Haemostatic measures

In all studies except two, gauze pressure was employed as the primary haemostatic measure, whether or not in combination with sutures (Supplementary Material,

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Table 1. Perioperative bleeding with minor oral surgery and multiple/single tooth extractions.

Authors (Year of publication)	LOE ^a	Perioperative outcome	Patient groups (<i>n</i> = number of patients)			Perioperative outcome results		Statistical significance
Minor oral surgery								
Girotra et al. ¹¹ (2014)	1	Persistent bleeding	SAPT1 (<i>n</i> = 310)	ASA		2/310	(0.6%)	↑ DAPT
			SAPT2 (<i>n</i> = 97)	Clopidogrel		5/97	(5.2%)	
			DAPT (<i>n</i> = 139)	ASA + clopidogrel		11/139	(7.9%)*	
			Control (<i>n</i> = 575)	No APT		15/575	(2.6%)	
Multiple tooth extractions								
Lillis et al. ¹⁵ (2011)	1	Persistent bleeding	SAPT1 (<i>n</i> = 42)	ASA		1/42	(2.4%)	↑ DAPT
			SAPT2 (<i>n</i> = 36)	Clopidogrel		1/36	(2.8%)	
			DAPT (<i>n</i> = 33)	ASA + clopidogrel		22/33	(66.7%)*	
			Control (<i>n</i> = 532)	No APT		2/532	(0.4%)	
Buhatem Medeiros et al. ¹⁶ (2017)	1	Perioperative volume of blood loss	DAPT (<i>n</i> = 38)	ASA + clopidogrel		±16.07 ml*		↑ DAPT
			Control (<i>n</i> = 35)	No APT		±6.10 ml		
Park et al. ¹⁷ (2012)	1	Perioperative volume of blood loss >30 ml	DAPT (<i>n</i> = 59)	ASA + clopidogrel		1/59	(1.7%)	None
			TAPT (<i>n</i> = 41)	ASA + clopidogrel + cilostazol		1/41	(2.4%)	
			Control (<i>n</i> = 100)	No APT		1/100	(1.0%)	
Dezsi et al. ¹⁸ (2015)	1	Perioperative bleeding time	DAPT1 (<i>n</i> = 63)	ASA + clopidogrel		41.03		↑ DAPT2
			DAPT2 (<i>n</i> = 66)	ASA + prasugrel		± 17.16 min		
						± 25.68 min*		
Olmos-Carrasco et al. ¹⁹ (2015)	3	Persistent bleeding	DAPT (<i>n</i> = 181)	ASA + clopidogrel/ prasugrel		16/181	(8.8%)	–
Single tooth extraction								
Sadeghi-Ghahrody et al. ²⁵ (2016)	1	Persistent bleeding	DAPT (<i>n</i> = 64)	ASA + clopidogrel		15/64	(23.4%)	None
			Control (<i>n</i> = 50)	No APT		7/50	(14%)	

ASA, acetylsalicylic acid; APT, antiplatelet therapy; DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy; TAPT, triple antiplatelet therapy.

* $P < 0.05$ = significant.

^a Level of evidence: 1 = prospective controlled cohort study; 2 = retrospective controlled cohort study; 3 = prospective case-series study.

Table 2. Postoperative bleeding after multiple tooth extractions.

Authors (Year of publication)	LOE ^a	Patient groups (n = number of patients)			Postoperative bleeding	Statistical significance
Yanamoto et al. ²¹ (2017)	2	SAPT (n = 141)	ASA/clopidogrel/cilostazol/other	SAPT	4/188 (2.1%)	↑DAPT ^b
		DAPT (n = 76)	ASA + clopidogrel/cilostazol/other	APT	4/76 (5.3%)*	

ASA, acetylsalicylic acid; APT, antiplatelet therapy; DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy.

* $P < 0.05$ = significant.

^a Level of evidence: 1 = prospective controlled cohort study; 2 = retrospective controlled cohort study; 3 = prospective case-series study.

^b Significant difference between SAPT and DAPT for postoperative bleeding based on univariate analysis, but not on multivariate analysis²¹.

Table S3). In five studies, patients were additionally treated with absorbable sponges (collagen, gelatin, or Gelfoam)^{12,13,20,22,23}. The use of tranexamic acid (TXA) paste or TXA-impregnated gauze as a primary haemostatic method was reported in only three studies^{16,19,24}.

Gauze pressure and re(suturing) were also selected as secondary haemostatic measures in the case that bleeding occurred. Nine studies reported their use^{11,12,14,15,20–23,25}. TXA measures such as TXA-impregnated gauze or sponges, TXA paste, and TXA mouthwash were applied in the case of bleeding in six studies^{12,14,16,19,22,23}. Sponges were used in

only two studies and a haemostatic dressing in only two studies^{11,12,14,25}. All studies confirmed that the local haemostatic measures were adequate in stopping the bleeding.

Risk of bias within studies

Selection bias was high for all studies because of their non-randomized nature. Any effect could have been due to uneven allocation to study groups rather than the antiplatelet treatment itself (Supplementary Material, Table S4). Six studies had an overall risk of bias score of 4 out of 5 points, indicating a low risk of bi-

as^{11,15,16,19,20,24}. Eight studies had a medium risk of overall bias (3.5 points), because the risk of detection bias could not be assessed. It was unclear how the outcome measure was detected in three out of these eight studies^{17,18,26} and the other five studies were retrospective^{13,14,21–23}. Retrospective studies are always subject to possible detection bias, because an outcome event may not have been recorded in the studied patient files. Furthermore, the study by Sadeghi-Ghahrody et al.²⁵ (3 points) had a high risk of reporting bias because not all predefined outcome measures were reported. Lastly, the study by Dudek

et al.¹² had the highest overall risk of bias (2 points), due to a high risk of attrition bias and reporting bias. This study had missing data without providing a reason, and did not report all predefined outcome variables.

Results of meta-analysis

A meta-analysis was performed to compare the intraoperative and postoperative bleeding risk between patients treated with DAPT and those treated with SAPT or those not taking antiplatelet drugs.

The perioperative bleeding risk for patients on DAPT was significantly higher than that for patients on SAPT (RR 10.16, 95% CI 1.74 to 59.28, $Z = 2.58$, $P = 0.010$) (Table 3), but did not differ significantly from the risk for patients not taking antiplatelet drugs (RR 6.50, 95% CI 0.94 to 44.77, $Z = 1.90$, $P = 0.057$) (Table 4). The risk difference was 35% higher for DAPT compared to SAPT, which was not significant (RD 35% or 0.35, 95% CI -0.27 to 0.96, $Z = 1.11$, $P = 0.269$) and 19% higher for DAPT compared to no APT, which was also not significant (RD 19% or 0.19, 95% CI -0.01 to 0.39, $Z = 1.88$, $P = 0.060$). There was substantial heterogeneity between studies in the meta-analysis for the perioperative bleeding risk (all $P < 0.05$ and $I^2 > 75\%$).

The postoperative bleeding risk for patients on DAPT was significantly higher than that for patients on SAPT (RR 2.61, 95% CI 1.26 to 5.42, $Z = 2.57$, $P = 0.010$) (Table 5) and patients not taking antiplatelet drugs (RR 3.63, 95% CI 1.09 to 12.03,

$Z = 2.11$, $P = 0.035$) (Table 6). However, the risk difference was only 1% higher (not significantly) for DAPT compared to SAPT (RD 1% or 0.01, 95% CI -0.00 to 0.03, $Z = 1.63$, $P = 0.103$) and only 1% higher (not significantly) for DAPT compared to no APT (RD 1% or 0.01, 95% CI -0.01 to 0.02, $Z = 0.81$, $P = 0.421$). Substantial heterogeneity between studies was not found in the meta-analysis for postoperative bleeding risk (all $P > 0.10$ and $I^2 = 0.0\%$).

Discussion

Bleeding

Two studies, one examining various minor oral procedures and another multiple dental extractions in particular, showed a significantly increased number of persistent bleeding events for DAPT compared to SAPT and no APT^{11,15}. Persistent bleeding was defined as bleeding persisting after 30 minutes of gauze pressure in both studies. The type of minor oral surgery was not associated with the risk of bleeding¹¹. Additionally, the volume of blood loss after multiple dental extractions was higher in patients on DAPT than in patients not taking antiplatelet drugs¹⁶. Another study reported no difference in the number of bleeding events exceeding 30 ml in patients on DAPT, triple antiplatelet therapy, or no antiplatelet drugs¹⁷. Both of these studies measured the volume of blood loss by subtracting the volume of irrigation fluid from the total volume of fluid in the surgery suction jar. This meth-

od may not be reliable. Furthermore, a study monitoring bleeding time in patients on aspirin plus prasugrel or plus clopidogrel in patients undergoing multiple tooth extractions noted an increased bleeding time, by an average of plus 10 minutes, in patients on aspirin plus prasugrel²⁹. This could be explained by the greater efficacy of prasugrel in comparison to clopidogrel for platelet inhibition, leading to an increased rate of haemorrhage³⁰. Otherwise, two cases of bleeding after 2–3 hours following extraction in patients treated with clopidogrel, and not with prasugrel, were recorded in the same study²⁹. Of note, the average bleeding time exceeded 30 minutes in both groups, corresponding to the higher number of persistent bleeding events in patients on DAPT found in the previously mentioned studies^{11,15}. Finally, the meta-analysis showed a significantly higher perioperative bleeding risk for patients on DAPT compared to SAPT, but not compared to no APT. In addition, the risk difference values did not differ significantly between DAPT and SAPT or between DAPT and no APT.

Postoperative bleeding after minor oral procedures was examined in multiple studies. Four studies including various minor oral procedures did not show a difference between DAPT, SAPT, and no APT^{11–14}. Seven other studies, focusing on multiple dental extractions in particular, supported this finding^{15,19–24}. Only one of these studies showed an increased risk for DAPT compared to SAPT²¹. Lastly, a study exclusively including single

Table 3. Meta-analysis for the risk ratio (RR) and risk difference (RD) of perioperative bleeding: DAPT vs. SAPT.

							Risk Ratio
Study	DAPT Events	Total	SAPT Events	Total	Weight	Risk Ratio [95% CI]	Risk Ratio, random-effect, 95% CI
Lillis et al. (2011)	22	33	2	78	45.7%	26.00 [6.48, 104.30]	
Girotra et al. (2014)	11	139	7	407	54.3%	4.60 [1.82, 11.64]	
Overall	33	172	9	485	100%	10.16 [1.74, 59.28]	
Heterogeneity $\chi^2 = 4.49$, $df = 1$, $p = 0.034^*$, $I^2 = 77.7\%$							
Test $RR = 1$, $z = 2.58$, $p = 0.010^*$							
Study	DAPT Events	Total	SAPT Events	Total	Weight	Risk difference [95% CI]	Risk Difference, random-effect, 95% CI
Lillis et al. (2011)	22	33	2	78	49.2%	0.64 [0.48, 0.81]	
Girotra et al. (2014)	11	139	7	407	50.8%	0.06 [0.02, 0.11]	
Overall	33	172	9	485	100%	0.35 [-0.27, 0.96]	
Heterogeneity $\chi^2 = 51.56$, $df = 1$, $p < 0.001^*$, $I^2 = 98.1\%$							
Test $RD = 0$, $z = 1.11$, $p = 0.269$							

Heterogeneity $\chi^2 = 51.56$, $df = 1$, $P < 0.001^*$, $I^2 = 98.1\%$.
Test RD = 0, $Z = 1.11$, $P = 0.269$.

CI, confidence interval; DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy.
* $P < 0.05$.

Table 4. Meta-analysis for the risk ratio (RR) and risk difference (RD) of perioperative bleeding: DAPT vs. no APT.

Study	DAPT		No APT		Weight	Risk Ratio [95% CI]	Risk Ratio, random-effect, 95% CI
	Events	Total	Events	Total			
Lillis et al. (2011)	22	33	2	532	25.5%	177.33 [43.55, 722.13]	
Park et al. (2012)	1	59	1	100	18.4%	1.69 [0.11, 26.59]	
Girotra et al. (2014)	11	139	15	575	28.2%	3.03 [1.42, 6.46]	
Sadhegi-G et al. (2016)	15	64	7	50	28.0%	1.67 [0.74, 3.79]	
Overall	49	295	24	1257	100%	6.50 [0.94, 44.77]	

Heterogeneity $\chi^2 = 33.98$, $df = 3$, $p < 0.001^*$, $I^2 = 91.2\%$
 Test $RR = 1$, $z = 1.90$, $p = 0.057$

Study	DAPT		No APT		Weight	Risk Difference [95% CI]	Risk Difference, random-effect, 95% CI
	Events	Total	Events	Total			
Lillis et al. (2011)	22	33	2	532	22.9%	0.66 [0.50, 0.82]	
Park et al. (2012)	1	59	1	100	26.7%	0.01 [-0.03, 0.05]	
Girotra et al. (2014)	11	139	15	575	26.6%	0.05 [0.01, 0.10]	
Sadhegi-G et al. (2016)	15	64	7	50	23.7%	0.09 [-0.05, 0.24]	
Overall	49	295	24	1257	100%	0.19 [-0.01, 0.39]	

Heterogeneity $\chi^2 = 101.92$, $df = 3$, $p < 0.001^*$, $I^2 = 97.1\%$
 Test $RD = 0$, $z = 1.88$, $p = 0.060$
 Heterogeneity $\chi^2 = 101.92$, $df = 3$, $P < 0.001^*$, $I^2 = 97.1\%$
 Test $RD = 0$, $Z = 1.88$, $P = 0.060$.
 APT, antiplatelet therapy; CI, confidence interval; DAPT, dual antiplatelet therapy.
 $^*P < 0.05$.

Table 5. Meta-analysis for the risk ratio (RR) and risk difference (RD) of postoperative bleeding: DAPT vs. SAPT.

Study	DAPT		SAPT		Weight	Risk Ratio [95% CI]	Risk Ratio, random-effect, 95% CI
	Events	Total	Events	Total			
Girotra et al. (2014)	2	139	2	407	14.0%	2.93 [0.42, 20.59]	
Bajkin et al. (2014)	1	43	0	117	5.3%	8.05 [0.33, 193.82]	
Lu et al. (2016)	1	24	4	250	11.5%	2.60 [0.30, 22.38]	
Yanamoto et al. (2017)	4	76	4	188	28.8%	2.47 [0.63, 9.64]	
Doganay et al. (2018)	5	60	6	162	40.4%	2.25 [0.71, 7.10]	
Napenas et al. (2009)	0	29	0	14		(Excluded)	
Lillis et al. (2011)	0	33	0	78		(Excluded)	
Overall	13	342	16	1124	100.0%	2.61 [1.26, 5.42]	

Heterogeneity $\chi^2 = 0.57$, $df = 4$, $p = 0.967$, $I^2 = 0.0\%$
 Test $RR = 1$, $z = 2.57$, $p = 0.010^*$

Study	DAPT		SAPT		Weight	Risk difference [95% CI]	Risk Difference, random-effect, 95% CI
	Events	Total	Events	Total			
Napenas et al. (2009)	0	29	0	14	2.5%	0.00 [-0.10, 0.10]	
Lillis et al. (2011)	0	33	0	78	13.2%	0.00 [-0.04, 0.04]	
Girotra et al. (2014)	2	139	2	407	58.7%	0.01 [-0.01, 0.03]	
Bajkin et al. (2014)	1	43	0	117	8.53%	0.02 [-0.03, 0.08]	
Lu et al. (2016)	1	24	4	250	3.87%	0.03 [-0.06, 0.11]	
Yanamoto et al. (2017)	4	76	4	188	8.73%	0.03 [-0.02, 0.09]	
Doganay et al. (2018)	5	60	6	162	4.5%	0.05 [-0.03, 0.12]	
Overall	13	404	16	1216	100.0%	0.01 [-0.00, 0.03]	

Heterogeneity $\chi^2 = 2.76$, $df = 6$, $p = 0.839$, $I^2 = 0.0\%$
 Test $RD = 0$, $z = 1.63$, $p = 0.103$
 Heterogeneity $\chi^2 = 2.76$, $df = 6$, $P = 0.839$, $I^2 = 0.0\%$
 Test $RD = 0$, $Z = 1.63$, $P = 0.103$.
 CI, confidence interval; DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy.
 $^*P < 0.05$.

tooth extractions also did not show an increased risk of postoperative bleeding²⁶. Nevertheless, the meta-analysis indicated a significantly higher postoperative bleeding risk for DAPT compared to SAPT and no APT, although the risk difference was only 1% higher compared to SAPT and 1% compared to no APT. These risk difference values did not differ significantly from zero.

The various definitions of postoperative bleeding used made it difficult to compare study outcomes directly. A standardized definition and distinction of postoperative bleeding could be employed to overcome this problem in future studies. Postoperative bleeding could be divided into major, moderate, and minor bleeding events, as published previously³¹. Major bleeding requires hospitalization or blood transfu-

sion, moderate bleeding necessitates a medical intervention, and minor bleeding does not require a medical intervention and can be resolved by the patient his/herself, with the application of gauze pressure for instance. Nevertheless, even with varying definitions, most studies detected a similar and low number of postoperative bleeding events for patients on DAPT. In addition, bleeding outcomes of various

Table 6. Meta-analysis for the risk ratio and risk difference of postoperative bleeding for DAPT vs. no APT.

Study	DAPT		No APT		Weight	Risk Ratio [95% CI]	Risk Ratio, random-effect, 95% CI
	Events	Total	Events	Total			
Girotra et al. (2014)	2	139	4	575	50.5%	2.07 [0.38, 11.18]
Bajkin et al. (2014)	1	43	0	105	14.2%	7.23 [0.30, 174.01]	
Lu et al. (2016)	1	24	10	1472	35.4%	6.13 [0.82, 46.04]	
Lillis et al. (2011)	0	33	0	532		(Excluded)	
Dudek et al. (2015)	0	55	0	33		(Excluded)	
Babaji et al. (2018)	0	73	0	78		(Excluded)	
Overall	4	206	14	2152	100.0%	3.63 [1.09, 12.03]	

Heterogeneity $\chi^2 = 0.88$, $df = 2$, $p = 0.643$, $I^2 = 0.0\%$
 Test RR = 1, $z = 2.11$, $p = 0.035^*$

Study	DAPT		No APT		Weight	Risk Difference [95% CI]	Risk Difference, random-effect, 95% CI
	Events	Total	Events	Total			
Lillis et al. (2011)	0	33	0	532	11.4%	0.00 [-0.04, 0.04]
Girotra et al. (2014)	2	139	4	575	42.7%	0.01 [-0.01, 0.03]	
Bajkin et al. (2014)	1	43	0	105	6.1%	0.02 [-0.03, 0.08]	
Dudek et al. (2015)	0	55	0	33	8.3%	0.00 [-0.05, 0.05]	
Lu et al. (2016)	1	24	10	1472	2.9%	0.03 [-0.05, 0.11]	
Babaji et al. (2018)	0	73	0	78	28.6%	0.00 [-0.03, 0.03]	
Overall	4	367	14	2795	100.0%	0.01 [-0.01, 0.02]	

Heterogeneity $\chi^2 = 1.52$, $df = 5$, $p = 0.911$, $I^2 = 0.0\%$
 Test RD = 0, $z = 0.81$, $p = 0.421$

Heterogeneity $\chi^2 = 1.52$, $df = 5$, $P = 0.911$, $I^2 = 0.0\%$.

Test RD = 0, $Z = 0.81$, $P = 0.421$.

APT, antiplatelet therapy; CI, confidence interval; DAPT, dual antiplatelet therapy.

* $P < 0.05$.

minor oral procedures were pooled for the meta-analysis. This should be taken into account when interpreting the results.

Overall, it is questionable whether patients on DAPT are more prone to bleed during minor oral surgical procedures than patients on SAPT and patients not taking antiplatelet drugs. After all, while the risk ratios were statistically significant in some comparisons, the risk differences were clinically very similar and also not statistically significant.

Haemostatic measures

All bleeding events could be managed with local haemostatic measures. Gauze pressure and (re)sutures were applied most frequently, both as primary and secondary measures. Supplementary methods to stop bleeding included sponges as a primary measure and TXA as a secondary measure. TXA methods were applied in six studies and seemed to efficiently stop bleeding^{12,14,16,19,22,23}. This is in accordance with the results of a recent systematic review investigating local haemostatic measures after dental extraction in anticoagulated patients³². However, that review did not specifically focus on patients on DAPT, but included patients treated with various antithrombotic agents. As the topical application of TXA results in minimal systemic absorption and accordingly may reduce oral bleeding without systemic effects, TXA

is an attractive local haemostatic agent³³. Despite the importance of local haemostatic measures for avoiding or stopping bleeding in oral surgical interventions, there is no consensus about which measures are ideal or superior.

Limitations

Some limitations of this review must be taken into account. First, most of the selected studies excluded patients with systemic or congenital diseases and those taking any medication (other than antiplatelet drugs) affecting haemostasis. The complication risk in these high-risk patients may be different from that in the patients examined in the included studies. Second, the method of extraction (simple vs. surgical) and the number of extracted teeth will influence the risk of bleeding. Bleeding with the extraction of mandibular molars, impacted molars, or multiple teeth in one single intervention is expected to be higher compared to that in straightforward or single tooth extractions³⁴. These variables could not be taken into account in this systematic review because of a lack of data. Lastly, due to the non-randomized nature of the studies, even though a lack of heterogeneity was found in some meta-analyses, this did not indicate a lack of bias. It is still possible that a consistent bias existed in all studies by some possible confounding factors, such as the medical history of the patients. The

random-effects model was thus always used in this research, regardless of whether heterogeneity was found to be significant. Nevertheless, the results of systematic reviews of observational studies should still be interpreted with caution.

In conclusion, the risk of perioperative bleeding with minor oral surgery is elevated for patients on DAPT compared to those on SAPT, but not compared to patients not taking antiplatelet drugs. The risk differences were not significant though. The postoperative bleeding risk is significantly higher for DAPT than for SAPT and no APT. Again, the risk differences were only 1% and not significant. Therefore, the higher bleeding risk for DAPT may be clinically irrelevant. Local haemostatic measures, such as gauze pressure and sutures, possibly supplemented by sponges or TXA measures, were sufficient to stop bleeding in all reported cases. Therefore, it is advisable to continue DAPT therapy before minor oral surgery such as dental extractions, and to apply at least gauze and sutures to prevent bleeding. Other haemostatic measures, such as sponges and TXA, can be applied additionally to prevent bleeding and to manage unexpected bleeding events.

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Competing interests

All authors have no conflicts of interest to declare.

Ethical approval

Not required.

Patient consent

Not required.

Appendix A. Supplementary data

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