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Prospective observational cohort study of the association between antiplatelet therapy, bleeding and thrombosis in patients with coronary stents undergoing noncardiac surgery

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Abstract

Background: The perioperative management of antiplatelet therapy in noncardiac surgery patients who have undergone previous percutaneous coronary intervention (PCI) remains a dilemma. Continuing dual antiplatelet therapy (DAPT) may carry a risk of bleeding, while stopping antiplatelet therapy may increase the risk of perioperative major adverse cardiovascular events (MACE).

Methods: Occurrence of Bleeding and Thrombosis during Antiplatelet Therapy In Non-Cardiac Surgery (OBTAIN) was an international prospective multicentre cohort study of perioperative antiplatelet treatment, MACE, and serious bleeding in noncardiac surgery. The incidences of MACE and bleeding were compared in patients receiving DAPT, monotherapy, and no antiplatelet therapy before surgery. Unadjusted risk ratios were calculated taking monotherapy as the baseline. The adjusted risks of bleeding and MACE were compared in patients receiving monotherapy and DAPT using propensity score matching.

Results: A total of 917 patients were recruited and 847 were eligible for inclusion. Ninety-six patients received no antiplatelet therapy, 526 received monotherapy with aspirin, and 225 received DAPT. Thirty-two patients suffered MACE and 22 had bleeding. The unadjusted risk ratio for MACE in patients receiving DAPT compared with monotherapy was 1.9 (0.93–3.88), P=0.08. There was no difference in MACE between no antiplatelet treatment and monotherapy 1.03 (0.31–3.46), P=0.96. Bleeding was more frequent with DAPT 6.55 (2.3–17.96) P=0.0002. In a propensity matched analysis of

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177 patients who received DAPT and 177 monotherapy patients, the risk ratio for MACE with DAPT was 1.83 (0.69–4.85), $P=0.32$. The risk of bleeding was significantly greater in the DAPT group 4.00 (1.15–13.93), $P=0.031$.
Conclusions: OBTAIN showed an increased risk of bleeding with DAPT and found no evidence for protective effects of DAPT from perioperative MACE in patients who have undergone previous PCI.

Keywords: acetylsalicylic acid; antiplatelet therapy; bleeding; major adverse cardiovascular events; outcome; percutaneous coronary intervention; surgery

Editor's key points

- There is only limited evidence that continuation of dual antiplatelet therapy (DAPT) in patients undergoing noncardiac surgery with previous percutaneous coronary intervention is beneficial in the prevention of major adverse cardiovascular events (MACE).
- The OBTAIN study suggests lack of protection by perioperative continuation of DAPT, while the risk of harm from bleeding is increased.
- The findings from the OBTAIN study should, however, be viewed in the light of its observational nature, the small sample size, and the lack of long-term and standardised monitoring of MACE.

The optimal management of antiplatelet agents in patients who have undergone recent percutaneous coronary intervention (PCI) requiring noncardiac surgery remains a vexed issue. Coronary stents are an effective technology for the prevention of coronary artery restenosis after angioplasty, but until they become covered by endothelium, however, the metal struts of coronary stents offer an ideal surface for the formation of thrombus.[1] Endothelial coverage can take 3 months for bare metal stents (BMS) and longer for drug eluting stents (DES), and late stent thrombosis may occur for up to 4 yr after PCI.[2,3]

Dual antiplatelet therapy (DAPT) with aspirin and a platelet $P2Y_{12}$ receptor blocker is commonly used to prevent stent thrombosis. It is recommended that DAPT be administered for at least 1 month after BMS implantation in stable coronary artery disease, for 6 months after new-generation DES implantation, and for up to 1 yr in patients after acute coronary syndrome, irrespective of revascularisation strategy.[4,5] After the introduction of coronary stents, mortality rates of up to 20% were reported in patients in whom antiplatelet agents were discontinued and noncardiac surgery performed in the first 2 months after PCI.[6] However, because of the increased risk of bleeding, it is preferable to avoid continuation of DAPT during surgery.[7] Surgery is the second common cause for withdrawal of antiplatelet therapy within 6 months of PCI and the most common cause of withdrawal between 6 months and 1 yr after PCI.[8–11]

The British National Formulary recommends withdrawing clopidogrel 7 days before surgery if an antiplatelet effect is not desirable.[12] There remains substantial uncertainty and limited evidence as to whether patients who undergo noncardiac surgery within 3 months of the placement of a BMS or 12 months of a DES should receive aspirin alone or DAPT throughout the perioperative period. The present study aimed to prospectively investigate antiplatelet use and the occurrence of major adverse cardiovascular events (MACE) and bleeding in patients who underwent noncardiac surgery within 4 yr of PCI.

Methods

The prospective cohort study 'Occurrence of Bleeding and Thrombosis during Antiplatelet Therapy In Non-Cardiac Surgery' (OBTAIN) included patients requiring elective or urgent noncardiac surgery who had undergone PCI in the preceding 4 yr. Urgent surgery was defined as surgery with a time from the decision to operate to surgery of at least 7 days (i.e. a sufficient interval to modify antiplatelet therapy). Patients requiring emergency surgery were excluded. Patients were approached either in the pre-assessment clinic or upon admission for surgery depending on local arrangements. The study was approved by Research Ethics Committees in each national jurisdiction and consent gained from patients at the time of enrolment. Details of national research ethics approvals are held by the European Society of Anaesthesiology Clinical Trials Network (ESA-CTN) Office.

The management of antiplatelet therapy through the perioperative period was at the discretion of the clinical teams. Data were collected on cardiovascular risk factors, antiplatelet agent management, MACE, and bleeding events. The occurrence of MACE and bleeding were compared in patients who received dual, single, or no antiplatelet therapy in the perioperative period.

Preoperative data collected included details of the most recent PCI (date of PCI, number of stents deployed, type of stents used), risk factors for stent thrombosis (age >79 yr, impaired left ventricular function, stent placed for acute coronary syndrome, multiple stents, diabetes, renal impairment), history of previous cardiovascular morbidity [myocardial infarction (MI), cerebrovascular accident (CVA), heart failure, angina), other perioperative cardiovascular risk factors (left ventricular hypertrophy, limited exercise tolerance, history of smoking), cardiovascular medication use, and risk factors for bleeding.[4,13,14] Operations were classified as low-, intermediate-, and high-risk groups, with estimated 30-day cardiac event rates of <1%, 1–5%, and >5%, respectively, as described in the 2009 European guidelines on preoperative cardiac risk assessment and perioperative cardiac management in noncardiac surgery.[15]

The effect of variation in the use of DAPT by country was included in the analysis. Countries were classified depending on whether their overall rate of use of dual therapy (as opposed to monotherapy) was <25%, 25–50%, or >50% (Table 1). This allowed us to take account of the observed differences in national practice whilst matching on three categories rather than at an individual country level.

Patients were considered to have discontinued aspirin, clopidogrel, or prasugrel before surgery if they stopped taking

Table 1 Participating countries classified into three groups according the percentage of patients who underwent surgery whilst receiving dual antiplatelet therapy. DAPT, dual antiplatelet therapy

Group 1 perioperative DAPT <25%	Group 2 perioperative DAPT 25–50%	Group 3 perioperative DAPT >50%
France	Belgium	Greece
The Netherlands	Portugal	Germany
UK	Spain	Lithuania
		Romania
		Turkey
		Kosovo

the agent ≥7 days before operation.[12] Monotherapy was considered to be treatment with aspirin alone, and dual therapy was treatment with aspirin and either clopidogrel or prasugrel. MACE that were detected as part of routine care were recorded. Additional surveillance with ECGs or cardiac biomarker assays was not performed as part of the study. Patients were considered to have suffered a major adverse event if they suffered an MI as defined by the Universal Definition of Myocardial Infarction (including cardiac arrest and cardiac death as described in this definition) or PCI for a cardiac event occurring after surgery.[16] Major perioperative bleeding events were considered to be reoperation for bleeding, gastrointestinal haemorrhage, intracranial haemorrhage, haemorrhagic stroke, spinal, or epidural haematoma. These outcomes were selected to be robust endpoints confirmed by investigation or intervention (reoperation, endoscopy, CT scan, or MRI scan) and to avoid subjective judgements, for example regarding the size and importance of a wound haematoma. Events were adjudicated within the local centre and discussed with the lead national investigator in cases of uncertainty. Blood transfusion was not included within the definition of major bleeding, as transfusion practice varies widely across different centres.[17,18]

Statistical analysis

The statistical software used was R (https://www.R-project.org/) with the MatchIt package.[19] A simple unadjusted comparison of the incidence of MACE and bleeding events between patients receiving DAPT, single antiplatelet therapy, and no antiplatelet therapy through the perioperative period was made using Pearson's χ^2 test. In addition, unadjusted relative risk ratios for bleeding and MACE were calculated taking the group who received monotherapy (aspirin alone) as the baseline group.

An important concern in this study was confounding by indication (i.e. bias as a result of those patients receiving dual therapy being at higher risk of MACE). Confounding was addressed by propensity score matching on variables shown to predict receipt of dual therapy as opposed to monotherapy. Logistic regression was used to identify factors associated with the propensity for dual therapy rather than monotherapy. The clustering of patients within centres was accounted for by fitting a random intercept for centre. The random intercept was to be dropped from the model if a lower Akaike's Information Criterion (AIC) was achieved without accounting for clustering: that is if clustering was seen to not improve the propensity model sufficiently. All subsets of factors in the propensity model were explored and the selected model had the lowest AIC with all factors providing a statistically significant association between the factor and the propensity for dual therapy. Propensity score matching was used to select two groups for comparison: those on monotherapy and those on dual therapy. Matching was performed using 1:1 nearest neighbour matching. Direct comparisons were undertaken between the two matched groups. Standardised differences of relevant clinical characteristics between the two groups are reported. There were too few events in the group of patients receiving no antiplatelet therapy to support a propensity matched analysis that included this subgroup of patients.

Power calculations were performed for both bleeding and MACE outcomes using the 'sampsi' function of State SE 9, StataCorp, College Station, TX, USA. Both calculations were based on a type 1 error of 0.05 and a power of 0.8. For MACE, the studies of Nuttall and colleagues[20] and Rabbitts and colleagues[21] suggest that the risk of perioperative MACE in a similar population is 5%. We assumed a doubling in the incidence of MACE if clopidogrel is discontinued (Iakovou and colleagues[4] reported a 90-fold increased risk of stent thrombosis if antiplatelet agents were discontinued in medical patients). Based on a discontinuation rate of 50% we calculated that 474 patients would be required in the mono and DAPT groups; a total of 948 patients. There were few data from large studies on the association between clopidogrel and perioperative bleeding in noncardiac surgery. Whilst carried out in cardiac surgery, the study of Kapetanakis and colleagues[22] which included 2359 patients and used robust definitions for bleeding outcomes was the best available evidence on which to base a power calculation. Kapetanakis and colleagues[22] reported a baseline incidence of 1.3% for reoperation for bleeding in cardiac surgery, rising to 5.8% for patients receiving clopidogrel. The adjusted odds ratio for bleeding associated with clopidogrel was 5.7 (1.81–18.15). For the purposes of this power calculation, we assumed a 1% baseline incidence of clinically significant bleeding and a relative risk of bleeding associated with clopidogrel of 4.0. Using these assumptions we calculated that 489 patients would be required in each group; a total of 978 patients. In order to allow for a 10% loss for follow-up and to allow for the development of a robust propensity score model we aimed to recruit 1400 patients. We were aware of the limitations of these calculations for an observational study. In particular, we could not be sure of a balance between the mono and DAPT groups.

Results

Nine hundred and seventeen patients from 41 centres in 12 countries were enrolled into the study between March 2011 and December 2013. The Steering Group made the decision to close the study after 917 patients had been recruited, because an interim analysis had shown a statistically significant association between dual antiplatelet therapy and bleeding. There was a higher incidence of MACE in the DAPT group than in the monotherapy group (the opposite direction to what had been expected).

Of the 917 patients recruited, 847 were eligible for inclusion (Fig. 1). Thirty-eight patients were excluded as they had undergone PCI more than 4 yr before noncardiac surgery. In 31 excluded patients, PCI and surgery were planned together, meaning that decisions regarding antiplatelet therapy for noncardiac surgery were made at the time of PCI and the PCI strategy may have been modified with noncardiac surgery in view. One patient who received bridging anticoagulant

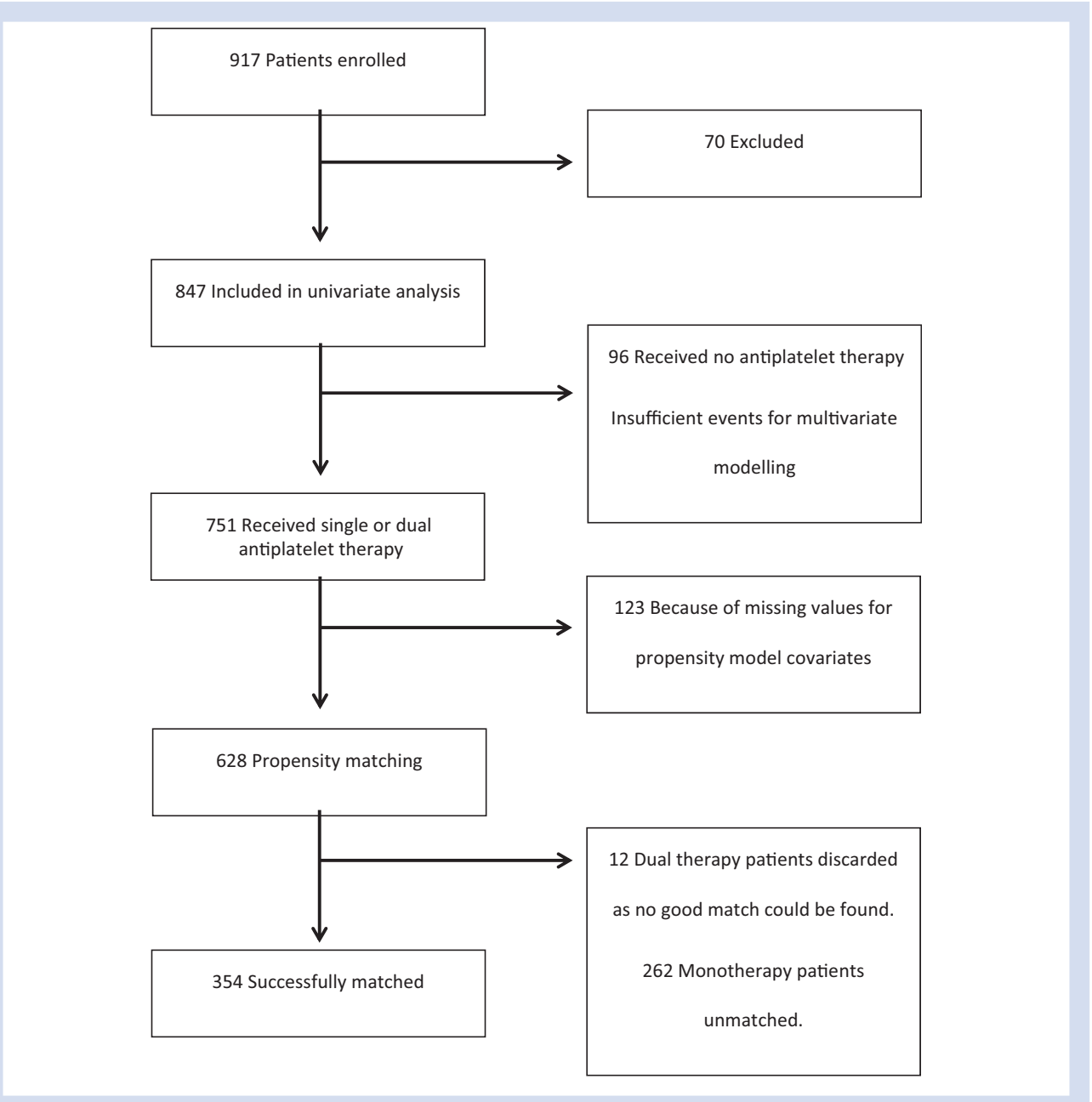

Fig 1. CONSORT flow diagram of recruitment of patients into Occurrence of Bleeding and Thrombosis during Antiplatelet Therapy in Non-Cardiac Surgery (OBTAIN).

therapy after the withdrawal of antiplatelet therapy was excluded. Differences in the use of perioperative DAPT were noted between different counties, as reported in Table 1.

Ninety-six patients received no antiplatelet therapy in the perioperative period, 526 received monotherapy with aspirin alone, and 225 received DAPT with aspirin and clopidogrel (194 patients) or prasugrel (31 patients). The clinical characteristics of these three groups of patients are reported in Table 2.

Thirty-two patients experienced MACE; three in the group who received no antiplatelet therapy, 16 in the monotherapy group, and 13 in the group who received DAPT. Of these, 28 patients suffered a perioperative cardiac event that fulfilled the 2007 universal definition of MI criteria, six patients underwent acute postoperative PCI (including two who were defined as having suffered an MI by the 2007 criteria), and one patient suffered a fatal postoperative MI. Twenty-two patients experienced clinically significant bleeding events; three of these patients received no antiplatelet therapy in the perioperative period, five received monotherapy, and 14 received DAPT. Eighteen patients underwent reoperation for bleeding, three patients suffered a postoperative gastrointestinal bleed, and one patient developed an epidural haematoma. As noted above, one patient died after a postoperative MI. No other deaths were reported.

Table 2 Patient characteristics. (Some percentages do not add up to exactly 100% because of rounding.) CVA, cerebrovascular accident; MI, myocardial infarction; PCI percutaneous coronary intervention

Factor		No aspirin, *n* (%)	Monotherapy, *n* (%)	Dual-therapy, *n* (%)	*P*-value
Subjects (number)		96	526	225	
Sex	Male	66 (68.8)	398 (75.7)	186 (82.7)	0.017
	Female	30 (31.2)	128 (24.3)	39 (17.3)	
Age (yr)	31–59	11 (11.5)	98 (18.6)	45 (20.0)	0.455
	60–69	30 (31.2)	163 (31.0)	75 (33.3)	
	70–79	38 (39.6)	191 (36.3)	80 (35.6)	
	80–91	17 (17.7)	74 (14.1)	25 (11.1)	
Country group	<25%	63 (65.6)	347 (66.0)	91 (40.4)	<0.001
	25–50%	15 (15.6)	140 (26.6)	82 (36.4)	
	>50%	18 (18.8)	39 (7.4)	52 (23.1)	
Smoking	Never	33 (34.4)	175 (33.3)	73 (32.4)	0.194
	Ex-smoker	43 (44.8)	247 (47.0)	95 (42.2)	
	Current	9 (9.4)	75 (14.3)	39 (17.3)	
	Not recorded	11 (11.5)	29 (5.5)	18 (8.0)	
Able to climb stairs	Able	62 (64.6)	356 (67.7)	140 (62.2)	0.698
	Unable	21 (21.9)	106 (20.2)	52 (23.1)	
	Not recorded	13 (13.5)	64 (12.2)	33 (14.7)	
Diabetes mellitus	Diabetic	31 (32.3)	112 (21.3)	73 (32.4)	0.002
	Non-diabetic	65 (67.7)	414 (78.7)	152 (67.5)	
Urgency of PCI	Elective	50 (52.1)	217 (41.3)	76 (33.8)	0.014
	Acute	38 (39.6)	266 (50.6)	135 (60.0)	
	Not recorded	8 (8.3)	43 (8.2)	14 (6.2)	
Time from PCI to surgery (days)	0–364	21 (21.9)	83 (15.8)	139 (61.8)	<0.001
	365–729	30 (31.2)	194 (36.9)	48 (21.3)	
	730–1459	45 (46.9)	249 (47.3)	38 (16.9)	
Number of stents	0 or1	65 (67.7)	290 (55.1)	120 (53.3)	0.012
	2+	27 (28.1)	215 (40.9)	103 (45.8)	
	Unknown	4 (4.2)	21 (4.0)	2 (0.9)	
Ejection fraction	Good or not recorded	82 (84.4)	462 (87.8)	167 (74.2)	0.012
	Impaired	14 (14.6)	64 (12.2)	58 (25.8)	
Surgery	Elective	95 (99.0)	517 (98.3)	211 (93.8)	0.002
	Acute	1 (1.0)	9 (1.7)	14 (6.2)	
Operation risk	Low	47 (49.0)	259 (49.2)	97 (43.1)	0.079
	Intermediate or high	49 (51.0)	267 (50.8)	128 (56.9)	
ASA physical status	1 or 2	28 (29.2)	167 (31.7)	47 (20.9)	0.017
	3	56 (58.3)	298 (56.7)	137 (60.9)	
	4	11 (11.5)	48 (9.1)	37 (16.4)	
	Not recorded	1 (1.0)	13 (2.5)	4 (1.8)	
Previous MI	Previous MI	33 (34.4)	159 (30.2)	88 (36.1)	0.058
	No previous MI	63 (65.6)	367 (69.8)	137 (63.9)	
Current angina	Angina	42 (43.8)	229 (43.5)	96 (42.7)	0.972
	No angina	54 (56.2)	297 (56.5)	129 (57.3)	
History of heart failure	Heart failure	5 (5.2)	20 (3.8)	18 (8.0)	0.056
	No heart failure	91 (94.8)	506 (96.2)	207 (92.0)	
Previous CVA	Previous CVA	9 (9.4)	29 (5.5)	21 (9.3)	0.104
	No previous CVA	87 (90.6)	497 (94.5)	204 (90.7)	
Urgency of surgery	Urgent	1 (1.0)	9 (1.7)	14 (6.2)	0.002
	Non-urgent	95 (99.0)	517 (98.3)	211 (93.8)	

The occurrences of MACE and significant bleeding in patients on dual, single, and no antiplatelet therapy during the perioperative period are shown in Table 3. Whilst the odds ratio for MACE in the DAPT as compared with the monotherapy with aspirin was greater than unity, this was not statistically significant with risk ratio (RR) 1.9 (0.93–3.88). The risk of MACE was almost identical in patients receiving no antiplatelet treatment and those receiving aspirin over the perioperative period [1.03 (0.31–3.46)]. Bleeding was significantly more frequent in patients on DAPT as compared with patients on aspirin alone [6.55 (2.39–17.96)].

As noted above, these unadjusted results were potentially affected by confounding by indication and we therefore undertook a propensity score matching analysis. This analysis was only possible for patients receiving single therapy or DAPT. Ninety-six patients received no antiplatelet therapy in the perioperative period. As this group experienced only three MACE and three bleeding events, further analyses were not performed and these patients were excluded from the propensity weighted analysis.

All variables listed in Table 2 were included in the logistic regression modelling process. The final propensity score model included the following covariates: country group, time since PCI, ejection fraction, urgency of surgery, and previous MI. One hundred and twenty-three patients were excluded from the matching process because of missing or unavailable data on covariates (e.g. data on ejection fraction was only available in patients who had undergone echocardiography or

Table 3 Association between antiplatelet therapy, bleeding, and major adverse cardiovascular events (MACE); unadjusted analysis. The percentage of MACE and bleeding events in each group is given in parenthesis. The overall *P*-value across the three groups for MACE and bleeding are given in the final column. The odds ratios (OR) for MACE and bleeding are given taking the monotherapy group as baseline

	No perioperative antiplatelet therapy, N=96, *n* (%)	Mono-therapy, N=526, *n* (%)	Dual therapy, N=225, *n* (%)	Overall *P*-value
MACE	3 (3.1) OR 1.03 (0.31–3.46) *P*=0.96	16 (3.0)	13 (5.8) OR 1.9 (0.93–3.88) *P*=0.08	0.115
Bleeding	3 (3.1) OR 3.29 (0.80–13.53) *P*=0.10	5 (1.0)	14 (6.2) OR 6.55 (2.39–17.96) *P*=0.0002	<0.001

other cardiac imaging). Six hundred and twenty eight patients (439 monotherapy and 189 dual therapy) were selected for propensity score matching. We matched at a ratio of 1:1 with the nearest propensity score match, without replacement. The use of a calliper was not found to be useful. Violin plots demonstrated propensities ranging from zero to unity for the monotherapy group, whereas for patients who received dual therapy, propensities ranged from 0.2 to unity. Thus, matching was undertaken for dual and monotherapy patients with propensities in the range 0.2 to unity. This led to us discarding 12 dual therapy patients without sufficiently close matches. A total of 177 monotherapy and 177 dual therapy patients (a total of 354) were matched. There were 29 MACE events amongst mono- and dual therapy patients in the study population as a whole and 17 in the matched study group. Two DAPT and 10 monotherapy patients with MACE were discarded in the matching process. There were 19 patients with bleeding events in the two groups in the study population as a whole and 17 in the matched population. Two DAPT and two monotherapy patients with bleeding events were discarded in the matching process. The clinical characteristics of the matched patients are shown in Table 4. The incidence of MACE and bleeding were compared in the matched single and DAPT groups. Amongst the 177 propensity matched patients who remained on DAPT, there were 11 MACE events, compared with six in the group on monotherapy. There was no statistically significant difference in the incidence of MACE between the two groups [RR 1.83 (0.69–4.85), *P*=0.32]. The incidence of clinically important bleeding was significantly greater in the dual therapy group than in the monotherapy group. There were 12 bleeding events in the 177 propensity matched patients receiving DAPT as compared with three in the monotherapy group giving an RR of 4.00 (1.15–13.93), *P*=0.031.

Discussion

Current guidelines are based on the premise that DAPT offers effective protection against perioperative MI in patients who have undergone PCI undergoing noncardiac surgery. The 2014 European Society of Cardiology and ESA (ESC/ESA) joint guidelines on noncardiac surgery recommend DAPT for at least 1 month after PCI and BMS implantation, for 6 months after the insertion of a new generation drug-eluting stent and for 12 months after an acute coronary syndrome.[23] The 2014 American College of Cardiology and American Heart Association guidelines on perioperative cardiovascular evaluation state that elective noncardiac surgery should not be undertaken within 30 days of BMS implantation or 12 months of DES implantation if DAPT will need to be discontinued.[24]

We were unable to demonstrate a protective effect of DAPT, and the continuation of two antiplatelet agents appeared to be associated with a risk of harm from clinically significant bleeding. The results of OBTAIN are consistent a nested case–control study comparing 284 patients who had undergone noncardiac surgery between 6 weeks and 2 yr after PCI, showing no association between the cessation of all antiplatelet therapy and major postoperative cardiac events.[25] Four earlier studies also found no reduction in perioperative MACE in patients who remained on DAPT.[20,21,26] In contrast, the RECO study, an observational study of 1134 patients who underwent noncardiac surgery after PCI,[27] showed no association between complete antiplatelet therapy interruption for >5 days and perioperative cerebrovascular or cardiovascular events.

Twenty-two patients in OBTAIN suffered major bleeding events, and 14 of these received DAPT in the perioperative period, supportive for an association between perioperative bleeding and DAPT in patients undergoing cardiac surgery.[13,28] In the TRITON-TIMI38 trial, prasugrel was found to be associated with a 13.4% incidence of major bleeding in patients who underwent coronary artery bypass graft procedures compared with 3.2% in patients who were not taking this drug.[29] The evidence for an association between bleeding and DAPT in noncardiac surgery is less clear. A study of 520 patients who underwent noncardiac surgery after PCI reported no association between antiplatelet agent use and transfusion.[21] Similarly, the RECO study found no association between perioperative antiplatelet therapy and bleeding.[27] The results of OBTAIN stand in contrast to these studies, and add substantially to the data suggesting a perioperative risk of bleeding associated with DAPT.

The Perioperative Ischaemic Evaluation-2 (POISE-2) study did not demonstrate a protective effect of perioperative aspirin in patients at risk of vascular complications after surgery.[30] OBTAIN did not show a difference between the incidence of MACE between patients taking DAPT and those on aspirin alone, while perioperative myocardial injury is associated with worse long-term outcome.[31] Moreover, the incidence of MACE was almost similar in patients who discontinued all antiplatelet therapy and patients who continued single antiplatelet therapy. In view of the increased incidence of bleeding in the DAPT group, OBTAIN therefore suggests that perioperative continuation of DAPT may harm some patients rather than protecting them from perioperative cardiac events. The failure of DAPT to offer protection from perioperative myocardial injury may reflect differing mechanisms of perioperative myocardial injury and non-operative MI, which was demonstrated in a study using optical coherence tomography in patients with MI during surgery.[32]

OBTAIN included patients who had undergone PCI up to 4 yr before surgery. Whilst current guidelines recommend DAPT for up to a year after PCI, late in-stent thrombosis has been

Table 4 Table showing balance between the characteristics of the matched groups receiving mono and dual antiplatelet therapy. (Some percentages do not add up to precisely 100% because of rounding.) It has been suggested that standardised differences of <0.1 or <0.25 represent acceptable matching.[4243] CVA, cerebrovascular accident; MI, myocardial infarction; PCI percutaneous coronary intervention

Factor		Monotherapy, *n* (%)	Dual-therapy, *n* (%)	Standardised difference
Subjects (number)		177	177	
Sex	Male	136 (76.8)	145 (81.9)	0.126
	Female	41 (23.3)	32 (18.1)	
Age (yr)	31–59	32 (18.1)	38 (21.5)	0.085
	60–69	56 (31.6)	59 (33.3)	0.036
	70–79	66 (37.3)	59 (33.3)	−0.083
	80–91	23 (13.0)	21 (11.9)	−0.034
Country group	<25%	85 (48.0)	77 (43.5)	−0.091
	25–50%	72 (40.7)	70 (39.5)	−0.023
	>50%	20 (11.3)	30 (16.9)	0.163
Smoking	Never	61 (34.5)	63 (35.6)	0.024
	Ex-smoker	89 (50.3)	84 (47.5)	−0.057
	Current	27 (15.3)	30 (16.9)	0.046
Able to climb stairs	Able	128 (72.3)	117 (66.1)	−0.135
	Unable	35 (19.8)	38 (21.5)	0.042
	Not recorded	14 (7.9)	22 (12.4)	0.150
Diabetes mellitus	Diabetic	37 (20.9)	51 (28.8)	0.184
	Non-diabetic	140 (79.1)	126 (71.2)	
Urgency of PCI	Elective	102 (57.6)	114 (64.4)	0.139
	Acute	75 (42.4)	63 (35.6)	
Days from PCI to surgery		440 (237–582)	310 (141–532)	−0.15
No. of stents	0 or1	98 (55.4)	94 (53.1)	0.045
	2+	79 (44.6)	83 (46.9)	
Ejection fraction	Impaired	34 (19.2)	42 (23.7)	0.139
	Good or not recorded	143 (80.8)	135 (76.3)	
Urgency of surgery	Elective	171 (96.6)	171 (96.6)	0.0
	Acute	6 (3.4)	6 (3.4)	
Operation risk	Low	79 (44.6)	79 (44.6)	0.000
	Intermediate	93 (52.5)	83 (46.9)	−0.113
	High	5 (2.8)	15 (8.5)	0.247
ASA physcial status	1 or 2	46 (26.0)	42 (23.7)	−0.052
	3	113 (63.8)	104 (58.8)	−0.105
	4	18 (10.2)	31 (17.5)	0.214
Previous MI	Previous MI	65 (36.7)	67 (37.9)	0.023
	No previous MI	112 (63.3)	110 (62.1)	
Current Angina	Angina	80 (45.2)	82 (46.3)	0.023
	No angina	97 (54.8)	95 (53.7)	
History of heart failure	Heart failure	7 (4.0)	12 (6.8)	0.126
	No heart failure	170 (96.0)	165 (93.2)	
Previous CVA	Previous CVA	5 (2.8)	17 (9.6)	0.284
	No previous CVA	172 (97.2)	160 (90.4)	

reported up to as late as 5.5 yr after PCI and the risk of in-stent thrombosis in non-surgical patients has been a cause of considerable concern.[8,9,33–36] A recent meta-analysis indeed showed that continuation of DAPT for 18–48 months after PCI was associated with a decreased incidence of stent thrombosis and MI, but with an increased risk of major bleeding.[37] Overall, there was weak evidence of increased mortality with prolonged DAPT. Nevertheless, DAPT beyond 1 yr after PCI may be of benefit in patients at higher risk of in-stent thrombosis. Based on the results of the PEGASUS study, the UK National Institute for Health and Care Excellence now recommends ticagrelor at reduced dose (60 mg bd) for up to 3 yr after the usual 12 months course in selected patients with recent MI.[38,39] In OBTAIN, patients were more likely to continue DAPT through the perioperative period if they underwent surgery in the 12 months immediately after PCI. However, there were too few MACE or bleeding events to allow an adequately powered examination of the interaction between the effect of continuing DAPT through the perioperative period and the interval between PCI and surgery.

Our study suggests a significant variation in the management of DAPT between countries. Patients from southern and eastern Europe who were included in OBTAIN were more likely to receive DAPT through the perioperative period, without particular reasons for this strategy. The international long-term observational study of acute coronary syndrome (EPICOR) also identified national variations in the continuation of DAPT beyond 12 months after the index cardiac event.[40] Country was a key determinant for the continuation of DAPT at 12 months beyond acute coronary syndrome in EPICOR, but whether this is because of cultural, economic, or organisational reasons remains unclear and requires further study. Moreover, there was no evidence of any difference in outcome between different participating countries.

Our power calculation suggested that approximately 980 patients should be recruited. However, the study was terminated

early as the data showed a clinically important association between DAPT and bleeding whilst suggesting an effect for MACE in the opposite direction to that expected (i.e. a greater incidence of MACE in the DAPT group) that could not be confirmed within the planned sample size. The power of the current study to confirm such a difference was calculated to be between 0.45 and 0.5, requiring the inclusion of 1700 patients to have an 80% power to confirm this difference, with the same proportion of patients remaining on DAPT. A prospective randomised controlled trial in which mono antiplatelet therapy (MAPT) and DAPT groups are equally matched would require approximately 1630 patients to have an 80% power to confirm this finding.

A limitation of OBTAIN is the absence of formal surveillance for perioperative MACE and cardiac troponin concentrations. The VISION study demonstrated that such events do have long-term prognostic implications, although the optimal management of a patient who has suffered a perioperative troponin increase remains unclear.[31]

Comparing the characteristics of the 354 matched patients (Table 4) with those of the 761 mono and dual therapy patients in the population as a whole suggests that the matched population is representative of the wider population. For most characteristics, the proportion of patients in the matched group was within 5% of that in the population as a whole. The proportion of patients with a history of previous MI was 30.4% in the monotherapy group in the population as a whole, but 36.7% in the monotherapy group in the matched population. There was also some difference in the distribution of ASA scores. Eighteen patients without ASA data were excluded from the matched analysis. In the monotherapy group, there were more ASA 1 and 2 patients amongst the monotherapy patients in the population as a whole than in the matched patients (31.7% *vs* 23.7%). For the dual therapy patients, there were more ASA 4 patients in the dual therapy group in the population as a whole (16.4% *vs* 8.5%). There was a difference in the history of stroke between the two groups in the population as a whole (monotherapy 5.5% *vs* dual therapy 9.3%) that was more marked the matched group (2.8% *vs* 9.6%). In the population as a whole, the monotherapy group included 66% of patients from countries where more than 75% of patients had DAPT discontinued. This compared with 40.4% in the dual therapy group. As might be expected, the matching process improved the balance between these two characteristics.

There is no absolute standard for assessing balance between propensity matched groups. Harder and colleagues[41] suggest a standardised mean difference of 0.25 as a 'rule of thumb' for balance between covariates whilst noting that others have suggested stricter cut-offs. The propensity matched model used in our analysis achieved standardised mean differences of <0.25 in all but one measured covariate (CVA). The analysis was limited by the sample size and some covariates did not meet the stricter matching criteria of a standardised mean difference of 0.1 suggested by Austin and colleagues.[42] However, the propensity matching process met the standard of model of achieving acceptable balance with an standardized mean difference (SMD) of <0.25 for those covariates of most importance to the outcomes of interest.[41] A frequent criticism of 1:1 propensity matching is that it leads to the discarding of a large number of observations and so reduces statistical power. This has been challenged on the basis that if the greater loss of subjects is from one group, then the loss of power may not be great and is offset by the advantages of comparing groups that are more similar.[43] The matching process reduced to about 20% the power of the study to confirm the significance of the observed difference in the incidence of MACE in MAPT and DAPT patients. As noted above, a substantially larger study would have been required to confirm this observation.

It is possible that there are unobserved characteristics of the patients that have influenced the findings. The fact that information on the type of stent or PCI urgency level was often not available reflects the difficulty of garnering these data retrospectively. However, OBTAIN supports the discussion that the continuation of DAPT in patients undergoing PCI requiring noncardiac surgery is a difficult one, and that it is unsure whether protection from perioperative MACE outweighs the risk for bleeding.

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Study design: SJH, SEH, RMW, SBW.
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Oversaw centre recruitment through the ESA-CTN Network and led Network support for the study: AH.
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Data and preliminary analyses: SEH, SJH. Final data analysis: RMW. Writing paper: SH.
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SJH Is an Editorial Board member and Director of the *British Journal of Anaesthesia* and has received consultancy payments from CSL Behring. SBW is an Editorial Board member of the *British Journal of Pharmacology* and has received lecture fees and travel support from AstraZeneca, Bayer and Abbott Vascular. AH has acted as a consultant for Medtronic, Edwards, BBraun and UPmed.

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