British Journal of Anaesthesia **107** (6): 899–910 (2011)
Advance Access publication 27 August 2011 · doi:10.1093/bja/aer274

BJA

CLINICAL PRACTICE

Impact of preoperative maintenance or interruption of aspirin on thrombotic and bleeding events after elective non-cardiac surgery: the multicentre, randomized, blinded, placebo-controlled, STRATAGEM trial†

J. Mantz[1,2,3]*, C. M. Samama[4,5], F. Tubach[2,6,7,8,9], P. J. Devereaux[10,11], J.-P. Collet[12,13], P. Albaladejo[14,15], B. Cholley[16], R. Nizard[2,17], J. Barré[18], V. Piriou[19], N. Poirier[20], A. Mignon[21], S. Schlumberger[22], D. Longrois[23,24,25], F. Aubrun[26], M. E. Farèse[2,6,7,8,10,11], P. Ravaud[4,5,6,7‡] and P. G. Steg[2,27,28‡], for the Stratagem Study Group

[1] APHP, Hôpital Beaujon, Service d'Anesthésie Réanimation et SMUR, Clichy F-92110, France
[2] Université Paris Diderot, Paris F-75018, France
[3] INSERM U 676, Paris F-75019, France
[4] Université Paris Descartes, Paris F-75005, France
[5] APHP, Hôpital Hôtel-Dieu, Centre d'Epidémiologie Clinique, Paris F-75004, France
[6] INSERM, UMR-S 738, Paris F-75018, France
[7] Université Paris Diderot, UMR-S 738, Paris F-75018, France
[8] INSERM, CIE 801, Paris F-75018, France
[9] APHP, Hôpital Bichat-Claude Bernard, Département d'Epidémiologie, Biostatistique et Recherche Clinique, Paris F-75018, France
[10] Department of Clinical Epidemiology and Biostatistics and [11] Department of Medicine, Michael de Groote School of Medicine, McMaster University, Hamilton, Ontario, Canada
[12] Institut de Cardiologie, INSERM UMRS 937, APHP, Hôpital Pitié-Salpétrière, Paris F-75013, France
[13] Université Pierre et Marie Curie, Paris F-75013, France
[14] Centre Hospitalier Universitaire, Pôle d'Anesthésie et de Réanimation, Grenoble, France
[15] Université Joseph Fourier, Grenoble F-38043, France
[16] APHP Hôpital Européen Georges Pompidou, Service d'Anesthésie Réanimation, Paris F-75015, France
[17] APHP, Hôpital Lariboisière, Service de chirurgie orthopédique, Paris F-75018, France
[18] Centre Hospitalier Universitaire, Service d'Anesthésie Réanimation, Reims F-51000, France
[19] Hôpitaux Universitaires de Lyon, Groupe Hospitalier Sud, Service d'Anesthésie Réanimation, Lyon F-69000, France
[20] Centre Hospitalier Universitaire, Service d'Anesthésie Réanimation, Angers F-49000, France
[21] APHP Hôpital Cochin, Service d'Anesthésie Réanimation, Université Paris Descartes, Paris F-75005, France
[22] CMC Foch, Service d'Anesthésie Réanimation, Suresnes F-92200, France
[23] INSERM U-676, Paris, France
[24] Université Paris Diderot, Paris, France
[25] APHP, Hôpital Bichat-Claude Bernard, Service d'Anesthésie Réanimation, Paris F-75018, France
[26] Hôpitaux Universitaires de Lyon, Groupe Hospitalier Nord, Service d'Anesthésie Réanimation, Lyon F-69000, France
[27] INSERM U-698, Paris, France
[28] AP-HP, Hôpital Bichat-Claude Bernard, Service de Cardiologie, Paris F-75018, France

* Corresponding author: Department of Anaesthesia and Critical Care Medicine, Beaujon University Hospital, 100 Boulevard du Général Leclerc, 92110 Clichy, France. E-mail: jean.mantz@bjn.aphp.fr

†Presented as an abstract form at the Annual Meeting of the American Society of Anesthesiologists, San Diego, CA, USA, October 16–20, 2010.
‡These two authors contributed equally to this study.

Editor's key points

- In this multicentre study, patients on anti-platelet therapy and undergoing non-cardiac elective surgery were studied.
- Aspirin or placebo (substituted for the anti-platelet drugs) was given for 10 days before operation.
- The outcome in the two groups was similar with regard to thrombotic or bleeding complications.
- Although a negative study, the data provide useful safety information regarding preoperative aspirin.

Background. Patients receiving anti-platelet agents for secondary cardiovascular prevention frequently require non-cardiac surgery. A substantial proportion of these patients have their anti-platelet drug discontinued before operation; however, there is uncertainty about the impact of this practice. The aim of this study was to compare the effect of maintenance or interruption of aspirin before surgery, in terms of major thrombotic and bleeding events.

Methods. Patients treated with anti-platelet agents for secondary prevention and undergoing intermediate- or high-risk non-cardiac surgery were included in this multicentre, randomized, placebo-controlled, trial. We substituted non-aspirin anti-platelets with aspirin (75 mg daily) or placebo starting 10 days before surgery. The primary outcome was a composite score evaluating both major thrombotic and bleeding adverse events occurring within the first 30 postoperative days weighted by their severity (weights were established *a priori* using a Delphi consensus process). Analyses followed the intention-to-treat principle.

Results. We randomized 291 patients (n=145, aspirin group, and n=146, placebo group). The most frequent surgical procedures were orthopaedic surgery (52.2%), abdominal surgery (20.6%), and urologic surgery (15.5%). No significant difference was observed neither in the primary outcome score [mean values (SD)=0.67 (2.05) in the aspirin group *vs* 0.65 (2.04) in the placebo group, P=0.94] nor at day 30 in the number of major complications between groups.

Conclusions. In these at-risk patients undergoing elective non-cardiac surgery, we did not find any difference in terms of occurrence of major thrombotic or bleeding events between preoperative maintenance or interruption of aspirin.
ClinicalTrials.gov identifier. NCT00190307.

Keywords: aspirin interruption; bleeding events; non-cardiac surgery; thrombotic events

Accepted for publication: 2 June 2011

A large body of work has established the clear benefit of long-term anti-platelet therapy (aspirin, clopidogrel) for secondary prevention after myocardial infarction or stroke and after coronary revascularization with bare-metal or drug-eluting stents.[1] Interruption of aspirin in patients exposed to anti-platelet single therapy is associated with a major increase in the risk of serious adverse cardiac thrombotic events in the non-operative setting.[2] Therefore, aspirin is recommended as a life-long therapy after stroke, myocardial infarction, and coronary artery stent insertion.[1] The perioperative period is a high-risk period for major thrombotic events due to the increase in platelet aggregability and decreased fibrinolysis that occurs during the perioperative period.[3–7] In a large randomized multicentre trial (PEP, 13 356 randomized patients), a significant increase in bleeding episodes (six per 1000 patients) was reported in those patients assigned aspirin before undergoing surgical repair of hip fracture.[8] Further, there was a trend towards a higher risk of fatal and non-fatal myocardial infarction among patients randomized to perioperative aspirin [hazard ratio 1.33; 95% confidence interval (CI) 1.00–1.78]. This large trial raises questions about the efficacy of perioperative aspirin, but it is limited in that it was restricted to hip fracture patients and they did not actively monitor for perioperative myocardial infarctions.

Perioperative consensus recommendations have recently been published.[9 10] Given the limitations of the trial evidence, these consensus recommendations are largely based on precautionary principles and on an empirical balance between the potential risk of vessel thrombosis when anti-platelet agents are stopped and the risk of surgical haemorrhage when they are continued. Given the limitations of the data, it is not surprising that there exists marked variation in practice regarding whether aspirin is continued or held before surgery.[11 12]

Whether anti-platelet therapy should be maintained or not during the perioperative period in patients treated for secondary prevention and undergoing non-cardiac surgery remains an unsolved issue.[13 14] We therefore conducted a blinded, prospective, multicentre, randomized, placebo-controlled trial to compare the impact of preoperative maintenance *vs* interruption of aspirin on major thrombotic and bleeding events. Our hypothesis was that maintenance of aspirin was superior to its discontinuation when considering a balance of both the major thrombotic and bleeding events measured by a composite outcome occurring within 30 days after surgery.

Methods

The study complied with the Declaration of Helsinki. The trial protocol was approved for all centres by the Ethics Committee of the Bichat University Hospital (Comité Consultatif de

Protection des Personnes se prêtant à la Recherche Biomédicale, ref. 2004/18). Written informed consent was obtained from all participants during the pre-anaesthetic consultation before randomization (Registration number: ClinicalTrials.gov identifier NCT00190307).

Patients were recruited from 25 French centres between June 2005 and September 2007. Eligible patients were ≥18 yr, receiving anti-platelet therapy (aspirin, clopidogrel, ticlopidine, or dipiridamole) for secondary prevention of coronary artery disease, stroke, transient ischaemic attack (TIA), or peripheral vascular ischaemic disease, and undergoing elective intermediate- or high-risk elective non-cardiac surgery (i.e. surgery planned for more than 2 h in duration and associated with significant volume changes).[15] Patients undergoing emergency surgery were excluded. All types of elective procedures (orthopaedic, abdominal, urologic, thoracic, oncologic ENT) were considered. Carotid endarterectomy and coronary bypass grafting were excluded because of a large consensus to maintain anti-platelet therapy until the day of surgery in these cases.[16] We excluded ophthalmologic surgery of the posterior chamber and intracranial neurosurgery because of the unacceptable risk of severe bleeding. Superficial surgery and colonoscopy were also excluded because these procedures are associated with a low cardiac risk. Other exclusion criteria were pregnancy, a recent (<30 days before randomisation) major cardiac event (i.e. unstable angina, myocardial infarction, or coronary revascularization), presence of a drug-eluting stent, active bleeding, absolute contraindications to aspirin or anti-coagulants, and patients in whom the haemorrhagic/(thrombotic) risk linked to maintenance/(interruption, respectively) was considered unacceptable from the attending anaesthetist, cardiologist, or surgeon's perspective.

Procedures

STRATAGEM was a multicentre, randomized, blinded placebo-controlled, parallel-group trial comparing the effect of perioperative treatment with discontinuation of a low-dose aspirin (75 mg) starting 10 days before surgery on major thrombotic or haemorrhagic events occurring from the day of randomization up to the 30th postoperative day. Patients were randomly assigned (1:1 ratio) to one of the two groups (aspirin or placebo) by a centralized 24 h phone service that utilized a computerized interactive voice response system. Concealment of randomization was achieved through this central randomization system and randomization was stratified by centre using blocks of four. Investigators, patients, health-care providers, data collectors, and outcome adjudicators were blinded to treatment allocation. For the patients allocated to the intervention group, anti-platelet treatment was substituted with DL-Lysine acetylsalicylate (Kardegic® 75 mg, Sanofi-Aventis, Paris, France, once daily) starting 10 days before the procedure and continued until the morning of surgery. For patients in the control group, treatment was substituted with placebo of DL-Lysine acetylsalicylate once a day starting 10 days before surgery and continued until the morning of surgery.[17] Kardegic® 75 mg and placebo for Kardegic® 75 mg were supplied as a powder for oral solution with the same taste and the same dosage. For all patients, the initial anti-platelet treatment was resumed after surgery as soon as the medical staff felt that the postoperative bleeding risk was considered clinically acceptable. Patients received low molecular weight heparin after non-cardiac surgery according to international guidelines for prophylaxis of thromboembolic events.[18]

Data collection

Investigators (anaesthetists) collected the following data: patient characteristics, cardiovascular treatments, history of cardiovascular diseases, risk factors for cardiovascular diseases, functional capacity, relevant preoperative blood results, and surgical information (e.g. duration, type of anaesthesia, and use of non-steroidal anti-inflammatory drugs after surgery). All patients had troponin T or I assay drawn 10 days before surgery on days 1, 2, and 30 after surgery and haematocrit was measured 10 days before surgery and before operation on the day of surgery and days 1, 2, and 3 after surgery. Investigators assessed patient outcomes (e.g. major thrombotic and bleeding events) in hospital and on days 7, 30, and 180 after surgery. All data were captured by investigators through a digital pen system provided by Kayentis™ (Gif-sur-Yvette, France).[19]

Outcome measures

The primary endpoint was a weighted composite endpoint that included the following events: death, major thrombotic events, and major bleeding events recorded between inclusion and day 30 after surgery. Major thrombotic events were defined as stroke, TIA, acute coronary syndrome, peripheral arterial ischaemia, mesenteric arterial ischaemia, deep proximal and distal venous thrombosis based on clinical symptoms, and pulmonary embolism. Major bleeding events were defined as cerebral haemorrhage, intra- or retroperitoneal haemorrhage documented by CT scan, bleeding requiring an intervention (i.e. surgical reoperation, endovascular embolization or an endoscopic intervention), or bleeding requiring 3 units of red blood cells. Weights (from 0 to 10) for each outcome were assigned from a Delphi consensus method in which a panel of anaesthetists and cardiologists rated the severity of the different events included in this endpoint (Appendix).[20] The final score for each patient was the score allocated for the most serious event encountered and was comprised between 0 (no event) and 10 (death=most serious event). Therefore, the higher a patient's composite outcome score, the more severe the event(s). All events of the primary endpoint occurring during the trial were reviewed and adjudicated by an expert committee involving two anaesthetists (D.L., F.A.) and a cardiologist (J.-P.C.); these individuals were unaware of treatment allocation. These committee members were provided with all the data available in the patients' charts. The adjudication committee

validated (or not) the diagnoses and rated the severity of the event to determine the corresponding weight. Secondary outcomes consisted of the weighted composite endpoint on days 7 and 180 after surgery and each element separately (death, major thrombotic events, major bleeding events).

Statistical analysis

We powered this trial assuming the superiority of aspirin for the primary unweighted composite endpoint at 30 days after surgery (with same events as the weighted composite endpoint). Owing to premature cessation of enrolment, it was then decided to turn from the initial unweighted composite endpoint to a weighted composite endpoint as described above to take into account the severity of the individual components of this composite outcome and increase the study power.[21] This decision was made before seeing any unblinded data.

Postoperative cardiovascular complications are classically estimated between 1% and 12%, depending on the type of surgery. On the basis of data from a previous study, the risk of perioperative complications was estimated at 15%.[22 23] On this basis, expecting that 15% of the patients would experience an event of the composite criteria in the placebo group, and to detect a relative reduction of the risk by 33% in the aspirin group, with a significance type I error of 0.05 (two-sided), and 80% power, 1421 participants were required. Interim analyses were planned after inclusion of 355, 710, and 1066 patients, with a final analysis planned after inclusion of 1421 patients. However, as mentioned above, the recruitment was prematurely stopped due to recruitment difficulties before the first planned interim analysis and before looking at the results (see the reasons for this in the Discussion section).

Categorical variables are reported as frequencies and percentages. Continuous variables are expressed as mean values and standard deviations. The analyses were performed according to the intent-to-treat principle. The primary endpoint (the weighted composite score) was considered as a numerical variable, ranging from 0 to 10. Patients with no event were assigned a zero score and those patients lost to follow-up before any event occurred. For patients who did not have surgery, we counted events from the time of randomization until 30 days later. Patients lost to follow-up were censored on the day of lost to follow-up. The primary endpoint had a score of zero for 87% of the patients and was strongly left-skewed. Accordingly, differences between groups were assessed using the Mann–Whitney–Wilcoxon signed-rank test. Secondary analysis involved the comparison of the weighted composite score on days 7 and 180 (both were assessed using the Mann–Whitney–Wilcoxon signed-rank test) and the comparison of occurrence of each of the events of the composite score (χ^2 or Fisher's test where appropriate). Finally, postoperative delays before the first event were compared by the Mann–Whitney–Wilcoxon signed-rank test. A *P*-value of <0.05 was considered the threshold for significance.

Data are expressed as mean (SD) or median (CIs) where appropriate. All data were analysed using R v2.11.1 software.[24] Statistical analysis was performed by a statistician blinded to treatment allocation.

Results

We stopped the trial after randomizing 291 patients because of major recruitment difficulties. Statistical analysis was performed after cessation of recruitment. Several explanations may account for the difficulties we encountered. First, a significant number of eligible patients could not be included because decisions of stopping aspirin before operation had already been taken by surgeons or physicians in charge of the patient before the patient presented for a pre-anaesthetic consultation. Secondly, since 2004, several publications suggested that stopping aspirin increased a patient's risk of a coronary or major thrombotic risk.[25–27] Even though these publications were about non-operative patients and stents, this had significant impact on many investigators for whom enthusiasm to include new patients in STRATAGEM markedly decreased.

Of the 291 randomized patients, 145 were assigned to the aspirin group and 146 were assigned to the placebo group. The flow chart is reported in Figure 1. One patient in the aspirin group had an acute coronary syndrome before surgery could be undertaken. This event was counted, according to the intention-to-treat strategy. Table 1 shows the baseline clinical characteristics, type of surgery, cardiovascular risk factors, cardiovascular treatments, and laboratory characteristics of patients. Most patients were male (76.3%). Two hundred and eleven (72.5%), 89 (30.6%), and seven (2.4%) patients were previously treated with aspirin, clopidogrel, and ticlopidine/other anti-platelet agents, respectively. The most frequent surgical procedures were orthopaedic surgery (52.2%), abdominal surgery (20.6%), urologic surgery (15.5%), and miscellaneous procedures including thoracic and vascular surgery (11.7%). Eighty-two per cent of the patients had general anaesthesia.

Outcomes

A total of 35 major adverse events occurred in 31 patients (10.7%; 18 in the aspirin group and 17 in the placebo group) by postoperative day 30; these included four deaths, 11 thrombotic events, and 20 haemorrhagic events. Nine of these 31 patients (29%) had a history of stroke and five had a previous acute coronary syndrome (16%). No significant difference was observed regarding the primary outcome score between the two groups [mean (SD)=0.67 (2.05) in the aspirin group *vs* 0.65 (2.04) in the placebo group, $P=0.94$]. The distribution of the Delphi scores in the two groups is presented in Table 2. Sixteen (11%) of the patients in the aspirin group and 15 (10.3%) in the control group had a primary outcome at 30 days. The same analysis was performed in the patients with at least one major postoperative event [death, thrombotic, or bleeding event, Delphi score of 3 or greater (16 patients in the aspirin group *vs* 15

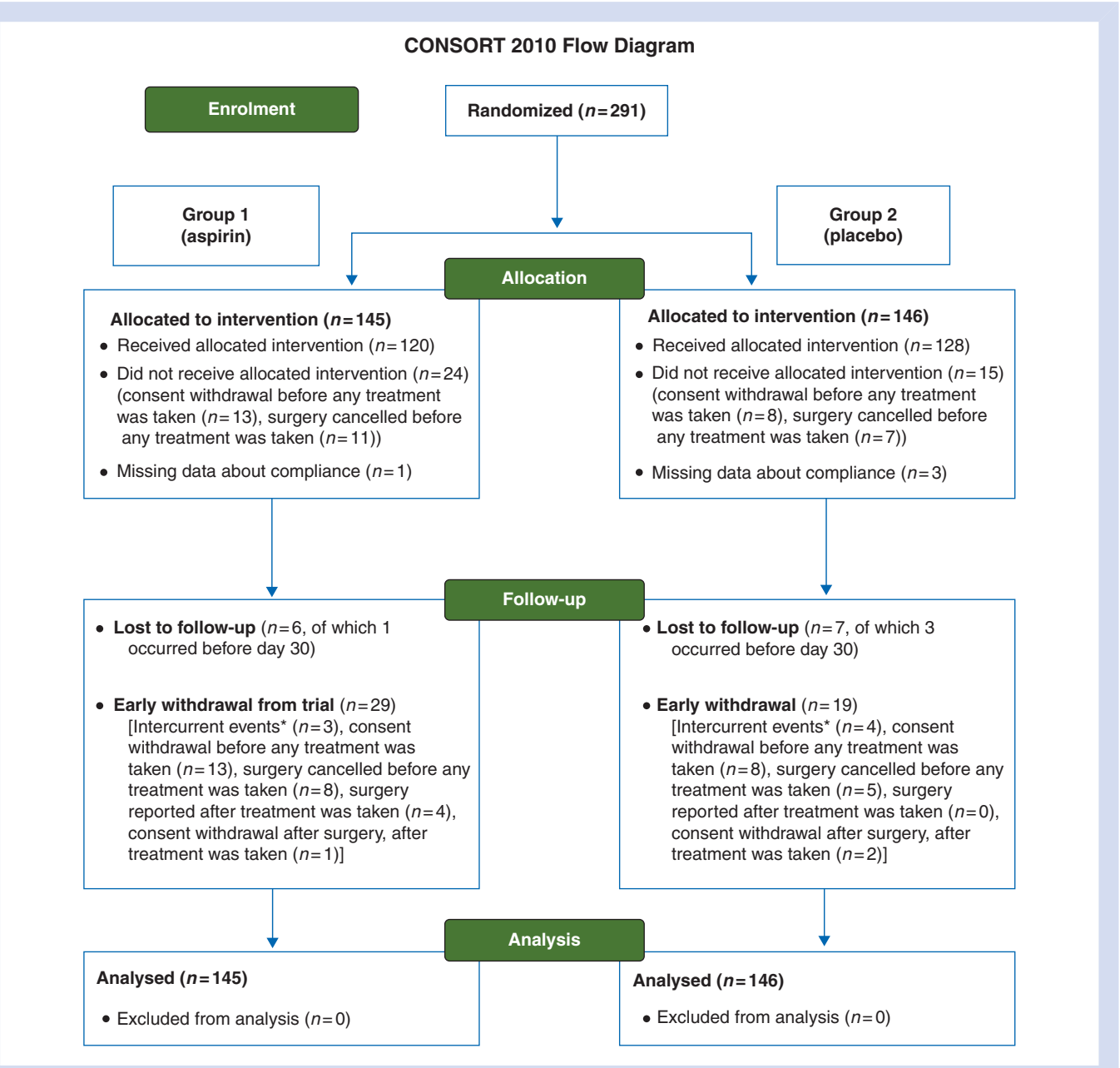

Fig 1 Patient flow chart. *Events not included in the definition of the primary outcome criteria.

patients in the placebo group)] and did not detect any significant difference in the nature of the events. For secondary outcome measures (Delphi score at days 7 and 180 after surgery), there was no difference in the event rates between the study groups ($P=0.54$ and 0.70, respectively, Table 2). There was no significant difference between the two groups regarding the occurrence of deaths, thrombotic events, haemorrhagic events, by days 7, 30, and 180 (Table 3), but the CIs were large. No significant difference in the incidence/nature of major thrombotic or bleeding events was detected between the two groups in patients with the same Delphi scores. Similar findings were obtained in the subgroups of patients with bare-metal coronary stents by days 7, 30, and 180, as illustrated for day 30 in Table 4.

The time course of the events is displayed in Figure 2. We did not find any significant difference in the postoperative delays before the occurrence of first thrombotic event in the two groups [the median time was 3 days in the aspirin group and 3.5 days in the placebo group ($P=0.88$)].

Discussion

The STRATAGEM trial did not identify a difference in the incidence of major thrombotic and bleeding events between a strategy of interruption of anti-platelets before elective

Table 1 Description of the patient population. Data are mean (SD) unless stated otherwise. NA, not available; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; HR, heart rate; TE, thromboembolic; ACS, acute coronary syndrome; CV, cardiovascular; ACE, angiotensin-converting enzyme; ATIIR, angiotensin II receptor; NSAIDs, non-steroidal anti-inflammatory drugs; LMWH, low molecular weight heparins; BBB, bundle branch block; HBP, high blood pressure. Treatments were collected at the moment of randomization (10 days before surgery)

Characteristics	All patients ($n=291$)	Aspirin ($n=145$)	Placebo ($n=146$)	NA [*n* (%)]
Age (yr)	70 (10)	70 (10)	69 (10)	
Sex (male) [*n* (%)]	222 (76.3)	115 (79.3)	107 (73.3)	
Weight (kg)	77.1 (15)	77 (14)	77.2 (16)	
Height (cm)	167.8 (8.5)	168 (8.2)	167.6 (8.7)	1 (0)
SAP (mm Hg)	140.2 (19.4)	141.2 (19.4)	139.2 (19.57)	4 (1)
DAP (mmHg)	76.9 (12.1)	77.8 (10.5)	75.9 (13.5)	4 (1)
HR (beats min^{-1})	70.6 (11.4)	70.5 (12.5)	70.7 (10.3)	8 (3)
Surgery				
Orthopaedic [*n* (%)]	152 (52.2)	78 (53.8)	74 (50.7)	
Abdominal [*n* (%)]	60 (20.6)	25 (17.2)	35 (24)	
Urologic [*n* (%)]	45 (15.5)	24 (16.6)	21 (14.4)	
Other [*n* (%)]	35 (12)	19 (13.1)	16 (11)	
Anaesthesia				
General (yes) [*n* (%)]	200 (82)	95 (81.2)	105 (82.7)	47 (16)
CV risk factors				
Smoking (yes) [*n* (%)]	167 (59.4)	87 (62.6)	80 (56.3)	10 (3)
Cig/day	22.9 (13.9)	23.4 (14)	22.3 (13.9)	18 (10)
Years of smoking	31.6 (12.3)	31.3 (12.7)	31.9 (11.9)	19 (11)
HBP [*n* (%)]	191 (65.6)	95 (65.5)	96 (65.8)	
Hypercholesterolaemia [*n* (%)]	183 (63.1)	93 (64.1)	90 (62.1)	1 (0)
Diabetes [*n* (%)]	70 (24.1)	36 (24.8)	34 (23.3)	
Obesity [*n* (%)]	69 (23.7)	35 (24.1)	34 (23.3)	
ACS [*n* (%)]	120 (41.2)	60 (41.4)	60 (41.1)	
Cardiac failure [*n* (%)]	16 (5.5)	6 (4.1)	10 (6.8)	
Stroke	38 (13.1)	20 (13.9)	18 (12.2)	
Venous TE disease [*n* (%)]	21 (7.2)	10 (6.9)	11 (7.5)	
Carotid endarterectomy [*n* (%)]	18 (6.2)	11 (7.6)	7 (4.8)	
Lower limb arteriopathy [*n* (%)]	73 (25.1)	37 (25.5)	36 (24.7)	
History of ischaemia [*n* (%)]	38 (13.1)	20 (13.9)	18 (12.3)	1 (0)
History of bleeding [*n* (%)]	1 (0.3)	0 (0)	1 (0.7)	2 (1)
Treatments				
Bare-metal coronary stents [*n* (%)]	38 (13.1)	21 (14.5)	17 11.7)	1 (0)
Anti-arrhythmics [*n* (%)]	42 (14.4)	19 (13.1)	23 (15.8)	
Beta-blockers [*n* (%)]	120 (41.2)	56 (38.6)	64 (43.8)	
Nitric oxide derivates [*n* (%)]	34 (11.7)	17 (11.7)	17 (11.6)	
Calcium channel blockers [*n* (%)]	96 (33)	54 (37.2)	42 (28.8)	
Alpha-2 agonists [*n* (%)]	8 (2.8)	4 (2.8)	4 (2.8)	1 (0)
ACE inhibitors [*n* (%)]	92 (31.6)	45 (31)	47 (32.2)	
ATIIR inhibitors [*n* (%)]	62 (21)	31 (21.4)	30 (20.5)	
Statins [*n* (%)]	164 (56.4)	87 (60)	77 (52.7)	
Lipid-lowering drugs. others [*n* (%)]	40 (13.7)	17 (11.7)	23 (15.8)	
Anti-diabetics [*n* (%)]	63 (21.6)	35 (24.1)	28 (19.2)	
Anti-platelets				
Aspirin [*n* (%)]	211 (72.5)	104 (71.7)	107 (73.3)	
Clopidogrel [*n* (%)]	89 (30.6)	48 (33.1)	41 (28.1)	
Ticlopidine+others [*n* (%)]	7 (2.4)	2 (1.4)	5 (3.4)	
NSAIDs [*n* (%)]	21 (7.2)	12 (8.3)	9 (6.2)	
Anti-coagulants (all) [*n* (%)]	22 (7.6)	6 (4.1)	16 (11)	
Anti-Vit K [*n* (%)]	4 (1.4)	0 (0)	4 (2.7)	

Continued

Table 1 *Continued*

Characteristics	All patients ($n=291$)	Aspirin ($n=145$)	Placebo ($n=146$)	NA [n (%)]
Heparin [n (%)]	2 (0.7)	0 (0)	2 (1.4)	
LMWH [n (%)]	16 (5.5)	5 (3.4)	11 (7.5)	
Others [n (%)]	1 (0.3)	1 (0.7)	0 (0)	
Laboratory				
Creatinine	92 (33)	91 (37)	93 (28)	8 (3)
Haematocrit	41 (5)	41 (4)	41 (5)	5 (2)
Haemoglobin	137 (20)	136 (21)	138 (18)	5 (2)
Platelet count	255 812 (85 356)	25 6375 (92 775)	255 253 (77 616)	6 (2)
ECG				
Abnormal [n (%)]	137 (48.8)	71 (50)	66 (47.5)	10 (3)
Q wave [n (%)]	52 (36.6)	31 (44.3)	21 (29.2)	12 (8)
R wave right anterior leads [n (%)]	22 (15.7)	6 (8.8)	16 (22.2)	14 (9)
Left BBB/arrhythmia [n (%)]	25 (17.7)	11 (15.9)	14 (19.4)	13 (8)
Ischaemic abnormality [n (%)]	34 (24.1)	17 (24.6)	17 (23.6)	13 (8)
Non-ischaemic abnormality [n (%)]	62 (44.3)	27 (39.7)	35 (48.6)	14 (9)

Table 2 Distribution of Delphi scores in the two groups

Score	0	3	4	5	6	7	8	9	10
Aspirin group	129	3	1	4	1	3	1	1	2
Placebo group	131	1	2	4	0	5	0	1	2

moderate-to-high-risk non-cardiac surgery and a strategy of preoperative maintenance of aspirin in stable patients chronically treated with anti-platelet therapy for secondary prevention. Because the trial was stopped early and hence underpowered, we cannot rule out a benefit or a harm of one of these two strategies. While our data suggest that the preoperative maintenance of aspirin until the day of non-cardiac surgery is safe, they do not necessarily support this strategy, because prior research has demonstrated that it increases the risk of bleeding.[8]

Only one prior randomized controlled trial was designed to address the issue of continuation or discontinuation of aspirin before surgery.[28] In this trial by Oscarsson and colleagues, patients were randomly allocated to continue or stop aspirin 7 days before surgery. Myocardial damage defined as the elevation of Troponin T was chosen as the primary endpoint. Four patients (3.7%) in the aspirin group developed myocardial damage, while 10 (9%) patients in the placebo group experienced this outcome. This difference did not reach statistical significance. Of the 12 patients with postoperative major cardiac events (cardiovascular death, myocardial infarction, severe arrhythmia during the first 30 postoperative days), nine were in the placebo group and three in the aspirin group ($P=0.02$). The trial was not powered, however, to inform the impact on bleeding events. A distinction between Oscarsson and collegues' trial and our trial is that in Oscarsson and colleagues' trial, the study drug was continued until the third postoperative day.[28] In our trial, the study drug was continued until the morning of surgery, and anti-platelet therapy was resumed as soon as the postoperative bleeding risk was considered acceptable, according to the French guidelines.[17] Five of the 11 major thrombotic events occurred between post-operative days 1 and 3 (Fig. 2). Our results differ from Oscarsson and colleagues' findings. Potential explanations include the differences in our protocols and chance associated with small trials with few events.

Although not designed to specifically address the effect of stopping *vs* continuing preoperative aspirin, the PEP Trial included patients on chronic aspirin and these patients were randomized to aspirin or placebo.[8] The authors did not report the results for this subgroup, and when one of our authors (P.J.D.) contacted the PEP investigators, they indicated that they did not have the data to allow them to determine the outcome for this subgroup of patients. This large trial of perioperative aspirin although encouraging for venous thrombosis prevention raises concerns, given that perioperative aspirin increased the risk of bleeding and suggested that aspirin may increase the risk of perioperative myocardial infarction (hazard ratio 1.33; 95% CI 1.00–1.78). Given the non-operative data that so clearly demonstrate that aspirin prevents myocardial infarction in the non-operative setting, many clinicians may dismiss the possibility that aspirin could increase the risk of myocardial infarction after non-cardiac surgery. Although there are reasons to be cautious about the PEP myocardial infarction data (e.g. the trial was restricted to hip fracture patients and did not actively monitor cardiac biomarkers or enzymes after surgery), it is possible that the perioperative myocardial infarction data are right. If perioperative myocardial infarction is due to supply–demand mismatch, as many authors suggest,[29] and not due to a thrombotic event, then perioperative aspirin will not prevent any myocardial infarctions but through excess bleeding may increase the risk of myocardial infarction. This highlights the need for further data to establish the impact of perioperative aspirin.

Table 3 Details of the adverse events (deaths, thrombotic, and bleeding events) in the two groups at postoperative days 7, 30, and 180 (a, b, and c, respectively). CI, confidence intervals; OR, odds ratios; DVT, deep venous thrombosis; ACS, acute coronary syndrome. The scores established by the Delphi are provided in the Appendix section

Criteria	All events	Aspirin group	Placebo group	OR	95% CI	*P*-value
a						
Day 7	*n*=291	*n*=145	*n*=146			
Deaths [*n* (%)]	4 (1.4)	2 (1.4)	2 (1.4)	0.99	0.07, 13.87	1.00
Thrombotic events [*n* (%)]	9 (3.1)	5 (3.4)	4 (2.7)	0.79	0.15, 3.75	0.75
Stroke [*n* (%)]	0	0	0			
ACS [*n* (%)]	6 (2.1)	3 (2.1)	3 (2.1)	0.99	0.13, 7.54	
Score 3	1 (0.3)	1 (0.7)	0 (0)			
Score 4	3 (1)	1 (0.7)	2 (1.4)			
Score 10	2 (0.7)	1 (0.7)	1 (0.7)			
Peripheral ischaemia [*n* (%)]	1 (0.3)	1 (0.7)	0 (0)	0	0, 38.73	
Score 6	1 (0.3)	1 (0.7)	0 (0)			
Mesenteric ischaemia [*n* (%)]	2 (0.7)	1 (0.7)	1 (0.7)	0.99	0.01, 78.4	
Score 9	1 (0.3)	1 (0.7)	0 (0)			
Score 10	1 (0.3)	0 (0)	1 (0.7)			
DVT [*n* (%)]	0	0	0			
Bleeding events [*n* (%)]	17 (5.8)	9 (6.2)	8 (5.5)	0.88	0.29, 2.64	0.81
Score 3	3 (1)	2 (1.4)	1 (0.7)			
Score 5	6 (2.1)	4 (2.8)	2 (1.4)			
Score 7	8 (2.7)	3 (2.1)	5 (3.4)			
Cerebral haemorrhage [*n* (%)]	0	0	0			
Total events [*n* (%)]	30	16	14			0.87
1 event	22 (84.6)	12 (85.7)	10 (83.3)			
2 events	4 (15.4)	2 (14.29)	2 (16.67)			
Patients with at least						
1 major adverse event [*n* (%)]	26 (8.9)	14 (9.7)	12 (8.2)	0.84	0.34, 2.04	0.69
1 major thrombotic event [*n* (%)]	9 (3.1)	5 (3.4)	4 (2.7)	0.79	0.15, 3.75	0.75
1 major bleeding event [*n* (%)]	17 (5.8)	9 (6.2)	8 (5.5)	0.88	0.29, 2.64	0.81
b						
Day 30	*n*=291	*n*=145	*n*=146			
Deaths [*n* (%)]	4 (1.4)	2 (1.4)	2 (1.4)	0.99	0.07, 13.9	1.0
Thrombotic events [*n* (%)]	11 (3.8)	6 (4.1)	5 (3.4)	0.82	0.19, 3.3	0.8
Stroke [*n* (%)]	0	0	0			
ACS [*n* (%)]	6 (2.1)	3 (2.1)	3 (2.1)			
Score 3	1 (0.3)	1 (0.7)	0 (0)			
Score 4	3 (1)	1 (0.7)	2 (1.4)			
Score 10	2 (0.7)	1 (0.7)	1 (0.7)			
Peripheral ischaemia [*n* (%)]	2 (0.7)	1 (0.7)	1 (0.7)			
Score 6	1 (0.3)	1 (0.7)	0 (0)			
Score 9	1 (0.3)	0 (0)	1 (0.7)			
Mesenteric ischaemia [*n* (%)]	2 (0.7)	1 (0.7)	1 (0.7)			
Score 9	1 (0.3)	1 (0.7)	0 (0)			
Score 10	1 (0.3)	0 (0)	1 (0.7)			
DVT [*n* (%)]	1 (0.3)	1 (0.7)	0 (0)			
Score 3	1 (0.3)	1 (0.7)	0 (0)			
Bleeding events [*n* (%)]	20 (6.9)	10 (6.9)	10 (6.8)	0.99	0.36, 2.8	1.0
Score 3	3 (1)	2 (1.4)	1 (0.7)			
Score 5	8 (2.7)	4 (2.8)	4 (2.7)			
Score 7	8 (2.7)	3 (2.1)	5 (3.4)			
Score 8	1 (0.3)	1 (0.7)	0 (0)			

Continued

Table 3 *Continued*

Criteria	All events	Aspirin group	Placebo group	OR	95% CI	*P*-value
Cerebral haemorrhage [*n* (%)]	0	0	0			
Total events [*n* (%)]	35	18	17			0.9
1 event	27 (87.1)	14 (87.5)	13 (86.67)			
2 events	4 (12.9)	2 (12.5)	2 (13.33)			
Patients with at least						
1 major adverse event [*n* (%)]	31 (10.7)	16 (11)	15 (10.3)	0.92	0.4, 2.09	0.8
1 major thrombotic event [*n* (%)]	11 (3.8)	6 (4.1)	5 (3.4)	0.82	0.19, 3.3	0.8
1 major bleeding event [*n* (%)]	20 (6.9)	10 (6.9)	10 (6.8)	0.99	0.36, 2.8	1.0

Table 4 Details of the adverse events (deaths, thrombotic, and bleeding events) in the patients with coronary bare-metal stents at postoperative day 30. DVT, deep venous thrombosis; ACS, acute coronary syndrome

Criteria	All stent patients (*n*=38)	Aspirin group (*n*=21)	Placebo group (*n*=17)
Day 30			
Deaths [*n* (%)]	1 (2.6)	0 (0)	1 (5.9)
Thrombotic events [*n* (%)]	2 (5.3)	0 (0)	2 (11.8)
Stroke [*n* (%)]	0	0	0
ACS [*n* (%)]			
Score 9	1 (2.6)	0 (0)	1 (5.9)
Peripheral ischaemia [*n* (%)]			
Score 10	1 (2.6)	0 (0)	1 (5.9)
Mesenteric ischaemia [*n* (%)]	0	0	0
DVT [*n* (%)]	0	0	0
Bleeding events [*n* (%)]	0	0	0
Total events [*n* (%)]	3	0	3
Patients with at least			
1 event [*n* (%)]	2 (5.3)	0 (0)	2 (11.8)
1 major thrombotic event [*n* (%)]	2 (5.3)	0 (0)	2 (11.8)
1 major bleeding event [*n* (%)]	0	0	0

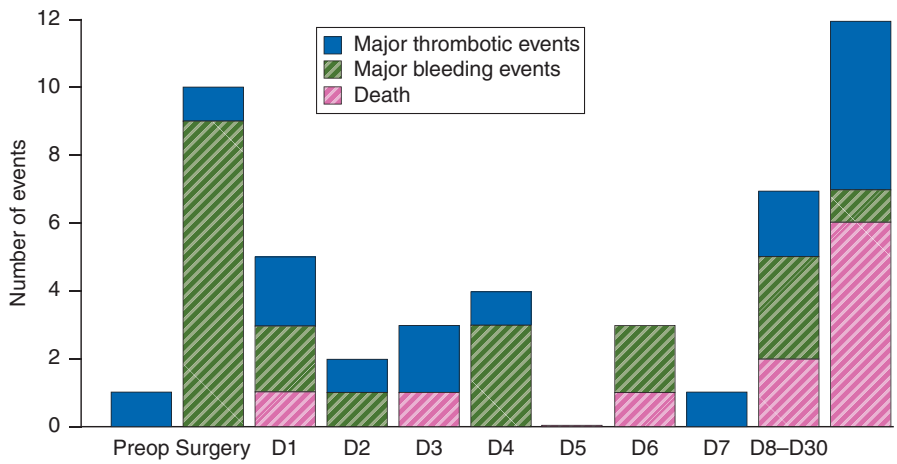

Fig 2 Time line of occurrence of postoperative deaths, major thrombotic, and bleeding events.

STRATAGEM is the largest randomized, blinded, controlled trial available to date addressing the issue of preoperative aspirin continuation *vs* discontinuation. The primary endpoint as a weighted composite endpoint of death and thrombotic and bleeding major adverse events occurring until postoperative day 30 defined in this study was a novel outcome-targeted approach based on a clinically relevant analysis of the risk:benefit balance. The classification of perioperative thrombotic and bleeding events based on their severity achieved by a Delphi consensus process with cardiologists and anaesthetists could be useful to clinicians managing perioperative anti-platelet therapy in routine practice. We believe that the primary goal of our trial was highly relevant to the clinical situation of at-risk patients undergoing major non-cardiac surgery.[21] We also included deep venous thrombosis with iliac extension or pulmonary embolism, a patient-important outcome, in the primary endpoint.

Before introducing a treatment or strategy into daily clinical practice, capturing the overall impact of a therapeutic strategy in terms of benefit and risk is a key step. This is a well-recognized advantage of composite outcomes, but their use relies on the assumption that patients will attach similar importance to each component.[30] However, this is rarely achieved. Most composite endpoints showed either a large or moderate gradient in importance to patients and weighting composite outcomes according to severity or importance to patients has been suggested as an alternative option to capture the true overall impact of treatment.[31 32] We did not find any difference in the incidence of major adverse events (thrombotic and haemorrhagic) between aspirin- and placebo-treated patients.

Platelet function was not tested before operation. However, biological tests of the efficacy of platelet aggregation exhibit some limitations, including failure to predict intraoperative red cell requirements.[33 34] Moreover, the efficacy of the enteral daily aspirin dose (75 mg) on platelet aggregation has been clearly shown.[35] It can be argued that selecting the worst event only for scoring patients having experienced more than one event may have led to an underestimation of the incidence of these events. This was observed in a limited number of cases (n=8, 2.7%). Of the patients with more than one event, death was one of these events in 100% of cases. Only two patients experienced both one major bleeding and one major thrombotic event (and then died). On the other hand, to take into account all adverse events in the composite score could have induced a bias, insofar as a cardiovascular cause could have explained deaths of unknown origin (e.g. sudden death at home). A patient dead at home because of an ongoing myocardial infarction would be considered as a death, while the same patient who died a few hours after admittance into the cardiology intensive care unit would be considered myocardial infarction plus death. In our trial, all the major thrombotic and bleeding events (secondary outcome criteria) were equally observed with the same incidence in each group. The median delay of occurrence of thrombotic and bleeding events was short (3 days and 1 day after surgery, respectively), which is consistent with previous studies.[28]

Our trial has limitations. Our trial was underpowered, due to premature termination of recruitment. Patients enrolled in STRATAGEM primarily underwent major orthopaedic, abdominal, and urologic surgery. Our results do not necessarily apply to patients undergoing carotid endarterectomy and intracranial neurosurgery, which were exclusion criteria. Similarly, while our results are relevant to patients with bare-metal stents, they are not extrapolatable to patients with drug-eluting stents, who were excluded from our trial.[36] Finally, our findings do not apply to other anti-platelets than aspirin, since all anti-platelet agents were substituted with aspirin (or placebo). Therefore, our results do not allow inferring about patients treated with other anti-platelets than aspirin until the day of surgery. Our trial although underpowered does not raise any safety concerns about stopping aspirin 10 days before surgery. Hopefully, the lack of major safety concerns demonstrated in our trial will allow physicians to be more open to a large perioperative aspirin trial, given that the PEP Trial raises concerns about the potential safety of perioperative aspirin.

In conclusion, in surgical patients on long-term anti-platelet therapy for secondary prevention of thrombotic events undergoing elective non-cardiac surgery, we did not demonstrate a difference in terms of the occurrence of major thrombotic and bleeding events between preoperative treatment with aspirin and preoperative interruption of anti-platelet therapy.

Acknowledgements

The authors are grateful to Sanofi-Aventis Pharmaceuticals, France, for the kind supply of Kardegic and placebo. We acknowledge Nathalie Garin and Isabelle Hoffmann (Unité de Recherche Clinique Paris Nord) for their implementation and coordination of the trial. The following experts are gratefully acknowledged for their participation in the study: Michel Bertrand, Emmanuel Teiger, Emile Ferrari, Yves Juillière, Marie Claude Morice, Pierre Aubry, Gérald Roul, Souhayl Dahmani, Jean-Paul Depoix, Hawa Keita-Meyer, Gilles Lebuffe, Dan Longrois, Hervé Dupont, Benoit Plaud, Jean-François Payen, Paul Zufferey, Benjamin Tremey, Philippe Vanderlinden, Sylvain Belisle, Jean François Hardy, Samir Jaber, Jean Luc Fellahi, Gérard Janvier, Vincent Minville, Karim Asehnoune. The members of the STRATAGEM Study Group are acknowledged with thanks for their active participation in the study: CHU Angers (N.P., Pr Granry), CHU Avicenne Bobigny (Dr Denantes, C.M.S.), CHU Beaujon Clichy (Dr Dahmani, Pr Mantz), CHU Besançon (Dr Pilly-Floury, Pr Samain), CHU Clermont-Ferrand (Dr Ferrier, Pr Bazin), CHU Cochin Paris (A.M., Pr Ozier), CHU Henri Mondor Créteil (P.A., Pr Marty), CMC Foch Suresnes (S.S., Pr Fischler), CHU Hotel-Dieu Paris (C.M.S.), Institut Gustave Roussy Villejuif (Dr Bonnet, Dr Bourgain), CHU Lariboisière Paris (B.C., Pr D. Payen), CHU Lille (Dr Lefebvre, Pr Vallet), CHU Lyon Bron (Dr Pierre, Pr Lehot), CHU Lyon Sud (Dr Capel, V.P.), CHU Nimes (Dr Jeannes, Pr

Ripart), CHU Reims (J.B., Pr Malinovsky), CHU Rennes (Dr Dessieux, Pr Ecoffey), CHU St Louis Paris (Dr Becq, Pr Jacob, Pr Eurin), Centre Médical Cesson Sévigné (Dr Le Hétêt), and CHU Tenon Paris (Dr Marret, Pr Bonnet).

Conflict of interest

None declared.

Funding

This work was supported by a research grant from the French Ministry of Health and sponsored by the Department of Clinical Research and Development, Assistance Publique des Hôpitaux de Paris (PHRC AOM 03026).

Appendix

Weighted composite endpoint obtained by the Delphi method. *Mesenteric ischaemia was considered as peripheral ischaemia and then classified as 'Life-threatening, disabling limb ischaemia requiring end-organ damage (i.e. limb loss)' and therefore with limb ischaemia requiring amputation.

Event	Score
Death	10
Ischaemic stroke with severe disability at 7 days	9
Limb ischaemia requiring amputation*	9
Non-fatal myocardial infarction with heart failure	9
Massive pulmonary embolism	9
Intracerebral haemorrhage with severe disability at 7 days	9
Ischaemic stroke with moderate disability at 7 days	8
Pulmonary embolism	8
Intracerebral haemorrhage with moderate disability at 7 days	8
Intra or retroperitoneal bleeding requiring interventions to maintain cardiac output	8
Ischaemic stroke with slight disability at 7 days	7
Non-fatal myocardial infarction without heart failure	7
Venous thrombosis other	7
Intracerebral haemorrhage with slight disability at 7 days	7
Bleeding requiring both redo surgery and interventions to maintain cardiac output	7
Bleeding requiring both transfusion of 3 units or more packed red blood cells and interventions to increase cardiac output	7
Ischaemic stroke with no symptom at 7 days	6
Limb ischaemia requiring heparin or intervention	6
Deep venous thrombosis with iliac extension	6
Intracerebral haemorrhage with no symptom at 7 days	6
Intra or retroperitoneal bleeding	6
Transient ischaemic attack	5
Limb ischaemia not requiring heparin or intervention	5
Venous thrombosis of the pectoral limb	5
Bleeding requiring redo surgery or endoscopic sclerosis	5
Bleeding requiring transfusion of 3 units or more packed red blood cells	5
Increased level of troponin	4
Under-popliteal deep venous thrombosis	3
Bleeding with increased length of stay	3
No event	0

References

1 Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction and stroke in high risk patients. *Br Med J* 2002; **324**: 71–86

2 Biondi-Zoccai GG, Lotrionte M, Agostoni P, *et al.* A systematic review and meta-analysis of the hazards of discontinuing or not adhering to aspirin among 50,279 at risk for coronary artery disease. *Eur Heart J* 2006; **27**: 2667–74

3 Rhee SJ, Yun KH, Lee SR, *et al.* Drug-eluting stents thrombosis during perioperative period. *Int Heart J* 2008; **49**: 135–42

4 Mahla E, Lang T, Vincenzi MN, *et al.* Thromboelastography for monitoring prolonged hypercoagulability after major abdominal surgery. *Anesth Analg* 2001; **92**: 572–7

5 Samama CM, Thiry D, Elalamy I, *et al.* Perioperative activation of hemostasis in vascular surgery patients. *Anesthesiology* 2001; **94**: 74–8

6 Beving H, Zhao C, Albage A, Ivert T. Abnormally high platelet activity after discontinuation of acetylsalicylic acid treatment. *Blood Coagul Fibrinolysis* 1996; **7**: 80–4

7 Schouten O, van Domburg RT, Bax JJ, *et al.* Noncardiac surgery after coronary stenting: early surgery and interruption of antiplatelet therapy are associated with an increase in major adverse cardiac events. *J Am Coll Cardiol* 2007; **49**: 122–4

8 Pulmonary Embolism Prevention (PEP) Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000; **355**: 1295–302

9 Fleisher LA, Beckman JA, Brown KA, *et al.* ACC/AHA 2007 Guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: executive summary. *Anesth Analg* 2008; **106**: 685–712

10 Grines CL, Bonow RO, Casey DE, *et al.* Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents. A Science Advisory from the American Heart Association, American College of Cardiology, Society of Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *Circulation* 2007; **49**: 734–9

11 Smout J, Stansby G. Current practice in the use of antiplatelet agents in the perioperative period by UK vascular surgeons. *Ann R Coll Surg Engl* 2003; **85**: 97–101

12 Hiralal R, Guyatt G, Bhandari M, *et al.* A survey evaluating surgeons' perioperative usage of acetyl-salicylic acid (ASA) and their willingness to enroll their patients in a perioperative ASA randomized controlled trial. *Clin Invest Med* 2010; **33**: E375–83

13 O'Riordan JM, Margey RJ, Blake G, O'Connell R. Antiplatelet agents in the perioperative period. *Arch Surg* 2009; **144**: 69–76

14 Eberli D, Chassot PG, Sulser T, *et al.* Urological surgery and antiplatelet drugs after cardiac and cerebrovascular accidents. *J Urol* 2010; **183**: 2128–36

15 Eagle KA, Berger PB, Calkins H, *et al.* ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary. *Circulation* 2002; **105**: 1257–67

16 Hirsch J, Guyatt G, Albers GW, Harrington R, Schünemann HJ. American College of Chest Physician. Antithrombotic and thrombolytic therapy: American College of Chest Physicians Evidence-Based Practice Guidelines (8th Edition). *Chest* 2008; **133**: (6 Suppl): 110–2S

17 Samama CM, Bastien O, Forestier F, *et al.* Antiplatelet agents in the perioperative period: expert recommendations of the

French Society of Anesthesiology and Intensive Care (SFAR)- 2001 summary statement. *Can J Anaesth* 2002; **49**: S26–35

18 Geerts WH, Bergqvist D, Pineo GF, *et al.* Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133**: 381–453S

19 Estellat C, Tubach F, Costa Y, Hoffmann I, Mantz J, Ravaud P. Data capture by digital pen in clinical trials: a qualitative and quantitative study. *Contemp Clin Trials* 2008; **29**: 314–23

20 Dechartres A, Albaladejo P, Mantz J, *et al.* Delphi consensus weights for ischemic and bleeding events to be included in a composite outcome for randomized controlled trials in thrombosis prevention. *Plos ONE* 2011; **6**: E18461

21 Myles PS, Devereaux PJ. Pros and cons of composite endpoints in anaesthesia trials. *Anesthesiology* 2010; **113**: 776–8

22 Neilipovitz DT, Bryson GL, Nichol G. The effect of perioperative aspirin therapy in peripheral vascular surgery: a decision analysis. *Anesth Analg* 2001; **93**: 573–80

23 Albaladejo P, Geeraerts T, Francis F, Castier Y, Lesèche G, Marty J. Aspirin withdrawal and acute lower limb ischemia. *Anesth Analg* 2004; **99**: 440–3

24 R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing, 2010. Available from http://www.R-project.org

25 Ferrari E, Benhamou M, Cerboni P, Marcel B. Coronary syndromes following aspirin withdrawal: a special risk for late stent thrombosis. *J Am Coll Cardiol* 2005; **45**: 456–9

26 Collet JP, Montalescot G, Blanchet B, *et al.* Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. *Circulation* 2004; **110**: 2361–7

27 Iakovou I, Schmidt T, Bonizzoni E, *et al.* Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *J Am Med Assoc* 2005; **293**: 2126–30

28 Oscarsson A, Gupta A, Fredrikson M, *et al.* To continue or discontinue aspirin in the perioperative period: a randomized, controlled, clinical trial. *Br J Anaesth* 2010; **104**: 305–12

29 Landesberg G, Beattie WS, Mosseri M, Jaffe AS, Alpert JS. Perioperative myocardial infarction. *Circulation* 2009; **119**: 2936–44

30 Guyatt GH, Cook DJ, Jaeschke R, Pauker SG, Schunemann HJ. Grades of recommendation for antithrombotic agents: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133**: 123–31S

31 Ferreira-González I, Busse JW, Heels-Ansdell D, *et al.* Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials. *Br Med J* 2007; **334**: 76

32 Braunwald E, Cannon CP, McCabe CH. An approach to evaluating thrombolytic therapy in acute myocardial infarction. The 'unsatisfactory outcome' end point. *Circulation* 1992; **86**: 683–7

33 Collyer TC, Gray DJ, Sandhu R, Berridge J, Lyons G. Assessment of platelet inhibition secondary to clopidogrel and aspirin therapy in preoperative acute surgical patients measured by thromboelastography platelet mapping. *Br J Anaesth* 2009; **102**: 492–8

34 Zisman E, Erport A, Kohanovsky E, *et al.* Platelet function recovery after cessation of aspirin: preliminary study of volunteers and surgical patients. *Eur J Anaesthesiol* 2010; **27**: 617–23

35 Patrono C, Rodriguez LAG, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. *N Engl J Med* 2005; **353**: 2373–83

36 Kim HL, Park KW, Kwak JJ, *et al.* Stent-related cardiac events after noncardiac surgery: drug-eluting stent vs bare-metal stent. *Int J Cardiol* 2008; **123**: 353–4