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To continue or discontinue aspirin in the perioperative period: a randomized, controlled clinical trial

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Background. Major adverse cardiac events (MACEs) are a common cause of death after non-cardiac surgery. Despite evidence for the benefit of aspirin for secondary prevention, it is often discontinued in the perioperative period due to the risk of bleeding.

Methods. We conducted a randomized, double-blind, placebo-controlled trial in order to compare the effect of low-dose aspirin with that of placebo on myocardial damage, cardiovascular, and bleeding complications in high-risk patients undergoing non-cardiac surgery. Aspirin (75 mg) or placebo was given 7 days before surgery and continued until the third postoperative day. Patients were followed up for 30 days after surgery.

Results. A total of 220 patients were enrolled, 109 patients received aspirin and 111 received placebo. Four patients (3.7%) in the aspirin group and 10 patients (9.0%) in the placebo group had elevated troponin T levels in the postoperative period (P=0.10). Twelve patients (5.4%) had an MACE during the first 30 postoperative days. Two of these patients (1.8%) were in the aspirin group and 10 patients (9.0%) were in the placebo group (P=0.02). Treatment with aspirin resulted in a 7.2% absolute risk reduction [95% confidence interval (CI), 1.3–13%] for postoperative MACE. The relative risk reduction was 80% (95% CI, 9.2–95%). Numbers needed to treat were 14 (95% CI, 7.6–78). No significant differences in bleeding complications were seen between the two groups.

Conclusions. In high-risk patients undergoing non-cardiac surgery, perioperative aspirin reduced the risk of MACE without increasing bleeding complications. However, the study was not powered to evaluate bleeding complications.

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Approximately 100 million adults undergo non-cardiac surgery worldwide every year[1] and up to 40% of these patients have or are at risk of coronary artery disease (CAD).[2] Four million patients have been estimated to have a major perioperative cardiovascular complication, including cardiac death, non-fatal myocardial infarction, and cardiac arrest per year.[2] Furthermore, data show that perioperative myocardial infarction is associated with an in-hospital mortality of 15–25%.[3–5] With a high prevalence of CAD, the appropriate perioperative management of high-risk patients treated with aspirin is a common clinical problem for the attending surgeon and anaesthetist.

Aspirin has been used for decades in secondary prevention of myocardial infarction or stroke in patients with ischaemic heart or cerebrovascular disease, and its efficacy has been well documented. The 2002 Antithrombotic Trialists' Collaboration reported that antiplatelet therapy

reduced the risk of non-fatal myocardial infarction by one-third, non-fatal stroke by one-fourth, and vascular events by one-sixth. Aspirin is therefore strongly recommended as a life-long therapy after coronary or cerebrovascular event.[6] Despite evidence to the benefit of antiplatelet therapy in patients at risk of cardiac and cerebrovascular complications, aspirin treatment is often discontinued before surgery due to the risk of perioperative bleeding.[7–9]

Thus, the question whether to continue or discontinue aspirin in the perioperative period remains unanswered. This study was therefore undertaken with the primary aim of assessing the incidence of perioperative myocardial damage in patients with or without low-dose aspirin treatment in the perioperative period. Our hypothesis was that low-dose aspirin reduces the incidence of myocardial damage and major adverse cardiac events (MACEs, defined as acute myocardial infarction, severe arrhythmia, cardiac arrest, or cardiovascular death) without increasing bleeding complications.

Methods

All regional ethics committees approved the protocol for this randomized, double-blind, placebo-controlled multicentre study (ASINC—aspirin in non-cardiac surgery, Eudract CT no. 2004-005136-76) and the study complied with the Declaration of Helsinki.

Patients

Patients undergoing elective, high- or intermediate-risk non-cardiac surgery[10] between November 2005 and December 2008 and having at least one of the following cardiac risk factors were eligible for inclusion: ischaemic heart disease (angina pectoris or previous myocardial infarction), congestive heart failure (previous diagnosis of heart failure), renal impairment (serum creatinine >170 μmol litre^{-1}), cerebrovascular accident [prior stroke or transient ischaemic attack (TIA)], or insulin-dependent diabetes mellitus. High-risk surgery was defined as surgery with a known cardiac risk of $>5\%$, and included procedures with large fluid shifts such as oesophageal, liver, and pancreatic surgery. Intermediate-risk surgery was defined as surgery with a cardiac risk of 1–5%, and included head and neck surgery, intraperitoneal and intrathoracic surgery, orthopaedic surgery, and prostate surgery.[10] In our study patients, undergoing advanced bowel surgery, gastric surgery, prostate surgery (open or transurethral), cystectomy, nephrectomy, hip or knee arthroplasty, and intra-abdominal or pelvic cancer surgery were included. Exclusion criteria were: unstable CAD, non-compensated congestive heart failure, shock, allergy to aspirin, age under 18 yr, a history of gastrointestinal bleeding or intracranial haemorrhage, or treatment with warfarin, clopidogrel, or methotrexate. In addition, patients undergoing vascular surgery were excluded since the Vascular Society in Sweden recommends continuation of aspirin in the perioperative period. In 2006, an amendment was made to the protocol and even patients with an intracoronary stent were excluded from the study.

Study design

After giving written informed consent, the patients were randomly assigned to receive either aspirin 75 mg or placebo using a computer-generated algorithm. The study product, and reference product, both of identical shape, weight, and appearance, was provided by Apoteket Production and Laboratories (APL), Kungens Kurva, Stockholm, Sweden. Study medication was started 7 days before surgery and continued until the third postoperative day. Patients previously on aspirin were restarted on aspirin treatment immediately thereafter. Patient characteristic data, medical history, and preoperative medication were obtained from the patients or from their medical records.

In addition to routine laboratory tests, troponin T (TnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were measured 1 h before surgery. TnT was also measured at 12, 24, and 48 h after operation and analysed by using Elecsys 2010®, Roche Diagnostics, Mannheim, Germany. Resting ECGs were recorded before operation, directly after surgery, and 24 and 48 h after operation. A clinical physiologist blinded to clinical symptoms, laboratory data, and ongoing patient management analysed the ECG data. Signs of myocardial ischaemia were defined as: ST-segment elevation or depression ≥ 1 mm or presence of new Q waves lasting ≥ 0.04 s and ≥ 1 mm deep in at least two adjacent leads. A cardiologist assessed all patients with signs of myocardial damage or myocardial ischaemia according to a standardized protocol. Myocardial damage was defined as TnT level ≥ 0.04 μg litre^{-1} on at least one occasion in the perioperative period. Acute myocardial infarction was defined according to the joint European Society of Cardiology (ESC) and the American College of Cardiology (ACC) consensus document.[11] In the event of myocardial damage in the preoperative period, the attending anaesthetist, cardiologist, and surgeon together evaluated the risk/benefit of the surgical procedure and surgery was rescheduled when appropriate. If a myocardial infarction was diagnosed, the study medication was terminated and aspirin therapy started. The anaesthetic and surgical techniques used were not defined in the protocol, but left to the judgement of the attending physicians.

Perioperative events, including haemodynamic instability (systolic arterial pressure $\pm 30\%$ of baseline), hypoxaemia (Sp_{O_2} $<90\%$ for >5 min), new arrhythmia, tachycardia (heart rate $+30$ beats min^{-1} from baseline for >5 min), or bradycardia (heart rate <45 beats min^{-1} for >5 min), were documented. In addition, perioperative

blood loss, fluid requirements, packed red blood cells, plasma, and platelet transfusions were recorded. The attending surgeon made a subjective assessment of intraoperative bleeding by using an ordinal scale from 1 to 5, where 1 was normal surgical bleeding and 5 was greatly increased surgical bleeding. Reoperations due to bleeding complications and major bleeding from other organs including epidural or intracranial haematoma, cerebrovascular complications, and death within 30 days were also recorded.

Study endpoints

Postoperative myocardial damage, as defined earlier, was considered to be the primary endpoint.

Secondary endpoints were:

(i) MACEs, including acute myocardial infarction, cardiac arrest, severe arrhythmia, or cardiovascular death within the first 30 postoperative days.
(ii) Cardio-cerebrovascular complications, including MACE or stroke/TIA within the first 30 postoperative days.
(iii) Perioperative blood loss and major bleeding, including postoperative bleeding resulting in reoperation, gastrointestinal bleeding, intracranial haemorrhage, or spinal/epidural haematoma within 30 days of surgery.
(iv) Packed red blood cell, plasma, and platelet transfusions.

Telephone interviews were conducted 30 days after surgery. In addition, computer-based medical records were assessed. Information about new cardiovascular complications, readmissions, and transfers to high-dependency units were documented. Excessive perioperative bleeding was also documented. If a patient died during the follow-up period, information on the cause of death was obtained from medical records, death certificates, and autopsy reports. The cause of death was classified as cardiovascular, malignancy, or other.

Statistical analysis

The statistical analyses were done on an intention-to-treat principle. In the case of missing data (data not entered in case report files or in computer-based medical records), patients were assumed not to have had an event. Sample size was calculated on the basis of two previous studies. In the first study, low-dose aspirin had been shown to decrease the risk of myocardial infarction by 50%.[12] In the second study, 14% of a subgroup of patients with similar inclusion criteria as patients in the present study had an elevated TnT in the postoperative period.[13] On the basis of these data, we calculated that the inclusion of 540 patients would be required to detect a 50% reduction in the number of patients with myocardial damage (as defined earlier) with a statistical power of 80% and an α level of 0.05.

An independent multidisciplinary data management and safety board planned an interim analysis after 100 included patients. The trial was to be stopped if there was a significant difference ($P<0.01$) between the groups in either the number of patients with myocardial damage or the occurrence of major bleeding between the groups. No significant differences were detected between the groups at the interim analysis, and therefore, the study was continued as planned. No other interim analyses were planned or performed during the study period.

Numerical variables were tested for normal distribution and are presented as mean (SD) or median (IQR). For analyses of continuous data, τ-test or Mann–Whitney U-test was used as appropriate, to detect differences between the groups. Dichotomous variables are described as numbers and percentage and were analysed by using χ^2 test or Fisher's exact test as appropriate. Absolute and relative risk ratios for cardiovascular complications were calculated and presented with their 95% CIs. In addition, numbers needed to treat were calculated. The level of statistical significance was specified as $P\leq0.05$ (two-tailed). All analyses were performed using STATA v10.1 (Stata Corp LP; College Station, TX, USA).

Results

Of the planned 540 patients, the study was terminated in December 2008 after inclusion of 220 patients at the seven centres. The study was stopped before full enrolment, without statistical analysis, for a number of reasons. The main reason was that during the study period, new recommendations on high-risk patients taking aspirin were published recommending a continuation of aspirin in the perioperative period.[7 14–16] Many of our investigators were therefore reluctant to continue randomizing high-risk patients into this study. Another reason for terminating the study was that we had difficulty in finding eligible patients for inclusion, especially after the amendment in 2006 that required exclusion of patients with intracoronary stents. Finally, we estimated that if recruitment of patients continued at the present rate, it would take at least another 5 yr before the study was completed, a period of time during which the continuing rapid changes in patient management by physicians would make it increasingly difficult to recruit patients and would delay dissemination of applicable information gained by this study.

Of the 220 patients included in the study, 109 patients received aspirin and 111 patients received placebo. In seven of the randomized patients, surgery was postponed, whereas 10 patients did not comply with the treatment (Fig. 1). All these patients were included in the statistical analyses. Patient characteristics, concomitant medication, and co-morbidities are described in Table 1. There were no significant differences between the groups in these variables.

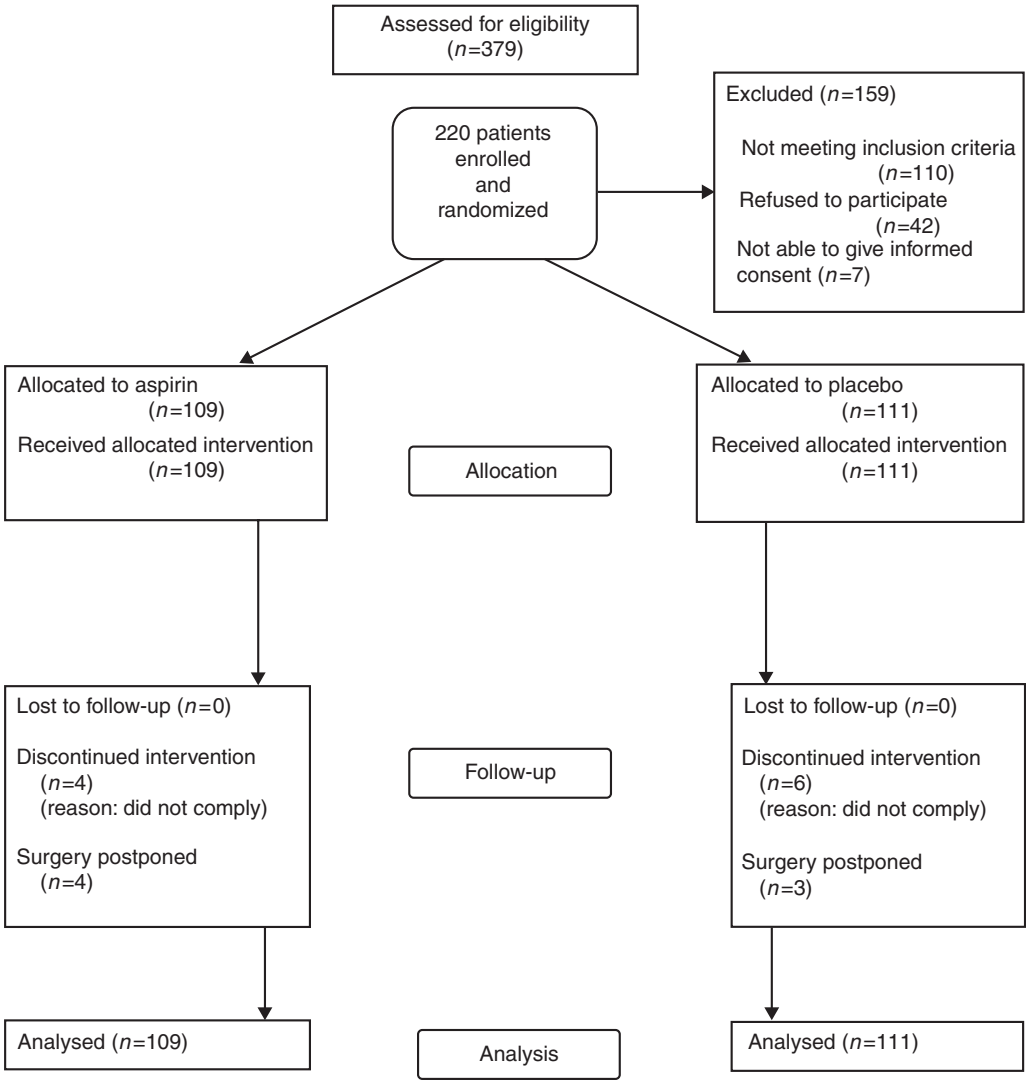

Fig 1 The ASINC flowchart.

Myocardial damage

Fourteen patients (6.4%) had a TnT $\geq$0.04 μg litre^{-1} on at least one occasion in the first 48 h after operation. Ten patients (9.0%) in the placebo group and four patients (3.7%) in the aspirin group had postoperative elevated TnT levels (P=0.10). Five patients had elevated TnT before surgery (Table 1). Three of these patients were treated with aspirin and two with placebo (P=0.60). One patient was transferred to a coronary care unit, and surgery was postponed. In one patient, surgery was delayed for further cardiac investigation. In the remaining three cases, surgery and anaesthesia were undertaken without any delay and intraoperative management was left to the attending anaesthetist. Thirty-nine patients who were included had a percutaneous coronary intervention in their medical history. Twenty-two of these patients received aspirin and 17 had placebo during the study period. One patient in the placebo group developed a TnT elevation in the postoperative period.

Other events

Twelve patients (13%) in the placebo group developed myocardial ischaemia on the ECG in the postoperative period, compared with 11 patients (11%) in the aspirin group (P=0.83). Tachycardia was seen significantly more often in the placebo group compared with patients treated with aspirin, eight patients in the placebo group (7%) compared with none in the ASA group (Table 2). Only one of the patients with tachycardia developed an MACE. In contrast, patients in the aspirin group had more frequent episodes of bradycardia (P=0.02).

MACEs and mortality

Twelve patients (5.4%) had an MACE, including myocardial infarction, severe arrhythmia, cardiac arrest, or cardiovascular death within 30 days of surgery (Table 3). Ten of these patients (9.0%) were in the placebo group and two patients (1.8%) were in the aspirin group (P=0.02)

Table 1 Baseline characteristics. All data are presented as *n* (%) unless otherwise stated. BMI, body mass index; CABG, coronary artery bypass grafting in the medical history. PCI, percutaneous coronary intervention. High-risk surgery, surgery with a known cardiac risk of >5%, in this study, including surgery with large fluid shifts such as oesophagus, liver, pancreatic surgery, or advanced bowel surgery; RCRI, revised cardiac risk index, which includes the following risk factors: high-risk surgery, history of ischaemic heart disease, history of congestive heart failure, history of cerebrovascular disease, preoperative treatment with insulin, preoperative serum creatinine >170 μmol litre^{-1}; Hs-CRP, high-sensitive C-reactive protein

	Aspirin (*n*=109)	Placebo (*n*=111)	*P*-value
Age (yr) [mean (range)]	71.8 (58–86)	72.6 (46–88)	0.51
BMI [mean (SD)]	27.5 (4.58)	27.3 (4.85)	0.81
Gender male [*n* (%)]	69 (63)	70 (63)	0.97
Ischaemic heart disease	74 (68)	78 (70)	0.81
Congestive heart failure	15 (14)	16 (14)	0.61
CABG	13 (12)	16 (14)	0.59
PCI	22 (20)	17 (15)	0.38
Insulin-dependent diabetes mellitus	19 (17)	31 (28)	0.06
Creatinine >170 mol litre^{-1}	4 (4)	4 (4)	0.98
Cerebrovascular disease	25 (23)	24 (22)	0.82
High-risk surgery	20 (18)	18 (16)	0.68
Revised cardiac risk index			
1	67 (62)	63 (57)	0.70
2	34 (31)	37 (33)	
≥3	8 (7)	11 (10)	
ASA classification			
I	1 (1)	0 (0)	0.42
II	65 (63)	61 (57)	
III	37 (36)	45 (42)	
IV	0 (0)	1 (1)	
Medication			
Beta-blocker	68 (62)	66 (59)	0.66
Calcium inhibitor	30 (28)	29 (26)	0.78
ACE-inhibitor	41 (38)	51 (46)	0.25
Diuretics	37 (34)	46 (41)	0.19
Organic nitrates	16 (15)	24 (22)	0.19
Aspirin	97 (90)	100 (90)	0.95
Insulin	19 (18)	30 (27)	0.09
Statins	60 (56)	65 (59)	0.65
Troponin T preop ≥0.04 μg litre^{-1}	3 (3)	2 (2)	0.68
NT-proBNP >900 ng litre^{-1}	27 (25)	28 (25)	0.94
Hs-CRP [median (IQR)]	2.5 (1–5.4)	2.2 (1–7.1)	0.62

Table 2 Perioperative characteristics. All data are presented as *n* (%) unless otherwise stated. Tachycardia, an increase in heart rate of >30 beats min^{-1} for >5 min. Bradycardia, heart rate <45 beats min^{-1} for >5 min. Hypo-/hypertension, ±30% of baseline systolic arterial pressure. Hypoxaemia, Sp_{O_2} <90% for >5 min

	Aspirin (*n*=109)	Placebo (*n*=111)	*P*-value
Type of surgery			
Abdominal	24 (22)	28 (25)	
Urology	33 (30)	28 (25)	
Orthopaedics	47 (43)	49 (44)	
Gynaecology	5 (5)	6 (5)	0.84
Type of anaesthesia			
General anaesthesia (GA)	28 (28)	21 (19)	
Regional	52 (52)	56 (53)	
GA+epidural	20 (18)	28 (27)	0.31
Duration of surgery (min) [mean (SD)]	123 (81)	139 (113)	0.23
Perop complications			
Tachycardia	1 (1)	6 (5)	0.06
Bradycardia	13 (12)	9 (8)	0.34
Hypertension	3 (3)	4 (4)	0.72
Hypotension	48 (44)	58 (52)	0.22
Hypoxaemia	0 (0)	1 (1)	1.00
Use of vasoactive drugs	52 (48)	64 (58)	0.14
Temperature postop (°C) [mean (SD)]	36.0 (0.7)	36.1 (1)	0.11
Postop complications			
Tachycardia	0 (0)	8 (7)	0.007
Bradycardia	9 (8)	2 (2)	0.03
Hypertension	3 (3)	4 (4)	0.68
Hypotension	13 (12)	13 (12)	0.96
Hypoxaemia	0 (0)	3 (3)	0.25

Table 3 Myocardial damage and cardio-cerebrovascular complications. Postoperative myocardial damage, defined as a TnT value ≥0.04 μg litre^{-1} on at least one occasion in the first 48 h after operation period. MACEs, including acute myocardial infarction, cardiac arrest, severe arrhythmia, or cardiovascular death within the first 30 postoperative days. Cardio-cerebrovascular events: MACE, TIA/stroke, or both. In patients with more than one event, only one event is included in the outcome variable. Statistical analysis was undertaken on an intention-to-treat basis. Patients were assumed not to have had an event when data were missing

	Aspirin (*n*=109)	Per cent	Placebo (*n*=111)	Per cent	*P*-value
Troponin T ≥0.04 μg litre^{-1} after operation	4	3.7	10	9.0	0.10
Acute myocardial infarction	2		7		
Severe arrhythmia	0		2		
Cardiac arrest	0		1		
Cardiovascular death	1		0		
TIA/stroke	2		2		
Major adverse cardiac events	2	1.8	10	9.0	0.02
Cardio-cerebrovascular events	3	2.7	10	9.0	0.049

(Table 3). Treatment with aspirin resulted in an absolute risk reduction of 7.2% [95% confidence interval (CI), 1.3–13%] and a relative risk reduction of 80% (95% CI, 9.2–95%) for postoperative cardiovascular events within the first 30 days after surgery. Numbers needed to treat were 14 (95% CI, 7.6–78).

None of the patients with preoperative-elevated TnT had an MACE in the first 30 postoperative days. There was no MACE in the subgroup of patients who had undergone percutaneous coronary intervention.

A majority of patients having MACE had it early in the postoperative period. One patient (1.1%) in the aspirin group and eight patients in the placebo group (8.2%) had MACE within the first three postoperative days (P=0.02).

Thirteen patients had cerebrovascular events (MACE and TIA/stroke) in the postoperative period. Ten of these patients were in the placebo group (9%) and three (2.7%) in the aspirin group (P=0.049).

In patients on chronic low-dose acetylsalicylic acid treatment before the study (n=196; 90% of the study population), 10 patients (10%) who were randomized to receive placebo developed an MACE compared with one patient (2%) receiving acetylsalicylic acid during the study period (P=0.03).

Table 4 Haemorrhagic complications. All data are presented as *n* (%) unless otherwise stated. Severe bleeding complications: including postoperative bleeding resulting in reoperation, gastrointestinal bleeding, intracranial haemorrhage, and spinal/epidural haematoma within 30 days of surgery. Packed red blood cells and plasma transfusions: number of patients who received transfusions. Bleeding tendency: the surgeon's assessment of preoperative bleeding tendency on a scale from 1 to 5, where 1 was normal bleeding and 5 was greatly increased bleeding

	Aspirin (*n*=109)	Placebo (*n*=111)	*P*-value
Perop bleeding (ml) [median (IQR)]	300 (100–600)	300 (90–600)	0.61
Severe bleeding complications			
Reoperation due to haemorrhage	2 (2)	0 (0)	0.24
Gastrointestinal bleeding	0 (0)	0 (0)	1.00
Intracranial haemorrhage	0 (0)	0 (0)	1.00
Spinal/epidural hematoma	0 (0)	0 (0)	1.00
Fluids perop			
Crystalloids (litre) [median (IQR)]	1.2 (1.0–2.0)	0.9 (0.5–1.0)	0.33
Colloids (litre) [median (IQR)]	0.9 (0.5–1.0)	1.0 (0.5–1.5)	0.02
Packed red blood cells	14 (13)	11 (10)	0.49
Plasma transfusion	3 (3)	5 (4)	0.83
Bleeding tendency 1–5 [median (IQR)]	2 (1–4)	2 (1–4)	0.27

Four patients (2%) died within 30 days of the surgical procedure (*n*=2 in each group). The cause of death in these patients was classified as cardiovascular in one patient. The remaining three causes of death were classified as other.

Bleeding complications

Two patients (2%) in the aspirin group but none in the placebo group had bleeding which required reoperation in the perioperative period (*P*=0.24) (Table 4). Both these patients underwent prostatic surgery, one transurethral resection of the prostate and the other open prostatectomy for benign prostatic hypertrophy. During the study period, a total of five adverse events due to bleeding were documented (three in the aspirin group and two in the placebo group). These events included bruising or greater perioperative bleeding than expected. No significant differences in the amount of per- or postoperative bleeding were seen between patients who were treated with aspirin compared with patients who were treated with placebo. The surgeon's assessment of peroperative bleeding tendency did not show any significant differences between the groups (Table 4). No statistically significant differences were detected in the amount of crystalloids, packed red blood cells, or plasma transfusions between the groups. However, patients in the placebo group received more colloids than those in the aspirin group (*P*=0.02).

Discussion

In this prospective randomized placebo-controlled multicentre study, we found that treatment with low-dose aspirin in the perioperative period reduced the relative risk of MACEs within 30 days of surgery by 80% (absolute risk reduction 7.2%). A trend was also seen towards a reduction in myocardial damage after operation. However, this trend did not reach statistical significance. In addition, we found that there were no significant differences between the groups in perioperative bleeding including severe haemorrhage, amount of perioperative bleeding, packed red blood cells and plasma transfusions, or the surgeon's assessment of the operative bleeding tendency.

Aspirin reduces platelet aggregation for the lifespan of the platelet, ~8–10 days.[17] Numerous publications on major morbidity and mortality have shown the efficacy of low-dose aspirin in secondary prevention of cardiovascular events[6 18 19] and aspirin should therefore be continued throughout life in patients at risk.[19 20] Recent data on the risk of discontinuing antiplatelet therapy in patients with coronary stents have highlighted the use of aspirin in the perioperative period.[21–23] As a result, the routine withdrawal of aspirin 7–10 days before surgery has been questioned and some recent publications recommend that aspirin should not be stopped routinely in the perioperative period.[14 15 24 25] However, these recommendations were not based on evidence from controlled trials elucidating the risk/benefit of aspirin in the setting of non-cardiac surgery. Indeed, prospective, randomized studies on this important problem are singularly lacking in the literature. Therefore, there are two important issues that need to be discussed. First, does stopping aspirin perioperatively cause any harm to patients who are at risk of a cardiovascular complication? Secondly, does continuing aspirin result in any significant increase in perioperative bleeding?

One of the problems with aspirin withdrawal is the risk of a rebound phenomenon. Abrupt cessation of aspirin results in an increase in thromboxane A2 activity and a decrease in fibrinolysis, resulting in increased platelet adhesion and aggregation.[26 27] In addition, the surgical trauma by itself creates a prothrombotic and proinflammatory state, including platelet activation/aggregation and reduced fibrinolytic activity.[28 29] One meta-analysis of the literature found that aspirin withdrawal was associated with a significantly increased risk of myocardial infarction and death.[27] We found, in the present study, that there was a statistically significant increase in the incidence of MACE within 30 days after surgery when aspirin was stopped as opposed to its continuation in the perioperative period. Since a vast majority of our patients were taking aspirin before operation (90%), it is impossible to be certain whether the effects seen were a consequence of aspirin treatment or aspirin withdrawal in patients already on antiplatelet therapy. There was a higher incidence of episodes of postoperative tachycardia in patients taking placebo compared with patients receiving acetylsalicylic acid. However, only one of these eight patients developed an MACE, and therefore, episodes of tachycardia alone cannot explain the higher incidence of MACE in the placebo group.

The incidence of myocardial damage was not significantly different between the groups. This could be due to the small number of patients recruited into this study but could also be due to several other factors including: (i) the small number of patients undergoing high-risk surgery (<20%) with a high revised cardiac risk index (<10%), (ii) all patients did not have ischaemic heart disease, and (iii) patients who had insulin-dependent diabetes mellitus without other evidence of CAD were included into this study. It is possible that the results of myocardial damage would have been different if we had only included patients with ischaemic heart disease or cerebrovascular disease where aspirin has the greatest benefit.

The next issue is whether continuing aspirin perioperatively increases the risk of bleeding? The mechanism of action of aspirin is well known and the decrease in platelet aggregation when using aspirin can lead to an increased risk of bleeding, even when used in low doses. A meta-analysis of 474 studies showed that the use of aspirin increased intraoperative bleeding by a factor of 1.5.[7] However, no increased risk in morbidity or mortality was found in this systematic review. In our present study, two patients in the aspirin group required to be reoperated due to bleeding. Both these patients underwent prostatic surgery (transurethral prostatectomy and open prostatectomy). There has been some concern among urologists about continuing aspirin perioperatively and a previous meta-analysis of studies did suggest a higher risk in patients undergoing urological surgery.[7] In the present study, there was no evidence of an increase in perioperative bleeding, packed red blood cells/plasma transfusions, or the surgeon's assessment of the operative bleeding tendency in the aspirin group compared with patients taking placebo. The overall incidence of perioperative bleeding was low and there were no statistical differences between the groups. However, we have to emphasize that this study was not primarily designed to assess the differences in bleeding complications between the groups. Therefore, future studies that are designed to assess bleeding complications with continuing aspirin treatment should specifically assess patients undergoing prostatectomy in order to detect potential risk of perioperative bleeding. We would like to stress that this study is underpowered to detect these differences.

There are some limitations to the results of our study. First and foremost, the study was stopped before the intended 540 patients were included. The main reasons for discontinuing the study are described under results.

Since our study is underpowered, it is more difficult to draw definite conclusions on the consequences of our findings. For example, we could not substantiate that aspirin reduced the risk of myocardial damage, which was our primary endpoint, although there was a clear trend towards this. However, we did establish that aspirin therapy did not increase perioperative morbidity or mortality. Therefore, since little harm was shown in continuing aspirin therapy perioperatively and a trend towards improved outcome was evident, we believe that our study adds to the previous evidence from non-controlled trials that aspirin should be continued perioperatively in high-risk patients.

In conclusion, we found a statistically significant reduction in MACE within 30 days of surgery in patients treated with aspirin compared with patients given placebo. No significant increase in haemorrhagic complications was observed in patients treated with aspirin. The relatively small number of patients recruited limits our conclusions and larger studies may need to be performed in order to confirm our findings.

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