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

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Aspirin: To Continue or Discontinue in the Perioperative Period.
A randomized, controlled clinical trial.

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The Aspirin in Non-Cardiac Surgery (ASINC) trial

Running Title: Aspirin reduces the risk of MACE in non-cardiac surgery

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Background

Major adverse cardiac events (MACE) are a common cause of death following 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 (75mg) or placebo was given 7 days prior to 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 a 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% CI 1.3-13%) for postoperative MACE. The relative risk reduction was 80% (95% CI 9.2-95%). Numbers needed to treat was 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.

Keywords: Surgery, non-cardiac; Complication, haemorrhage; Heart, ischaemia

Introduction

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, nonfatal myocardial infarction and cardiac arrest per year. [2] Furthermore, data show that perioperative myocardial infarction (PMI) 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 cerebro-vascular 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 cerebro-vascular event. [6] Despite evidence to the benefit of antiplatelet therapy in patients at risk of cardiac and cerebro-vascular complications, aspirin treatment is often discontinued prior to 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 MACE (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 multi-center study (ASINC- Aspirin in non-cardiac surgery, Eudract CT number 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 $\mu mol \cdot L^{-1}$), cerebro-vascular accident (prior stroke or transient ischaemic attack) 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 & 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, nefrectomy, hip or knee arthroplasty, and intrabdominal or pelvic cancer surgery were included. Exclusion criteria were: unstable coronary artery disease, non-compensated congestive heart failure, shock, allergy to aspirin, age under 18 years, 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 75 mg aspirin or placebo using a computer-generated algorithm. The study product, as well as

reference product, both of identical shape, weight and appearance, was provided by Apoteket Production & 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. Demographic data, medical history and preoperative medication were obtained from the patients or their medical records.

In addition to routine laboratory tests, Troponin T (TnT) and NT-proBNP were measured one hour prior to surgery. Troponin T was also measured at 12 hrs, 24 hrs and 48 hrs postoperatively and analyzed by using Elecsys 2010®, Roche Diagnostics, Mannheim, Germany. Resting electrocardiograms were recorded preoperatively, directly after surgery and 24 and 48 hrs postoperatively. A clinical physiologist blinded to clinical symptoms, laboratory data and ongoing patient management analyzed 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 $\mu g \cdot L^{-1}$ 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 judgment of the attending physicians.

Perioperative events, including haemodynamic instability (systolic blood pressure ± 30% of baseline), hypoxaemia (SpO_2 < 90% for > 5 min), new arrhythmia, tachycardia (heart rate + 30 beats $minutes^{-1}$ from baseline for > 5 minutes) or bradycardia (heart rate < 45 for > 5 minutes) 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 as well as major bleeding from other organs including epidural

or intracranial haematoma, cerebro-vascular complications and death within 30 days were also recorded.

Study endpoints

Postoperative myocardial damage, as defined earlier, was considered to be the primary end-point.

Secondary endpoints were:

1) Major adverse cardiac events (MACE), including acute myocardial infarction, cardiac arrest, severe arrhythmia or cardiovascular death within the first 30 postoperative days.
2) Cardio-cerebro-vascular complications, including MACE or stroke/transient ischaemic attack within the first 30 postoperative days.
3) 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.
4) Packed red blood cell, plasma and platelet transfusions.

Follow-up

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 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] Based on 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 & 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 (interquartile range). For analyses of continuous data τ-test or Mann-Whitney U test were used as appropriate, to detect differences between the groups. Dichotomous variables are described as numbers and percentage and were analyzed 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% confidence intervals. In addition, numbers needed to treat was calculated. The level of statistical significance was specified as $p \leq 0.05$, (two-tailed). All analyses were performed using STATA v10.1 (Stata Corp LP; College Station, Tx, USA).

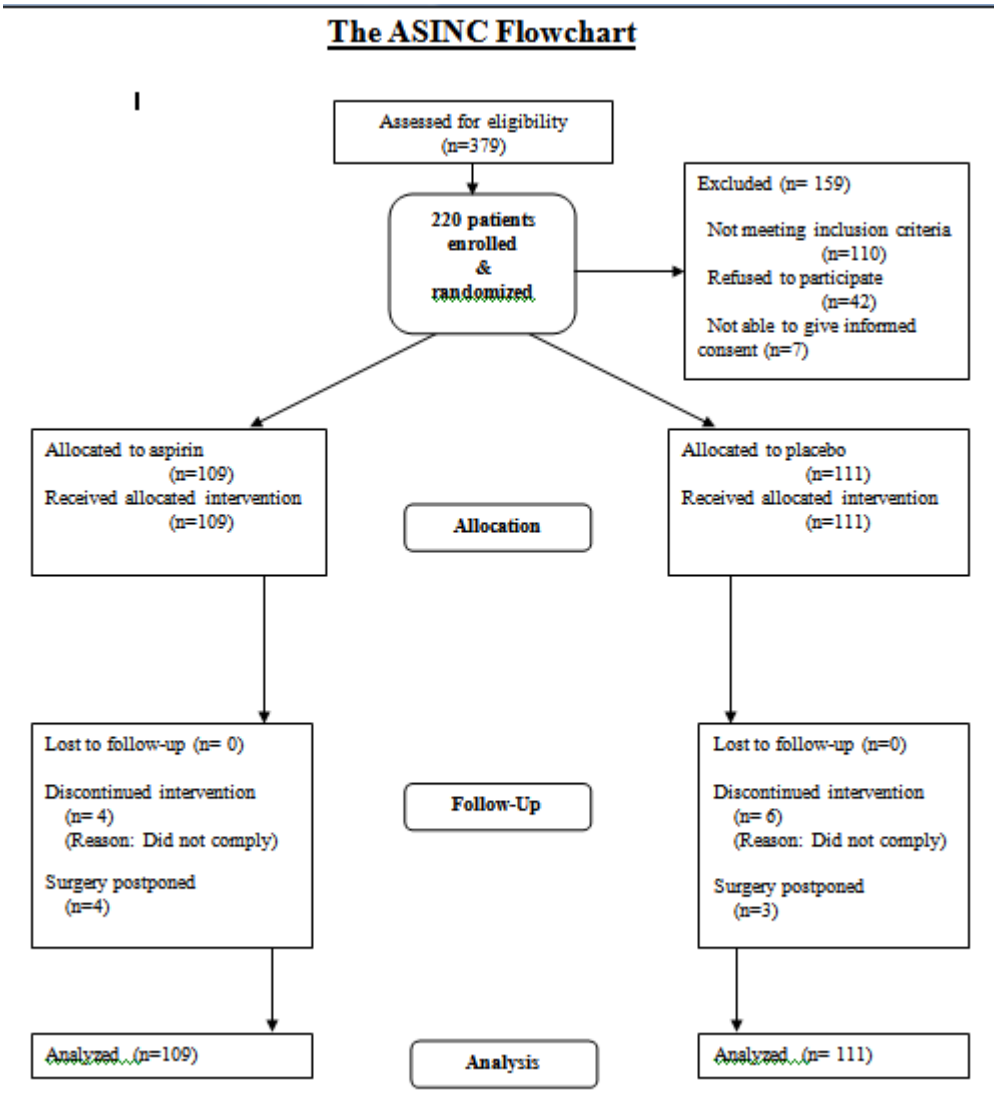
Results

Of the planned 540 patients, the study was terminated in December 2008 after inclusion of 220 patients at the seven centers. The study was stopped prior to full enrollment, 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 five years 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, one hundred and nine patients received aspirin and 111 patients received placebo. In seven of the randomized patients, surgery was postponed, while ten patients did not comply with the treatment, Figure 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.

Myocardial Damage

Fourteen patients (6.4%) had a TnT $\geq 0.04 \mu g \cdot L^{-1}$ on at least one occasion in the first 48 hours postoperatively. 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 prior to 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 that



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 to11 patient (11%) in the aspirin group, (p= 0.83). Tachycardia was seen significantly more often in the placebo group compared to patients treated with aspirin, eight patients in the placebo group (7%) compared to none in the ASA group, Table 2. Only one of the patients with tachycardia developed a MACE. In contrast, patients in the aspirin group had more frequent episodes of bradycardia, (p=0.02).

Table 1: Baseline characteristics

		Aspirin n=109		Placebo n=111		p
Age yr *(mean±SD)*		71.8	7.56	72.6	9.27	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 µmol·L^{-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)	
	2	34	(31)	37	(33)	
	≥3	8	(7)	11	(10)	0.70
ASA classification						
	1	1	(1)	0	(0)	
	2	65	(63)	61	(57)	
	3	37	(36)	45	(42)	
	4	0	(0)	1	(1)	0.42
Medication:						
Betablocker		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·L-1		3	(3)	2	(2)	0.68
NT-ProBNP > 900 ng·L-1		27	(25)	28	(25)	0.94
Hs-CRP (*median±IQR)*		2.5	1-5.4	2.2	1.0-7.1	0.62

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 factor:
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·L^{-1}

Hs-CRP: High-sensitive C-reactive protein

Table 2: Per- & postoperative characteristics

	Aspirin n=109		Placebo n=111		p
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 anesthesia					
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

All data are presented as n (%) unless otherwise stated.
Tachycardia: an increase in heart rate of > 30 for > 5 minutes.
Bradycardia: heart rate < 45 for > 5 min
Hypo-/ hypertension: ± 30% of baseline systolic blood pressure.
Hypoxaemia: SpO_2 <90% for > 5 minutes.
Patients were assumed not to have had a complication in case of missing data.

Major Adverse Cardiac Events & Mortality

Twelve patients (6 %) had a major adverse cardiac event, 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 2 patients (1.8%) were in the aspirin group, (p =0.02), Table 3. Treatment with aspirin resulted in an absolute risk reduction

of 7.2% (95% 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 was 14 (95% CI 7.6-78).

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

TABLE 3: MYOCARDIAL DAMAGE & CARDIO-CEREBRO-VASCULAR COMPLICATIONS

	ASPIRIN N=109	**%**	**PLACEBO** N=111	**%**	**P**
TROPONIN T ≥ 0.04 MG·L^{-1} POSTOPERATIVELY	**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-CEREBRO-VASCULAR EVENTS	**3**	**2.7**	**10**	**9.0**	**0.049**

POSTOPERATIVE MYOCARDIAL DAMAGE, DEFINED AS A TROPONIN T VALUE ≥0.04 μG·L^{-1} ON AT
LEAST ONE OCCASION IN THE FIRST 48 HOURS POSTOPERATIVELY PERIOD.
MAJOR ADVERSE CARDIAC EVENTS (MACE), INCLUDING ACUTE MYOCARDIAL INFARCTION, CARDIAC ARREST,
SEVERE ARRHYTHMIA OR CARDIOVASCULAR DEATH WITHIN THE FIRST 30 POSTOPERATIVE DAYS.
CARDIO-CEREBRO-VASCULAR EVENTS: MACE AND/OR TIA/STROKE
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 WAS MISSING.

A majority of patients having MACE had it early in the postoperative period. One patient (1.1%) in the aspirin group and 8 patients in the placebo group (8.2%) had MACE within the first three postoperative days, p=0.02.

Thirteen patients had cerebro-vascular 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 prior to the study (n=196; 90% of the study population), 10 patients (10%) who were randomized to receive placebo developed a MACE compared to 1 patient (2%) receiving acetylsalicylic acid during the study period, p= 0.03.

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 (3 in the aspirin group and 2 in the placebo group). These events included bruising or greater per-operative bleeding than expected. No significant differences in the amount of per- or postoperative bleeding were seen between patients who were treated with aspirin compared to 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).

TABLE 4: HAEMORRHAGIC COMPLICATIONS					
	ASPIRIN N=109		**PLACEBO** N=111		**P**
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 ML *(MEDIAN±IQR)*	1200	1000-2000	900	500-1000	0.33
COLLOIDS ML *(MEDIAN±IQR)*	900	500-1000	1000	500-1500	0.02
PACKED RED BLOOD CELLS NR PAT	14	13	11	10	0.49
PLASMA TRANSFUSION NUMBER OF PATIENTS	3	3	5	4	0.83
BLEEDING TENDENCY 1-5 *(MEDIAN±IQR)*	2	1-4	2	1-4	0.27

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 HEMATOMA WITHIN 30 DAYS OF SURGERY.
PACKED RED BLOOD CELLS AND PLASMA TRANSFUSIONS: NUMBER OF PATIENTS THAT 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.

Discussion

In this prospective randomized placebo-controlled multi-center study, we found that treatment with low-dose aspirin in the perioperative period reduced the relative risk of major adverse cardiac events within 30 days of surgery by 80% (absolute risk-reduction 7.2%). A trend was also seen towards a reduction in myocardial damage postoperatively. 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, approximately 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 anti-platelet therapy in patients with coronary stents has highlighted the use of aspirin in the perioperative period. [21-23] As a result, the routine withdrawal of aspirin 7-10 days prior to 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. Firstly, 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 preoperatively (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 to patients receiving acetylsalicylic acid. However, only one of these eight patients developed a 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: a) the small number of patients undergoing high-risk surgery (<20%) with a high revised cardiac risk index (< 10%), b) all patients did not have ischaemic heart disease and c) patients who had insulin-dependent diabetes mellitus without other evidence of coronary artery disease 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 cerebro-vascular 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 re-operated due to bleeding. Both these patients underwent prostatic surgery (transurethral prostatectomy and open prostatectomy). There has been some concern amongst 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 to 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 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 was not designed to detect differences in bleeding complications between the groups and therefore it is underpowered to detect these differences.

Study Limitations

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 to 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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