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Review

Prophylactic Perioperative Anti-Thrombotics in Open and Endovascular Abdominal Aortic Aneurysm (AAA) Surgery: A Systematic Review CME

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WHAT THIS PAPER ADDS?

- The perioperative administration of heparin for the prevention of arterial thrombo-embolic complications during and after reconstructive arterial surgery is widely advised and used. However, this systematic review did not find sound scientific evidence for the efficacy of heparin in open and endovascular surgery for (ruptured) abdominal aortic aneurysm (AAA). On the contrary, evidence was found indicating that heparin increases operation time, blood loss and blood transfusion requirements. The CAPPA study group will promote a well-designed and properly conducted randomised controlled trial (RCT) to provide evidence on the benefits and risks of the use of heparin during AAA surgery.

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ABSTRACT

Objective: Heparin is used worldwide by vascular surgeons as prophylaxis for arterial thrombo-embolic complications during open and endovascular arterial surgery. Possible harmful effect of heparin use is more perioperative blood loss, resulting in a higher morbidity and mortality. To evaluate the evidence for the use of heparin during aorto-iliac arterial surgery a review was performed.
Methods: A systematic review was performed of literature from MEDLINE, EMBASE and Cochrane databases, last search performed on March 8, 2012.
Results: For open surgery for abdominal aortic aneurysm (AAA), only 5 studies were eligible for review and for endovascular aneurysm repair (EVAR) only 1 study. Overall methodological quality of the included studies was poor. One randomised trial could be retrieved. Possible harmful effects of heparin were found of increasing operation time, more blood loss and more transfusion requirements when heparin was used for open AAA surgery in one study. No data were found comparing heparin to no intervention for EVAR. One study compared heparin to a direct thrombin antagonist during EVAR, showing no differences in clinical outcomes.
Conclusion: Despite limitations this review showed no compelling evidence on the beneficiary effect of the prophylactic perioperative use of heparin during open surgery for (r)AAA. Authors will promote a randomised controlled multi-center trial on this topic for elective open surgical repair of AAA.

Ever since Murray in 1940[1] produced experimental and (sparsely) clinical evidence that heparin could prevent thrombosis during and after arterial reconstructions and embolectomies, local or systemic perioperative heparinisation has been adapted worldwide by vascular surgeons as a standard procedure to reduce perioperative arterial thrombo-embolic complications (ATECs).

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However, the possible disadvantages of using heparin during arterial reconstructive surgery were also soon recognised. Heparin can increase peri- and post-operative bleeding and the need for blood transfusions. The negative side effects of blood transfusions are well recognised.[2,3] Increased blood loss is also related to a prolonged operation time, both independently enhancing infectious complications resulting in increased morbidity and mortality.

Another factor complicating the prophylactic perioperative use of heparin during arterial surgery is the unpredictable pharmacokinetic response of individual patients. Heparin has no linear dose–response and elimination curve after the administration of a standard dose.[4] This phenomenon is enhanced by the deregulated coagulation cascade[5,6] in vascular surgical patients. For this reason, monitoring the level of anti-coagulation produced by heparin is recommended.[4,7] The preferred method is to measure the activated clotting time (ACT), which correlates with the anti-thrombotic effect of heparin better than the activated partial thromboplastin time (APTT).[8] Nevertheless, measuring heparin activity perioperatively has not gained widespread use.[9]

Since the introduction of heparin in 1940 only one randomised controlled trial (RCT) has examined the benefits of perioperative prophylactic use of heparin in open surgery for abdominal aortic aneurysm (AAA).[10] Despite this lack of evidence, some guidelines strongly advocate the use of heparin during open or endovascular AAA surgery. In the 2008 American College of Chest Physicians (ACCP) guidelines, Sobel et al.[11] stated that level 1A evidence exists for the intra-operative use of heparin for patients undergoing vascular reconstructive surgery. The Society for Vascular Surgery (SVS) guidelines for the care of patients with an AAA[12] state that heparinisation is used by almost all vascular surgeons, although no references were supplied. Finally, the Society of Interventional Radiology (SIR) stated in their recent Standards of Practice[13] on endovascular aneurysm repair (EVAR), "Although there are no trial data regarding routine use of intra-operative heparin during EVAR, the open surgical experience with heparinisation has been widely applied to endograft procedures."

Surveys on heparin use in the daily practice of vascular surgeons and interventional radiologists have been performed throughout Europe,[14,15] the UK[16–18] and the United States (US).[9,19] They showed wide variation in the prophylactic use of heparin (and protamine for heparin reversal) perioperatively in reconstructive arterial surgery, both for open and endovascular procedures.

We performed a systematic review and meta-analysis when possible to assess the beneficial and possibly harmful effects of heparin or any other antithrombotic drug in open as well as in endovascular aorto-iliac arterial surgery. We also investigated whether other pharmaceuticals have been compared with heparin (in randomised clinical trials (RCTs)) for open or endovascular abdominal aorto-iliac arterial surgery.

Methods

This systematic review was performed in accordance with the PRISMA 2009 (Preferred Reporting Items for Systematic reviews and Meta-Analyses)[20] and MOOSE (Meta-analysis Of Observational Studies in Epidemiology Group)[21] guidelines.

Search strategy

On 2 February, 2011, two independent investigators (AW and CB) searched Medline (from January 1966 to February 2011) and EMBASE (from January 1988 to February 2011) databases and the Cochrane Database of Systematic Reviews (from 1990 to February 2011). The following combinations of medical subject headings (MESH) were used: iliac aneurysm, Leriche syndrome, AAA, abdominal aorta, iliac artery, surgery, anti-coagulants or anti-thrombotics. No filters or other restrictions were applied. By cross-referencing the bibliographies cited in the included articles, additional studies were identified and assessed for suitability. From all of the studies identified in the search, the same independent investigators selected potentially eligible studies according to the information provided by titles and abstracts. Review of Materials & Methods sections led to further exclusion of studies. Final inclusion was performed after full-text review. Any disagreement between the investigators was reconciled by a repeated review of the studies in question until consensus was reached. The flowchart for studies on open AAA surgery is presented in Fig. 1. On 8 March 2012, the same search was performed again, to capture any recent publications. The above method was followed in detail to search for articles concerning EVAR and periprocedural use of anti-coagulants and/or anti-thrombotics. To minimise the risk of missing any articles on this subject, a separate MESH search was performed using the extension 'surgery or endovascular surgery' in the above depicted search strategy. No new hits were found.

Inclusion criteria

This review included RCTs and prospective and retrospective case series on open or endovascular abdominal aorto-iliac arterial reconstructive surgery (EVAR, endarterectomy, grafting procedures or combinations) for both occlusive and aneurismal diseases. Studies had to compare patient groups with and without intra-operative arterial thrombosis prophylaxis or to compare heparin prophylaxis with another anti-thrombotic agent. Reported outcomes should include postoperative mortality, morbidity from myocardial infarction (MI) or arterial thrombotic complications (ATEC). Data on blood loss and blood transfusion requirements during and immediately after the operation should be evaluated. Only studies reported in English language were included.

Exclusion criteria

Reports with an unsuitable study design (e.g., dose finding studies or lacking a group of patients without anti-thrombotic prophylaxis) or with surrogate 'end' points (e.g., clotting time after heparin administration) were excluded.

Methodological assessment

Two authors (AW and VJ) separately assessed the methodological quality of the included articles. A checklist was used that included the following items:

- Clear definition of study population?
- Sufficient exclusion of selection bias?
- Method of intervention clearly described?
- Outcomes clearly described?
- Independent or blinded observers for data collection?
- Complete follow-up for hospital stay up to discharge?
- Detailed information on exclusion criteria and excluded patients?
- Information on confounders available?

To further assess the quality of the selected studies, a system was developed to score the study characteristics. Items recorded from studies were: consecutive series of patients reported, prospective or retrospective series, detailed information about surgical procedure, details about heparin and protamine usage, details on blood loss, detailed information on blood-transfusion requirements and incidence of MI and ATEC. Differences in

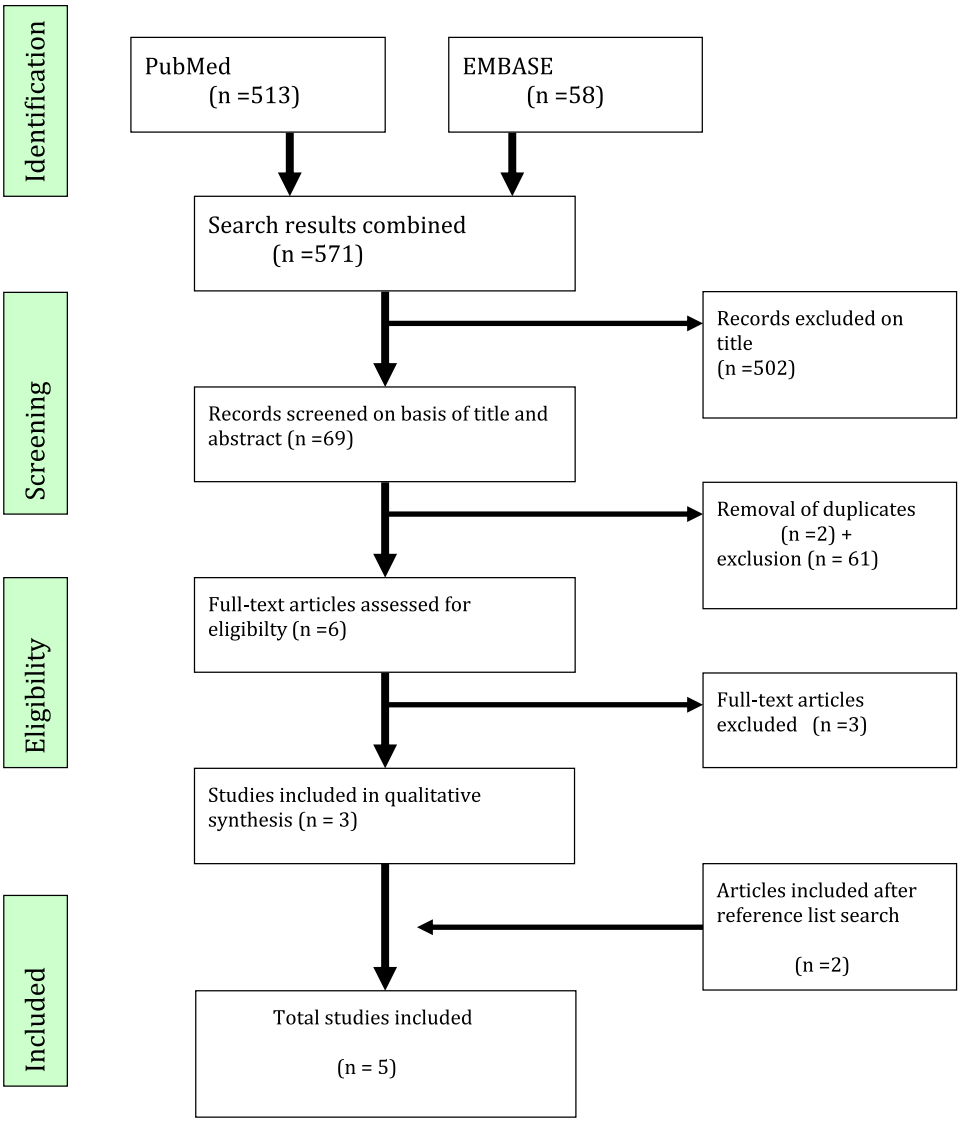

Figure 1. Flowchart of literature search.

assessments between AW and VJ were solved by discussion. Methodological quality of the study was not an exclusion criterion.

Data extraction

Data were extracted from eligible studies by two independent authors (AW and VJ). AW extracted data from included studies using a data extraction sheet, and VJ checked the extracted data. Disagreement was followed by repeated review, and consensus was reached. Data were labelled as 'no details' if they were not reported explicitly in text or tables. Two authors of included studies were contacted by AW to provide further details that were not revealed in the original publication.[22,23]

Standardisation of outcome measures

Mortality should preferably be defined as mortality within 30 days of the operation. Morbidity from MI and ATEC should be reported in the same time window as outcome measures. Mortality was death by any cause. Morbidity from MI should preferably be documented by an increase in cardiac enzymes in peripheral blood samples and/or electrocardiography (ECG) changes or post-mortem findings. ATEC was defined as: any thrombosis or embolism in the arterial vascular system during or after surgery that did or did not require (surgical) intervention, including mesenteric ischaemia and trash foot.

Statistical analysis

Continuous data were expressed as means and standard deviations. For continuous outcomes, if mean values were not available, medians were used. Relative risk with 95% confidence interval was calculated for dichotomous variables. Statistical analysis was performed using IBM SPSS®, version 19.

Results for Open AAA Surgery

Literature search

A total of 571 studies were identified, of which 502 publications were excluded after evaluation of the title. The remaining 69 were studied by evaluation of abstracts. Two duplicate studies were excluded. No perioperative intervention was performed in two studies, and no groups with and without heparin or other anti-

thrombotic were present in 15 studies. In 21 publications, no open abdominal vascular surgery was examined. No suitable end points were reported in 23 studies. The remaining six articles were studied by full-text analysis. It was then found that 3 studies did not include groups with or without intervention. After adding two articles from the reference list of the three remaining articles, five studies met all criteria for inclusion. See Fig. 1 for flowchart. Two studies were performed in the UK; the other studies were performed in Canada, Australia and the United States, respectively.

Characteristics of included studies

The selected reports were published between 1988 and 2008, representing a total study population of 1491 patients. Data were collected prospectively in three studies[22,24,25] and retrospectively in one study.[26] One study concerned an RCT.[10] In all studies, heparin was administered intravenously before cross-clamping and results were compared to a blank control group.

One study was designed as an RCT.[10] In all studies intravenous administration of heparin before cross-clamping was used and results were compared to a blank control group. One study[26] included 38 patients with aortic-iliac occlusive disease (AIOD) and 161 with aneurismal disease. The authors excluded the patients with AIOD from evaluation, and we consequently excluded them from this review. The four other studies included patients with ruptured AAA (rAAA)[24], elective AAA repair[10,25] included elective repair of AAA and both asymptomatic and symptomatic patients with non-ruptured AAA.[22]

In all studies, blood loss and transfusion requirements were assessed to evaluate whether increased bleeding occurred when heparin was used. Overall mortality and incidence of non-fatal and fatal MI for the heparin and the no-heparin groups was evaluated in three studies.[10,24,25] The incidence of ATEC could be retrieved from four studies.[10,24–26] Mortality details were reported as data within 30 days of the operation in three studies,[10,22,24] details for MI and ATEC within 30 days in two studies,[10,24] one study[26] provided the in-hospital data and from one study[26] no details could be retrieved about the time relation between surgery and postoperative mortality and morbidity. Main patient and study characteristics are shown in Table 1.

Methodological quality

The results of the quality assessment and the checklist for methodological quality are shown in Table 2. The overall methodological quality of the included studies was poor with only one RCT.[10] Selection bias was suspected in all other studies,[22,24–26] and in three studies a selective loss to follow-up could not be excluded.[22,25,26] None of the studies presented details about exclusion criteria and excluded patients. A clear description of confounders could not be retrieved from any of the studies. Only one study[25] offered adequate details about operative technique and anti-thrombotic dosage. There was substantial clinical heterogeneity between studies, concerning both study populations and interventions. This obstructed a sensible pooling of data.

Heparin and protamine

Neither the type nor manufacturer of heparin was specified in any of the studies. The protocol for heparin administration varied widely between the studies. In two studies,[24,26] administration of heparin depended on the surgeon's preference. In the RCT[10] the options were local surgeon's normal intra-operative heparin regimen or no heparin at all. Using heparin selectively for multiple pre-defined reasons was the protocol in one study[25] and in another study heparin was used according to local hospital protocol,[22] which resulted in 85% of patients receiving heparin.

In all studies, heparin was administered intravenously (i.v.), with a standard dosage of 5000 IU in three studies,[10,24,25] irrespective of patient weight. One study[22] did not give details about dosage and in another[26] 5000, 7500 and >7500 IU were used depending on the length of operation.

Heparin was administered before cross-clamping of the aorta in four studies,[10,22,24,26] with one study[26] specifying administration of heparin 3 min before cross-clamping. In one study[25] heparin was administered selectively after cross-clamping in 10 patients. Repeated unspecified doses of heparin were given in one study "if clotting became a problem during prolonged procedures." [26]

In four studies, protamine was used to reverse the effect of heparin.[10,22,25,26] In one study the standard dose of 5000 IU of heparin was reversed with protamine 50 mg in all patients.[25] If post-reversal bleeding took 'longer than expected', the ACT was measured and more protamine (usually 10 mg) was given. In two other studies, the dose of protamine had to be sufficient to reverse one-half of the given heparin.[10,26] In one of these studies, this resulted in a standardised dose of 25 mg in only 13/145 patients (9.0%)[10] and in the other study protamine was given "in most instances in a dose usually sufficient to reverse one-half of the administered heparin."[26] In some patients with short clamping times the entire heparin dose was reversed. The two remaining studies,[22,24] did not give details on the use of protamine. In one study "most often (at individual surgeon's preference), protamine was given after completion of the arterial reconstruction at a dose of 50–100 mg, depending on the original dose of heparin. The use of protamine was not APTT related."[22] (personal communication AW and first author).

Operative details

The abdominal aorta was cross-clamped above the renal arteries in 45 patients (6.8%) in one study[22] and in 38 patients (37%) in another.[25] When suprarenal clamping was indicated, heparin use was mandatory.[25] No differences in outcomes between heparin or no-heparin groups and level of cross-clamping were found in these studies. In the other three studies,[10,24,26] the site of cross-clamping was not specified.

In the study by Johnston et al.,[22] the average cross-clamping time of the abdominal aorta was 55 ± 31 min. No differences in outcomes could be identified between the heparinised and non-heparinised groups related to clamp times. Clamp times over 70 min were associated with a higher incidence of postoperative MI, but there was no difference in mortality. Furthermore, there was no significant difference in the incidence of cardiac events and mortality between suprarenal and infrarenal clamping. The other studies did not address the details of aortic cross-clamping time. Thompson et al.[10] reported slightly longer operation times in heparinised patients compared to non-heparinised cases (120 vs. 105 min, $p = 0.06$). Samson et al.,[25] also found longer operation times in heparinised patients than in non-heparinised patients treated with tube grafts (median 150 vs. 132 min, $p < 0.004$).

Blood loss

Two subsets of patients showed a statistically significant difference for blood loss in favour of no-heparin usage (Table 3). One subset constituted those treated with a tube graft in the study by Samson et al.[25] However, in this group operation time was substantially less than in the group with heparinised patients with tube grafts. Burnett et al.[26] grouped their patients into three operation time periods (<2.5 h, 2.5–3.5 h and >3.5 h) and analysed

Table 1
Main patient and study characteristics for open and endovascular AAA surgery.

Authors, Year	Study design	# of patients	Male/Female	Age in years
Chinien et al.	Prospective data collection	131	hep +: 78% / 22%	hep +: 75 (median, 54–86)
2008	Jan. 1999–Jan. 2004		hep −: 79% / 21%	hep −: 75 (median, 53–87)
rAAA	Use of heparin up to surgeon's preference.		79% / 21%	
Samson et al.	Prospective data evaluation	249	86% / 14%	73 (median, 46–93)
2002	Study period not stated.			
	Selective use of heparin.			
Thompson et al.	Randomised prospective multi-center trial	284	hep +: 82% / 18%	no details retrieved
1996	Study period not stated.		hep −: 88% / 12%	
	Randomized, sealed envelop.			
	Surgeon's normal intraoperative heparin or no-heparin.			
Burnett et al.	Retrospective data analysis	161	92% / 8%	66 (median, 56–88)
1988	Jan 1984–June 1986			
	2 surgeons using heparin, 1 no heparin			
Johnston et al.	Prospective data collection multi-center	666	80% / 20%	69.2 (mean, +/− 7,7)
1988	March 1986–Dec. 1986			
	Heparin use local hospital protocol.			
Total open AAA		1491		
Stamler et al.	Prospective data collection	740	heparin: 88% / 12%	heparin: 75.7 (mean ± 7.7)
2009	March 1994 − November 2006		bivalirudin: 91% / 9%	bivalirudin: 76.1 (mean ± 7.5)
EVAR	Use of heparin or bivalirudin up to interventionalist' preference.		90% / 10%	
Total EVAR		740		

Authors, Year	Type of disease	Heparin +/−	Protamine use in heparin group
Chinien et al.	rAAA	63/68	No details
2008		Standard dose 5000 IU	
rAAA			
Samson et al.	AAA	103/146	+ : 100%
2002		Standard dose 5000 IU	
Thompson et al.	AAA	145/139	13/145 (9%)
1996		Standard dose 5000 IU	
Burnett et al.	AAA	125/36	+ : no details
1988		No details on dosage	"most instances"
		5000 − > 7500 IU	
Johnston et al.	AAA	566/100	+ : no details
1988		Dose not stated	"most often"
Total open AAA		1002/489	
Stamler et al.	EVAR for AAA	642/98	None
2009	elective	(heparin/bivalirudin)	
EVAR			

the relationship between blood loss and heparin dose. Categories were 0, 5000 IU, 7500 IU and >7500 IU. Only for the shortest operation time group (<2.5 h) could a meaningful comparison be made. In this group, mean blood loss increased significantly with each increment of heparin ($P < 0.05$). Increased operation time, however, was also significantly associated with increased blood loss for each heparin dose category ($P < 0.05$). In this study, heparin increased blood loss significantly ($P < 0.05$) in both the tube- and bifurcated-graft group; heparin increased operation time only in the tube-graft group.

Table 2
The results of the quality assessment and the checklist for methodological quality for both open and endovascular AAA surgery.

Author	Year	Study Population	No selection bias	Method of intervention	Description of outcomes	Independent observers	No selective loss to FU	Description of confounders	Details on exclusion criteria and excluded patients
Chinien	2008	+	−	+/−	+	−	−	+/−	−
Samson	2002	+	−	+	+	−	−	+/−	−
Thompson	1996	+	+	−	+	−	+	+/−	+/−
Burnett	1988	+/−	−	+/−	+/−	−	+	+/−	−
Johnston	1988	+	−	−	−	−	−	−	−
Stamler	2009	+	−	+	+/−	−	+	+/−	−

Author	Year	Consecutive series of pt.	Prospective series of pt.	Surgery details	Heparin details	Blood loss details	Transfusion details	Myocardial infarction	ATE events details	Total Score (maximum = 16)
Chinien	2008	0	2	0	0	2	1	2	2	9
Samson	2002	0	1	2	1	2	2	2	2	12
Thompson	1996	0	2	1	0	2	2	2	2	11
Burnett	1988	2	1	0	1	2	0	0	1	7
Johnston	1988	2	2	1	0	1	1	0	0	7
Stamler	2009	2	0	2	2	2	2	0	1	11

0 = no details retrieved from study, 1 = incomplete details retrieved, 2 = complete details retrieved.

Table 3
Results for open and endovascular AAA surgery.

Authors, Year	Blood loss median value heparin +/−	Blood transfusion details heparin +/−				
Chinien et al. 2008 rAAA	2000/2500 ml. P = NS	P = NS, no further details				
Samson et al. 2002	Tubegraft: 1350/700 ml. P < 0.004 P < 0.004	cell saver: 600/250 ml P < 0.004	post-operation: 11.9% / 3.8%			
	Bifurcated graft: 1200/775 ml. P = NS	500/500 ml P = NS	11.4% / 6.3% P = NS			
Thompson et al. 1996	1400/1500 ml. P = NS	3–6/4–6 units P = NS				
Burnett et al. 1988	2270/280 ml. (mean value) P < 0.05	no details				
Johnston et al. 1988	P = NS "no difference"	P = NS "no difference"				
	Blood loss: retroperitoneal bleeding/hematoma heparin/ bivalirudin	Blood loss: minor bleeding heparin/bivalirudin	Blood loss: major bleeding heparin/bivalirudin	Blood transfusion: PRBC heparin/bivalirudin	Blood transfusion: any heparin/bivalirudin	Blood transfusion: > 2 heparin/bivalirudin
Stamler et al. 2009 EVAR	0.3% / 1% $n = 2/n = 1$	14% / 12% $n = 90/ n = 12$	14% / 10% $n = 91/n = 10$	12% / 16% $n = 79/n = 16$	8% / 6% $n = 50/n = 6$	11% / 13% $n = 68/n = 13$
	RR 3.28 (95% CI 0.29–36.52)	RR 0.87 (95% CI 0.46–1.66)	RR 0.72 (95% CI 0.36–1.44)	RR 1.33 (95% CI 0.74–2.39)	RR 0.79 (95% CI 0.33–1.89)	RR 1.25 (95% CI 0.66–2.36)

Authors, Year	Overall mortality heparin +/−	Myocardial infarction (≈) heparin +/−	Arterial thrombo-embolic complications heparin +/−
Chinien et al. 2008 rAAA	16% / 43% (*) $n = 10/n = 29$	16% / 10% (*) $n = 10/n = 7$	22% / 27% (*) $n = 14/n = 18$
	RR 0.37 (95% CI 0.16–0.85)	RR 1.54 (95% CI 0.55–4.33)	RR 0.84 (95% CI 0.38–1.87)
Samson et al. 2002	3.9% / 0.7% (‡) $n = 4/n = 1$ RR 5.67 (95% CI 0.62–51.49)	2.9% / 0% (‡) $n = 3/n = 0$ 2.9 (95% CI 0.76–8.90) 0 (95% CI 0–3.2)	2.9% / 3.4% (‡) $n = 3/n = 4$ RR 1.06 (95% CI 0.23–4.84)
Thompson et al. 1996	4.1% / 7.9% (*) $n = 6 /n = 11$ RR 0.52 (95% CI 0.19–1.45)	2.0% / 8.6% (*) $n = 3/n = 12$ RR 0.24 (95% CI 0.07–0.87)	4.8% / 7.9% (*) $n = 7/n = 11$ RR 0.61 (95% CI 0.23–1.62)
Burnett et al. 1988	No details retrieved	No details retrieved	4.8% / 0% $n = 6/n = 0$ 4.8 (95% CI 1.97–10.60) 0 (95% CI 0–12,01)
Johnston et al. 1988	"No difference" Total for heparin + and −: 4.8% (*)	"No difference"	"No difference"
	Overall mortality heparin/bivalirudin	Myocardial infarction heparin/bivalirudin	Arterial thrombo-embolic complications heparin/bivalirudin
Stamler et al. 2009 EVAR	No statistically significant difference No details retrieved (*)	No statistically significant difference No details retrieved (*)	1.9% / 1% (*) $n = 12/n = 1$ RR 0.79 (95% CI 0.10–6.17)

(≈) = fatal and non-fatal, (*) = 30 days post-operative, (‡) = in hospital.

The other three studies did not find significant differences in blood loss between heparinised and non-heparinised patients.[10,22,24] However, Chinien et al.[24] encountered clinically significant blood loss (defined as blood loss over 5000 ml) in only one heparinised patient compared to 12 non-heparinised patients. This counter-intuitive finding indicates selection bias in their patients with rAAA, massively bleeding patients apparently being spared of ill-advised heparin administration.

Transfusion requirements

Samson et al.[25] found that the non-heparinised patients were significantly less likely to require cell-save and postoperative blood transfusions ($P < 0.004$) when a tube graft was implanted, but not for bifurcated grafts (Table 3).

Three studies[10,22,24] stated that no difference was found in the transfusion requirements of heparinised and non-heparinised patients, without providing detailed information. One study did not mention transfusion requirements at all.[26] Details on transfusion requirements are depicted in Table 3.

Overall mortality

All-cause mortality is shown in Table 3. Chinien et al.[24] found a significant difference in favour of heparin in the case of rAAA (16% vs. 43%, relative risk (RR) 0.37, 95% confidence interval (CI)

0.16–0.85). This finding however is heavily biased by the fact that haemodynamically unstable patients were cross-clamped as quickly as possible, even before heparin could be given. Two studies on elective AAA repair found no statistically significant differences in mortality.[25,10] The other two studies did not report mortality at all[26] or did not report mortality separately for heparinised and non-heparinised patients.[22]

It was learned from personal communication that intra-operative heparin use did not influence mortality in the latter study.[22]

Myocardial infarction

The overall incidence of MI is depicted in Table 3. Chinien et al.[24] found fatal and non-fatal MI were diagnosed in 10 (16%) heparinised patients compared to seven (10%) in non-heparinised patients (RR 1.54, 95% CI 0.55–4.33). In the study by Samson et al.[25] three patients (2.9%) in the heparin group had a fatal MI, while no MIs occurred in the no-heparin group. Thompson et al.[10] reported that 1 patient (0.7%) in the heparin group and 4 (2.8%) patients in the no-heparin group developed a non-fatal MI. Fatal MI was diagnosed in 2 (1.4%) patients in the heparin group and in 8 (5.6%) patients in the no-heparin group (RR 0.24, 95% CI 0.05–1.15). Combining fatal and non-fatal MI in both groups resulted in a significant difference ($n = 3$ vs. $n = 12$: RR 0.24, 95% CI 0.07–0.87) in favour of the heparinised group. Thompson et al.[10] commented on this observed difference: "As this surprising result was serendipitous and outside the original study design, no stratification for cardiac risk factors was available for analysis, but in view of the large numbers in the two categories it is felt that the groups should be comparable." Two other studies did not provide details on MI incidence. Johnston et al. did not observe differences in MI incidence between heparinised and non-heparinised patients (personal communication AW).

Arterial thrombo-embolic complications

Overall incidences of ATEC for all studies are shown in Table 3. In the study by Chinien et al.,[24] embolectomy after completion of surgery was necessary in five patients (8%) from the heparin group and in eight (12%) patients from the no-heparin group. When patients who died intra-operatively were excluded, these figures were 8% for the heparin group versus 14% for the no-heparin group. Other ATECs in both groups were listed as: stroke (4), limb ischaemia (5), bowel ischaemia (8) and paraplegia (2), all showing no significant difference between the heparin and the no-heparin group (All ATECs: $n = 14$ vs. $n = 18$: RR 0.84, 95% CI 0.38–1.87). In the study by Samson et al.,[25] one non-heparinised patient receiving a tube graft died 2 months after operation because of colonic ischaemia and respiratory failure, and another non-heparinised patient developed colonic ischaemia without necessitating surgical treatment. In the heparin group, they found one athero-embolic event that resolved spontaneously without tissue loss. Distal embolectomy was performed in four patients, two from the heparin group and two from the no-heparin group. In summary, there were three (2.9%) ATECs in the heparin group vs. four (2.7%) in the no-heparin group (RR 1.06, 95% CI 0.23–4.84). In the study by Thompson et al.,[10] three (2.1%) patients from the heparin group versus eight (5.8%) patients from the no-heparin group underwent distal embolectomy (RR 0.36, 95% CI 0.09–1.39). Furthermore athero-emboli, responding well to conservative treatment, occurred in four and three patients in the heparin and no-heparin group, respectively – total ATEC: $n = 7$ vs. $n = 11$, 4.8% vs. 7.9% (RR 0.61, 95% CI 0.23–1.62). Burnett et al.[26] reported that six (3.7%) patients from the heparin group suffered distal ischaemic episodes: four cases of micro-embolic trash syndrome involving the feet, treated conservatively, and two with major vessel occlusion treated with embolectomy. Johnston et al.[22] stated in personal communication with no differences in ATEC for both groups.

Meta-analysis

A pooled meta-analysis of the above-described results was considered not justified because of the quality of included studies, heterogeneity in and between studies and detected bias towards the use of heparin.

Results for Endovascular AAA Surgery

Literature search

We found no publications comparing outcomes after EVAR between patients receiving perioperative arterial thrombosis prophylaxis and patients who did not. One study compared outcomes with heparin and bivalirudin (a direct thrombin antagonist) during EVAR.[23]

Characteristics of study

Details are listed in Table 1. The selected study was a retrospective analysis of a prospectively maintained database of 740 consecutive patients treated with elective EVAR for AAA between March 1994 and November 2006 in the USA. Outcomes were compared for 642 patients receiving UFH and 68 using bivalirudin. Procedural outcomes were scored according to the reporting standards for endovascular AAA repair.[27] Major complications, minor and major bleeding complications and the need for transfusions were retrieved. Details on mortality and MI were not reported.

Methodological quality

Details and score for study quality are shown in Table 2. No randomisation was performed for heparin or bivalirudin. The choice of anti-coagulant was left to the discretion of the interventionalist and no specific guidelines were supplied for this choice, thereby creating selection bias. No detailed description of confounders was retrieved from the article.

Heparin and bivalirudin

Heparin was administered i.v. as a bolus of 100 IU kg^{-1} before placement of an arterial sheath and bivalirudin i.v. as a bolus of 0.75 mg kg^{-1} followed by continuous infusion of 1.75 mg kg^{-1} h^{-1} for the duration of the procedure. No (details on) measurements of anti-coagulation values were depicted either for heparin or for bivalirudin.

Operative details

Types of anaesthesia and arterial access differed for both groups: 39 (39.8%) of patients from the bivalirudin group were operated under general anaesthesia compared to 129 (20.1% from the heparin group (RR 1.98, 95% CI 1.25–3.10). Some 48 patients (49%) from the bivalirudin group and 462 (72%) from the heparin group were operated on with regional anaesthesia (RR 0.68, 95% CI 0.44–1.05). Arterial access in the combination of cutdown/percutaneous was used in 12 (12.2%) of patients in the bivalirudin group and in 238 (37.1%) from the heparin group (RR 0.33, 95% CI 0.18–0.62).

Blood loss and blood transfusion

There were no statistically significant differences in bleeding complications between both groups (Table 3).

Overall mortality and myocardial infarction

No details could be retrieved regarding in-hospital or 30-days mortality. These patients are included in the major complications grade 3. There was no statistically significant difference in grade 3 complications between the heparin and bivalirudin groups: 4% versus 2% (RR 0.5, 95% CI 0.12–2.14).

No details on fatal and non-fatal MI could be retrieved from the article. These patients are included in major complications grade 1, 2 and 3. Only grade 1 complications occurred less often in the bivalirudin group: 12.2% versus 25.1% (RR 0.49, 95% CI 0.26–0.92). The definition of grade 1 cardiac complications is: little or no haemodynamic consequences.

ATECs

Only 1 major complication could be attributed to ATEC in the bivalirudin group (1.5%) compared to 12 in the heparin group (1.9%) (RR 0.79, 95% CI 0.10–6.17).

Discussion

Since the introduction of heparin more than 70 years ago for the "prevention of thrombosis when operation for repair of blood vessels is undertaken,"[1] this concept has never been really challenged. Inventories concerning perioperative arterial thrombosis prophylaxis in open reconstructive arterial surgery showed a wide variety of regimens amongst vascular surgeons throughout the world for the past 20 years.[9,14–17] This variety also exists for arterial endovascular procedures.[18,19] To assess the efficacy of this prophylaxis in open or endovascular aorto-iliac arterial surgery, the CAPPA study group from the Netherlands performed a systematic review of the literature on this subject.

For open aorto-iliac surgery, only five studies[10,22,24–26] could be included in this review. The overall methodological quality of the included studies was poor. Only one RCT[10] could be retrieved. Clinical heterogeneity between studies was significant, concerning both studied populations and methods of intervention. All studies used heparin as a prophylactic anti-thrombotic drug. Only two studies reported detailed information about the use and dosage of protamine for the reversal of heparin.[10,25]

Two studies[25,26] reported significantly more blood loss and a longer operation time in heparinised patients treated with tube grafts, and one of these studies[26] found that blood loss increased when heparin dosage increased. Statistically significantly more blood transfusions were needed in heparinised patients compared to non-heparinised patents in one study.[25]

One study[24] (on rAAA) reported a lower operative mortality in heparinised patients (16% vs. 43%: RR 0.37, 95% CI 0.16–0.85). This finding appears heavily biased because particularly unstable patients ended up in the non-heparinised group because their aortas were hurriedly cross-clamped before heparin could be administered. In addition, senior registrars began operations in these patients prior to the arrival of a consultant surgeon. These facts readily could explain the signalled difference in mortality between heparinised and non-heparinised patients in this study. The other four studies[10,22,25,26] did not report statistically significant differences between heparinised and non-heparinised patients for non-fatal MI, fatal MI or operative mortality. However, in the RCT,[10] the combination of fatal and non-fatal MIs proved to be significantly more frequent in non-heparinised patients (8.6% vs. 2.0%: RR 0.24, 95% CI 0.07–0.87). This outcome was, however, outside the original study design and the distribution of cardiac risk factors over both groups was unknown. Therefore, this difference could result from over-presentation of patients prone to cardiac ischaemia in the non-heparinised group. Furthermore, this study excluded patients taking acetylsalicylic acid (ASA), thereby excluding the cardio-protective effect of ASA perioperatively. In all included studies, no statistically significant differences were found for the incidence of ATEC between heparin and no-heparin groups.

A meta-analysis could not be justified, because of the quality of the included studies, the detected heterogeneity in and between studies and the bias found to be present in studies.

No studies comparing heparin with no-heparin were found in the literature for EVAR nor studies comparing another anti-thrombotic than heparin to a no-anti-thrombotic group of patients. The only study that could be included was a retrospective, non-randomised analysis of a small group ($n = 98$) receiving bivalirudin and a larger group ($n = 642$) receiving periprocedural heparin.[23] No significant reduction in bleeding complications or blood transfusions was observed. Further, mortality and incidence of MI and ATEC were not statistically significant different. Thus, a reduction of bleeding complications when using a direct thrombin antagonist (bivalirudin) instead of heparin, as documented for coronary and peripheral endovascular procedures,[28,29] could not be established for EVAR.

The present systematic review has several limitations. A small number of studies were eligible for open AAA surgery and only one for EVAR. Moreover the studies for open AAA surgery were published over a time period of 20 years. In those 20 years, the perioperative care of vascular surgery patients has improved considerably, resulting in better outcomes for AAA patients undergoing surgery. For example, the introduction of statins and the increased use of beta-blockers nowadays in the perioperative period may influence the incidence of MI. The methodological quality of the studies was poor, numbers of patients studied relatively small and there was significant clinical heterogeneity between studies.

Despite these limitations this systematic review showed no sound evidence on the beneficial effect of the prophylactic perioperative use of heparin during open surgery for (r)AAA. This review showed that possible harmful effects of increased operation time, more blood loss and greater transfusion requirements when heparin was used in open surgery could be present. For EVAR, no trial data could be found comparing heparin to no-heparin. Despite promising results of direct thrombin antagonists in cardiovascular surgery and endovascular coronary- and peripheral interventions, no studies could be found on these drugs during open AAA surgery. During EVAR, a direct thrombin antagonist (bivalirudin) showed no clear benefit compared to heparin in one retrospective study. Since more evidence of the efficacy and safety of heparin is clearly needed, the CAPPA study group will promote a multi-centre RCT evaluating the use of heparin versus no-heparin and possibly versus a direct thrombin antagonist before aortic cross-clamping in patients undergoing open elective surgical repair of AAA. The hypothesis of such an RCT could be a reduction of 30% of blood loss, a 50% reduction of blood transfusion and a 50% reduction in bleeding-related wound complications. A power calculation based on these assumptions showed that we would need 197 patients with open AAA repair in each group ($\alpha = 0.05$ and $\beta = 0.10$). For EVAR, a 50% reduction of blood transfusion would require 85 patients per group for heparin or no-heparin.

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None.

Conflict of Interest

None.

References

1 Murray DWG. Heparin in surgical treatment of blood vessels. *Arc Surg* 1940;**40**:307–25.
2 Serious Hazards of transfusion, Annual Reports. The Serious Hazards of Transfusion Steering Group, www.shotuk.org2010.
3 CBO Richtlijn Bloedtransfusie. *Guideline blood transfusion the Netherlands*, www.cbo.nl; 2011.
4 Kroneman H, Eikelboom BC, Knot EAR, de Smit P, Groenland THN, de Maat MPM, et al. Pharmacokinetics of low-molecular-weight heparin and unfractionated heparin during elective aortobifemoral bypass grafting. *J Vasc Surg* 1991;**14**(2):208–14.
5 Holmberg A, Siegbahn A, Westman B, Bergqvist D. Ischaemia and reperfusion during open abdominal aortic aneurysm surgery induce extensive thrombin generation and activity. *Eur J Vasc Endovasc Surg* 1999;**18**(1):11–6.
6 Davies RS, Abdelhamid M, Wall ML, Vohra RK, Bradbury AW, Adam WJ. Coagulation, fibrinolysis, and platelet activation in patients undergoing open and endovascular repair of abdominal aortic aneurysm. *J Vasc Surg* 2011 Sep; **54**(3):865–78.
7 Mabry CD, Thompson BW, Read RC, Campbell GS. Activated clotting time monitoring of intraoperative heparinization: our experience and comparison of two techniques. *Surg* 1981;**90**(5):889–95.
8 Nath FC, Muller DW, Rosenschein U, Ellis SG, Topol EJ. Heparin monitoring during coronary intervention: activated clotting time versus activated partial thromboplastin time. *Can J Cardiol* 1993 Nov;**9**(9):797–801.
9 Wakefield TW, Lindblad B, Stanley TJ, Nichol BJ, Stanley JC, Bergqvist D, et al. Heparin and protamine use in peripheral vascular surgery: a comparison between surgeons of the Society for vascular surgery and the European Society for vascular surgery. *Eur J Vasc Surg* 1994;**8**(2):193–8.
10 Thompson JF, Mullee MA, Bell PR, Campbell WB, Chant ADB, Darke SG, et al. Intraoperative heparinisation, blood loss and myocardial infarction during aortic aneurysm surgery: a Joint Vascular Research Group study. *Eur J Vasc Endovasc Surg* 1996;**12**:86–90.
11 Sobel M, Verhaeghe R. Antithrombotic therapy for peripheral artery occlusive disease: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). *Chest* 2008;**133**:815S–43S.
12 Chaikof EL, Brewster DC, Dalman RL, Makaroun MS, Illig KA, Sicard GA, et al, Society for Vascular Surgery. The care of patients with an abdominal aortic aneurysm: the Society for Vascular Surgery practice guidelines. *J Vasc Surg* 2009;**50**(4 Suppl.):S2–49.
13 Walker TG, Kalva SP, Yeddula K, Wicky S, Kundu S, Drescher P, et al, Society of Interventional Radiology. Clinical practice guidelines for endovascular abdominal aortic aneurysm repair: written by the standards of practice committee for the Society of interventional radiology and endorsed by the cardiovascular and interventional radiology Society of Europe and the Canadian interventional radiology association. *J Vasc Interv Rad* 2010;**21**:1632–55.
14 Assadian A, Senekowitsch C, Assadian O, Eidher U, Hagmuller GW, Knobl P. Antithrombotic strategies in vascular surgery: evidence and practice. *Eur J Vasc Endovasc Surg* 2005;**29**:516–21.
15 Debus ES, Daum H, Wintzer C, Diener H, Schulenburg BM. Perioperativer prophylaxe nach arterieller revaskularisation. *Gefasschirurgie* 2006;**11**: 334–40.
16 Robinson MH, Studley JG, Powis SJ. Anticoagulation in abdominal aortic aneurysm surgery: the approach of vascular surgeons in Great Britain and Ireland. *Eur J Vasc Surg* 1989;**3**:141–3.
17 Moussa O, Jonker L, Joseph T. Marked variation in venous thromboprophylaxis management for abdominal aortic aneurysm repair; results of survey amongst vascular surgeons in the United Kingdom. *Eur J Vasc Endovasc Surg* 2011; **42**(5):591–5.
18 Durran AC, Watts S. Current trends in heparin use during arterial vascular interventional radiology. *Cardiovasc Intervent Radiol* 2012 Jan 13 [Epub ahead of print].
19 Miller DL. Heparin in angiography: current patterns of use. *Radiology* 1989 Sep;**172**(3 Pt 2):1007–11.
20 Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009 Jul 21;**339**. b2700.
21 Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000 Apr 19;**283**(15):2008–12.
22 Johnston KW, Scobie TK. Multicenter prospective study of nonruptured abdominal aortic aneurysms. I. Population and operative management. *J Vasc Surg* 1988 Jan;**7**(1):69–81.
23 Stamler S, Katzen BT, Tsoukas AI, Baum SZ, Diehm N. Clinical experience with the use of bivalirudin in a large population undergoing endovascular abdominal aortic aneurysm repair. *J Vasc Interv Radiol* 2009; **20**:17–21.
24 Chinien G, Waltham M, Abisi S, Smith A, Taylor P, Burnand KG. Systemic administration of heparin intraoperatively in patients undergoing open repair of leaking abdominal aortic aneurysm may be beneficial and does not cause problems. *Vascular* 2008;**16**(4):189–93.
25 Samson RH, Showalter DP. A selective approach to heparin use during elective abdominal aortic aneurysm resection: techniques, precautions, and advantages. *Ann Vasc Surg* 2002 May;**16**(3):279–85.
26 Burnett J, Payne J, Gray-Weale AC, Lusby RJ. Selective use of heparin in aortic surgery. *Aust N Z J Surg* 1988 Oct;**58**(10):811–5.
27 Chaikof EL, Blankesteijn JD, Harris PL, White GH, Zarins CK, Bernhard VM, et al. Reporting standards for endovascular aortic aneurysm repair. *J Vasc Surg* 2002;**35**:1048–60.
28 Singh S, Molnar J, Arora R. Efficacy and safety of bivalirudin versus heparins in reduction of cardiac outcomes in acute coronary syndrome and percutaneous coronary interventions. *J Cardiovasc Pharmacol Ther* 2007;**12**: 283–91.
29 Maclean AA, Pena CS, Katzen BT. Bivalirudin in peripheral interventions. *Tech Vasc Interv Radiol* 2006;**9**:80–3.