

# Prognostic importance of preoperative anti-PF4/heparin antibodies in patients undergoing cardiac surgery

## A systematic review

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### Summary

It was the objective of this study to obtain best estimates of the prevalence of anti-PF4/heparin antibodies in patients not suspected to have clinical heparin-induced thrombocytopenia (HIT) prior to undergoing cardiac surgery and to determine whether preoperative antibody status and antibody class is predictive of postoperative thromboembolic outcomes, non-thromboembolic outcomes, length of stay, and mortality. PubMed and EMBASE online databases were searched up to July 2011, and we included studies involving adults undergoing cardiac surgery examining the relationship between preoperative anti-PF4/heparin antibodies (ELISA) and postoperative clinical outcomes. Five studies involving a combined total of 2,332 patients met our inclusion criteria. Preoperative anti-PF4/heparin antibodies were detected in 5–22% of patients. No study demonstrated an association between preoperative anti-PF4/heparin antibodies and postoperative thromboembolic outcomes or mortality. Three studies demonstrated a statistically significant association between preoperative anti-PF4/heparin antibodies

and length of stay while two showed an association with non-thromboembolic complications. In the one study that examined outcomes by anti-PF4/heparin antibody class, IgM antibodies predicted non-thromboembolic complications and length-of-stay. None of the studies reported prior heparin exposure, and most studies did not examine the relationship of the absolute value of antibody titres (ELISA OD) and risk, nor the incidence of true/clinical HIT in preoperative positive or negative patients. In conclusion, pre-formed anti-PF4/heparin antibodies are common in patients undergoing cardiac surgery, but the available literature does not support that they predict postoperative thromboembolic complications or death. There does appear to be an association between anti-PF4/heparin antibodies and non-thromboembolic adverse events, but a causal relationship is unlikely.

### Keywords

Heparin, anti-PF4/H, antibodies, cardiac surgery

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## Introduction

Unfractionated heparin (UFH, hereafter referred to as heparin) is used in large doses to prevent thromboembolic complications in patients undergoing cardiac surgery while on pump, and at times as part of postoperative anticoagulation regimens. Heparin is a negatively charged polysaccharide that forms multimolecular complexes with a cationic protein, platelet factor 4 (PF4), which are highly immunising (1). Studies have shown that 1–3% of cardiac surgery patients form platelet-activating anti-PF4/heparin antibodies developing a pro-thrombotic adverse drug reaction, immune heparin-induced thrombocytopenia (HIT) (2–4). The highly devastating life- and limb-threatening consequences of HIT are characterised by platelet-activating antibodies and thrombocytopenia, leading to increased rates of arterial or venous thrombosis (30–70%), mortality and hospital costs (5–7).

Heparin is commonly used to treat or to prevent thrombosis in patients with cardiovascular disease and for anticoagulation during invasive procedures, such as coronary angiography and percutaneous coronary interventions. Thus, there is the potential for patients who undergo cardiac surgery to have pre-formed circulating anti-PF4/heparin antibodies, either platelet-activating or non-platelet-activating. While those patients diagnosed as having HIT are at a greater risk for adverse clinical outcomes, particularly thrombosis, it is not yet known if anti-PF4/heparin antibodies alone are independent predictors of thromboembolic or other complications in cardiac surgery patients.

In order to clarify these issues, we performed a systematic review of studies that reported the prevalence of anti-PF4/heparin antibodies prior to surgery and outcomes after surgery. Our specific objectives were two-fold: i) to obtain best estimates of the prevalence of anti-PF4/heparin antibodies in patients prior

to undergoing cardiac surgery, and ii) to determine whether preoperative antibody status in patients not suspected of having clinical HIT, is predictive of postoperative thromboembolic outcomes, non-thromboembolic outcomes, length of stay, and mortality. We also explored whether antibody class is associated with outcome.

## Methods

A protocol detailing the objectives, literature search, study selection criteria, data retrieval and planned analyses was developed.

### Search strategy

We searched PubMed (National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, MEDLINE) up to May 2011 using the terms “platelet factor 4” and “heparin” and “surgery”. We searched EMBASE from the earliest achievable date to July 2011 using the following keyword and subject heading search strategy:

1. exp heparin platelet factor 4 antibody/
2. PF4.mp.
3. antibody.mp. or antibody/
4. exp heparin induced thrombocytopenia/
5. 2 and 3
6. 3 and 4
7. 1 or 5 or 6
8. cardiac surgery.mp. or heart surgery/
9. 7 and 8

We also hand-searched bibliographies of relevant citations.

### Inclusion criteria

We selected studies if they met all of the following criteria: a) included adult patients ( $\geq 18$  years of age); b) included patients undergoing cardiac surgery of any type; c) reported the preoperative prevalence of anti-PF4/heparin antibodies; and d) reported the association between preoperative anti-PF4/heparin antibodies and postoperative outcomes. We excluded duplicate publications, case reports and case series studies. No language restrictions were applied.

We used a hierarchical approach for inclusion of studies based on title, abstracts and if necessary, the full publication. Disagreements among reviewers concerning study eligibility were resolved through consensus.

### Data extraction

Data were extracted in duplicate. Consensus was obtained on issues of disagreement. Extracted data included the number of pa-

tients enrolled in each study, preoperative anti-PF4/heparin antibody status, postoperative outcome event rates, and the association of preoperative antibody status with these postoperative events, including the corresponding summary estimate, 95% confidence intervals (CIs) and p-values.

### Classification of outcomes

We categorised outcomes reported in the individual studies as follows: thromboembolic complications, non-thromboembolic complications, length-of-stay, and death.

### Methodological quality

The following indicators of study validity were collected: the method of patient selection, blinding of clinicians and outcome assessors to the results of laboratory testing, and completeness of follow-up.

### Statistical analysis

When not reported in the publication, unadjusted odds ratios (ORs) were calculated to determine the association between preoperative anti-PF4/heparin antibody status and outcomes. In cases where unadjusted ORs were calculated for a group with zero events, 0.5 events were added to all groups. In studies that categorised antibody status as negative, intermediate or positive, we combined intermediate and negative groups. This approach is consistent with the ELISA manufacturers' recommendations for a single threshold of 0.4 or 0.5 optical density units (ODU).

Due to substantial heterogeneity between studies with regards to their design, methods of antibody measurement, and outcome definitions, we decided not to pool data across the trials.

## Results

### Literature search

Our PubMed search yielded 258 citations, of which 235 were excluded based on title alone. Of the 23 remaining citations, 18 were excluded based on abstract or the full manuscript, leaving five studies for inclusion in the systematic review. A total of 89 citations were identified in the search of EMBASE, of which four had already been selected through the PubMed search. Eleven citations were reviewed in full text format but no additional studies were identified.

## Study characteristics

Study characteristics are summarised in ► Table 1. The five studies selected for inclusion (2–4, 8, 9) were published between 1996 and 2010. The study sizes ranged from 51 to 1,113 patients, and the studies collectively included 2,332 patients. All five were cohort studies. One (9) was retrospective but used an REB-approved consent waiver to include unselected consecutive patients while enrolment in all other studies was restricted to patients who provided written informed consent (2–4, 8). The study by Bennett-Guerrero (3) excluded patients undergoing emergency operations, while the other four studies (2, 4, 8, 9) included both emergency and non-emergency cardiac surgery. Four of the five studies (2, 4, 8, 9) were conducted at a single-centre whereas the study by Bennett-Guerrero (3) involved two centres.

## Patient characteristics

Sixty-one to 83% of patients were male. Three studies (3, 8, 9) included patients undergoing on-pump coronary artery bypass graft (CABG), valve or concurrent CABG/valve procedures, while two (2, 4) included patients that required cardiopulmonary bypass but did not report the type of cardiac surgery.

## Heparin use

All patients received heparin; three studies used porcine heparin (3, 4, 9), one study used bovine heparin (2), and one study did not specify the type of heparin used (8). In the study by Visentin (8), 7/51 patients received low-molecular-weight heparin (LMWH)

(enoxaparin, median dose 280 mg) for surgical anticoagulation. All patients received a preoperative bolus injection of heparin (10,000U in Visentin; 300U/kg in Bauer, Bennett-Guerrero, Kress; amount not specified in Selleng) and additional heparin doses during surgery to maintain activated clotting times of between 400 and 450 seconds. Patients in the Selleng (4) study were treated with either UFH or LMWH after surgery for an unspecified period of time. The patients receiving preoperative UFH in the Visentin (8) study received IV UFH for 1–3 days postoperatively, but no postoperative heparin for the subset of patients administered LMWH. In the Bauer and Bennett-Guerrero studies (2, 3), heparin was not used postoperatively. Kress (9) did not specify whether patients received heparin postoperatively.

## ELISA assays

Two studies used the GTI ELISA assay (8, 9) (GTI Diagnostics Inc., Waukesha, WI, USA), two used the Asserachrom H-PF4 ELISA kits (2, 3) (Diagnostica STAGO, Parsippany, NJ, USA), and one used an in-house assay (8) that had been previously calibrated with commercial assays. The GTI and STAGO assays measured total anti-PF4/heparin antibody titres whereas the in-house assays used by Selleng (4) and the GTI assays used by Visentin (8) measured total antibody titres as well as IgA, IgM, and IgG isotypes independently. Patients were classified into antibody positive and negative groups based on upper limit of normal (ULN) optical density cut-offs, ranging from 0.4 to 0.5 OD units, as per the manufacturers' instructions. Bauer (2) classified patients into positive ( $\geq 0.5$  ODU), intermediate ( $\geq 0.25$  and  $< 0.5$  ODU), and negative ( $< 0.25$  ODU) groups.

**Table 1: Summary of study designs.**

Study	Date	Design/enrollment	Population size	Patient description	Assay	Perioperative heparin exposure
Visentin (8)	1996	Prospective cohort	51	CABG, valve surgery, or both	ELISA HPF4 assay (GTI)	44 patients administered UFH, and 7 patients administered LMWH
Bauer (2)	1997	Prospective cohort, non-consecutive, consenting patient enrollment	111	CPB	ELISA (Stago), Ig (G/A/M), ULN 0.5 OD	Beef-lung heparin, UFH
Bennett-Guerrero (3)	2005	Prospective cohort, non-consecutive, consenting patient enrollment, 2 hospitals (time period not stated)	466	CABG, valve surgery, or both	ELISA (Stago), Ig (G/A/M), ULN 0.5 OD	Bypass: intraoperative porcine UFH; no information provided re: postoperative heparin use
Kress (9)	2007	Retrospective cohort, consecutive (consent waived), single center enrollment (Mar 2002 through Dec 2004)	1113	CABG, valve surgery, or both	ELISA (GTI), Ig (G/A/M), ULN 0.4 OD	Bypass: porcine UFH; no information provided re: postoperative heparin
Selleng (4)	2010	Prospective cohort, non-consecutive, consenting, single-center patient enrollment (Jan 2007 through Dec 2007)	591	CPB	ELISA, combined and class specific, in house, ULN 0.5 OD	Bypass: porcine UFH; all patients also received postoperative UFH or LMWH

CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; ELISA, enzyme-linked immunosorbent assay; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin.

## Clinical outcomes

The five studies reported a wide range of clinical outcomes. Thromboembolic outcomes included stroke, myocardial infarction, peripheral arterial thrombosis/embolism, deep-vein thrombosis, pulmonary embolism and acute limb ischaemia.

Non-thromboembolic outcomes included postoperative infections, haemorrhagic/cardiogenic shock, psychosis, respiratory failure, renal failure/complications, ventilator time >96 hours (h) and gastrointestinal complications.

Length-of-stay (LOS) was reported as time spent in the intensive care unit, total in-hospital time, and as part of a composite outcome that included death.

Death/mortality was reported as a 30-day outcome, in-hospital event, and as a composite outcome with LOS.

## Preoperative prevalence of anti-PF4/heparin antibodies

Preoperative antibody prevalence is summarised in ►Table 2. Antibodies were detected preoperatively in 5–22% of patients. When analysed by antibody class, 6–7% of patients had IgG, 0–6% IgA, and 13–18% IgM anti-PF4/heparin antibodies.

Kress et al. (9) defined antibodies that were detected within four days of surgery as “preoperative” based on the assumption that anti-PF4/heparin antibodies that develop in response to intraoperative heparin exposure are not detectable until after postoperative day 4, an assumption we deemed reasonable and supported by the literature (10). However, 98.6% of testing for preoperative antibodies in the Kress study was performed using blood samples collected before or on the day of surgery.

## Association of antibody status to clinical outcomes

The association between preoperative anti-PF4/heparin antibody status and postoperative clinical outcomes are summarised in ►Table 3.

Anti-PF4/heparin antibodies were not predictive of thromboembolic complications, including thrombosis of any kind, myocardial infarction, or stroke in any of the studies with one exception. In an analysis adjusted for age, presence of peripheral vascular disease, creatinine levels, stroke and urgency of surgery, Kress (9) reported a significant independent association between anti-PF4/heparin antibodies and acute limb ischaemia.

Non-thromboembolic complications were assessed in two of the five studies included in this review (4, 9). Kress (9) reported an independent association between anti-PF4/heparin antibodies and the development of renal failure or the need for dialysis (OR=2.2, 95% CI=1.1–4.3,  $p=0.03$ ), the requirement of >96 h on the ventilator (OR=1.9, 95% CI=0.92–4.1,  $p=0.02$ ) and the development of gastrointestinal (GI) complications (OR=2.9, 95% CI=1.3–6.6,  $p=0.01$ ). Each of these analyses adjusted for age, presence of peripheral vascular disease, ventricular ejection fraction and urgency of surgery. Additionally, creatinine levels were considered for the renal failure and ventilation outcomes; presence of arrhythmia, stroke and congestive heart failure were included in the model for ventilation; and mitral insufficiency, body mass index (BMI) and presence of diabetes were evaluated for GI outcomes. In the study by Selleng (4), the association between total preoperative anti-PF4/heparin antibodies and non-thromboembolic complications was not statistically significant, however when analysed by antibody class independently, IgM isotypes alone (but not IgG nor IgA) were predictive of non-thromboembolic events (OR=1.73, 95% CI=1.15–2.61). This finding was further confirmed when antibody titers were analysed as a continuous variable of IgM ELISA OD values predicting non-thromboembolic events.

Length of stay was evaluated by three of the included studies (3, 4, 9). Bennett-Guerrero (3) reported a statistically significant inde-

**Table 2: Pre-cardiac surgery anti-PF4/heparin antibody prevalence.**

Study	Population size (n)	Antibody positive n (%)	Antibody negative n (%)
Visentin (8)	51	IgG/A/M: 11/51 (22)	IgG/A/M: 40/51 (78)
		IgG (6)	IgG (94)
		IgA (0)	IgA (100)
		IgM (18)	IgM (82)
Bauer (2)	111	IgG/A/M: 21/111 (19)	IgG/A/M: 90/111 (81)
Bennett-Guerrero (3)	466	IgG/A/M: 59/466 (13)	IgG/A/M: 407/466 (87)
Kress (9)	1113	IgG/A/M: 59/1113 (5)	IgG/A/M: 1054/1113 (95)
Selleng (4)	591	IgG/A/M: 128/591 (22)	IgG/A/M: 463/591 (78)
		IgG (7)	IgG (93)
		IgA (6)	IgA (94)
		IgM (13)	IgM (87)

Table 3: Clinical outcomes by preoperative antibody status.

Study	Antibody class	Event category	Outcome	Ab+ events n (%)	Ab- events n (%)	P-value	OR/HR	95% CI
Visentin (8)	IgG/A/M	TE events	Thrombosis	0/11 (0)	0/40 (0)	--	--	--
Bauer (2)	IgG/A/M	TE events	Thrombosis	0/21 (0)	2/90 (2)	--	0.84*	--
		Death	Death, unspecified	1/21 (5)	2/90 (2)	--	2.2*	--
Bennett-Guerrero (3)	IgG/A/M	Death/LOS	Death (in-hosp) and/or LOS > 10 days	20/59 (34)	88/407 (22)	0.0284	1.98	1.06–3.62
Kress (9) <sup>1</sup>	IgG/A/M	TE events	MI	0/59 (0)	1/1054 (0)	>0.2	5.94*	--
			Stroke	4/59 (7)	37/1054 (4)	>0.2	2.00*	--
			Acute Limb Ischemia	3/59 (5)	10/1054 (1)	0.03	4.9	1.2–20.2
		Non-TE events	Renal/Dialysis	12/59 (20)	111/1054 (11)	0.03	2.2	1.1–4.3
			Ventilator > 96h	12/59 (20)	97/1054 (9)	0.02	1.9	0.92–4.1
			GI Complications	9/59 (15)	62/1054 (6)	0.01	2.9	1.3–6.6
		LOS	Post-op LOS	14.0 days	9.8 days	0.05	--	--
			ICU LOS	188.8 hrs	101.2 hrs	0.08	--	--
Death	Mortality (in-hosp)	3/59 (5)	42/1054 (4)	>0.2	1.29*	--		
Selleng (4)	IgG/A/M	TE events		5/128 (4)	25/463 (5)	--	0.72**	0.28–1.89
		Non-TE events		38/128 (30)	115/463 (25)	--	1.29**	0.90–1.87
		LOS		15.5 days	15.1 days	0.70	--	--
		Death, 30 days		3/128 (2)	17/463 (4)	--	0.64**	0.18–2.22
	IgG	TE Events		3/44 (7)	27/547 (5)	--	1.39**	0.42–4.60
		Non-TE Events		11/44 (25)	142/547 (26)	--	0.90**	0.49–1.64
		LOS		15.9 days	15.2 days	0.95	--	--
		Death, 30 days		3/44 (7)	17/547 (3)	--	1.49**	0.41–5.44
	IgA	TE complications		0/36 (0)	30/555 (5)	--	0.03**	0.00–2.27
		Non-TE complications		8/36 (2)	145/555 (26)	--	0.76**	0.36–1.64
		LOS		15.3 days	14.7 days	0.84	--	--
		Death, 30 days		1/36 (2)	19/555 (3)	--	0.91**	0.12–6.79
	IgM	TE complications		3/79 (4)	27/512 (5)	--	0.76**	0.23–2.50
		Non-TE complications		30/79 (38)	123/512 (24)	--	1.73**	1.15–2.61
		LOS		16.4 days	15.1 days	0.021	--	--
		Death, 30 days		0/79 (0)	20/512 (4)	0.09	--	--

Classification of Event Categories: 1) TE (Thromboembolic) Events: stroke, myocardial infarction, peripheral arterial thrombosis/embolism, deep vein thrombosis, pulmonary embolism. 2) Non-TE (non-thromboembolic) Events: post-operative infections, hemorrhagic/cardiogenic shock, psychosis, respiratory failure, renal failure/complications. Abbreviations: Ab, antibody; CI, Confidence Interval; GI, Gastrointestinal; HR, Hazard Ratio; Ig, Immunoglobulin; ICU, Intensive Care Unit; LOS, Length-of-Stay; MI, Myocardial Infarction; OR, Odds Ratio; \*, unadjusted/calculated odds ratio; \*\*, hazard ratio. <sup>1</sup>NOTE: Within the 1114 patients analyzed in the Kress article HIT developed in 36 (3.2%) patients, of which 23 had preoperative anti-PF4/heparin antibodies and postoperative thrombocytopenia, and 13 sero-converted postoperatively with postoperative thrombocytopenia. Outcomes for patients with HIT could not be isolated from non-HIT patients.

pendent association of anti-PF4/heparin antibodies with the composite of in-hospital death and LOS>10days (OR=1.98, 95% CI=1.06–3.62, p=0.0284) after adjusting for the Parsonnet risk score. In an unadjusted analysis, Kress (9) reported an increased LOS in patients that were positive for anti-PF4/heparin antibodies compared to those that were not (p=0.05). Selleng (4) did not find a statistically significant difference between antibody positive and negative patients when considering total anti-PF4/heparin antibodies, but did when considering the IgM isotype alone (p=0.021).

Preoperative antibodies were not significantly associated with mortality in any study.

### Methodological quality

One study (9) enrolled consecutive cardiac surgery patients and included 92.1% of all patients during the study period. No reason

was given for the exclusion of 95 patients. This study also reported that 36 of the 1,114 (3%) patients included developed immune HIT as defined by the presence of anti-PF4/heparin antibodies and thrombocytopenia. In 23 of these patients, the antibodies were detected preoperatively while seroconversion during the course of the study occurred in 13 patients. Only nine of these patients developed subsequent thrombosis. These patients were not removed from the analysis and whether they accounted for higher rates of clinical outcomes was not analysed. The other four studies included only consenting patients (2–4, 8).

Two studies (3, 4) reported that investigators and health-care providers were blinded to anti-PF4/heparin antibody status and in a third study (2) the laboratory measurements were “usually” performed after patient discharge. Visentin (8) did not report on blinding whereas Kress (9) provided clinicians with the results of antibody testing. In this study, one patient with a positive antibody status was treated with lepirudin instead of heparin during cardiac surgery and was therefore removed from the analysis. The duration of follow-up in each of the studies was typically the length of hospital stay, approximately 10 (3, 8) to 14 (9) days. Selleng (4) followed their subjects for 30 days while the study by Bauer (2) did not report a length of follow-up. There were no patients lost to follow-up in any of the included studies.

## Discussion

Our systematic review demonstrated that pre-formed anti-PF4/heparin antibodies are present in as many as 1/5 patients undergoing cardiac surgery and do not appear to predict postoperative thromboembolic complications or mortality. However, preoperative antibodies are predictive of non-thromboembolic complications and length of stay, an association that was shown in one study to be specific to anti-PF4/heparin antibodies of the IgM class. All findings, both associative and non-associative, pertain to patients who have not had and were not suspected of having clinical HIT.

Stribling et al. (11) recently reported a narrative review on association between anti-PF4/heparin antibodies and outcome in cardiac and non-cardiac patients and concluded that there was an association in several high-risk patient populations including haemodialysis patients and those undergoing cardiac surgery. However, Stribling did not specifically examine the association between preoperative anti-PF4/heparin antibodies in patients undergoing cardiac surgery and postoperative outcomes.

The studies in this review demonstrated an unexpected trend towards a statistically significant association of preoperative antibody status with postoperative non-thromboembolic complications. Current knowledge of the mechanisms of antibody-mediated immune HIT does not provide an explanation for a causal relationship between anti-PF4/heparin antibodies and these outcomes. However, compromised patients are believed to be more likely to develop anti-PF4/heparin antibodies than those that are stable (12, 13). Therefore, the presence of antibodies without im-

mune HIT may be a non-specific marker of illness that is associated with adverse outcomes.

The strongest association between anti-PF4/heparin antibodies and thromboembolic events in patients with confirmed HIT appears to be the IgG class of antibodies. Thus, we hypothesised that if there was an association between pre-formed anti-PF4/heparin antibodies and thromboembolic events in cardiac surgery patients it would preferentially involve antibodies of the IgG class. The only study included in our systematic review that analysed antibody classes separately did not show an association between IgG anti-PF4/heparin antibodies and thromboembolic events (4). Rather, this study found that anti-PF4/heparin antibodies of IgM class – an antibody class that is not associated with platelet-activating properties nor with an association with immune HIT (14) – were associated with increased length of stay and non-thromboembolic complications.

The strength of our analyses is that we systematically reviewed the literature and included all relevant published studies that measured preoperative anti-PF4/heparin antibodies in patients undergoing cardiac surgery and explored their association with adverse outcomes.

This review is limited by the modest total number of patients evaluated in the included studies and the fact that only one paper explored the prognostic importance of different antibody classes.

Apart from the study by Selleng (4), the relationship between continuous antibody titre levels (ELISA OD) and outcome was not adequately explored. Selleng's analysis of anti-PF4/heparin ELISA OD levels in a Cox logistic regression model as a continuous variable further confirmed the lack of association between IgG/A antibody classes and postoperative outcomes, whereas IgM antibodies were again associated with an increased risk for non-thromboembolic complications; however the remaining studies did not analyse this. All other studies classified patients into antibody positive/negative groups, or into positive/intermediate/negative groups (2, 3). It is possible that many of the patients deemed to have positive preoperative antibody tests in fact had relatively low (with respects to 0.4–0.5 OD cut-offs) and clinically inconsequential antibody levels, compared to preoperatively positive patients that had postoperative outcomes.

Although this review was designed to examine the relationship of antibodies independent of clinical HIT, two studies reported the onset of clinical HIT (Kress and Selleng). While Kress reported the development of HIT in 3.2% of patients, only 0.5% of patients within the Selleng study were reported to have typical-onset HIT (4, 9). The 3.2% rate of HIT in the Kress paper is likely overstated, reflecting their definition of HIT as a platelet drop of >50% at any point after baseline, whereas Selleng defined HIT as the same platelet drop specifically between postoperative days 5–10, reporting a more likely incidence rate of 0.5%.

Furthermore, in the absence of adjusted analyses, it is unclear from the studies that demonstrated an association between anti-PF4/heparin antibodies and non-thromboembolic events whether the antibody test results provide incremental prognostic information compared with known clinical predictors of outcome.

We conclude that there is currently no justification for preoper-

ative testing for anti-PF4/heparin antibodies in the majority of patients undergoing cardiac surgery, specifically those not suspected of having clinical HIT. Even if such antibodies do indeed correlate with increased length-of-stay and non-thrombotic complications, the lack of any plausible association with HIT infers that substituting heparin with a non-heparin anticoagulant for routine use during cardiac surgery is unlikely to alter outcomes. This differs greatly from patients believed to have clinical onset HIT, where changes in anticoagulation therapy and patient management are warranted. Physicians should refer to ACCP consensus guidelines on how to best approach and manage these patients (15, 16).

Future studies that explore this question should analyse anti-PF4/heparin antibodies by class and should also examine whether there is a correlation between antibodies and other prognostic markers, such as C-reactive protein, that would support the conclusion that the reported association with non-thromboembolic complications is a marker of inflammation or other characteristics of sicker patients. As antibody titre OD levels may be more informative at predicting risk than cut-offs (17, 18), investigators may wish to examine the relationship of anti-PF4 antibodies and risk along a continuous scale. It may also be worth investigating whether differences exist in formation of antibodies and complication rates between bovine and porcine heparin, as proposed by Aquino et al. (19).

#### Conflict of interest

T. E. Warkentin has received lecture honoraria from GlaxoSmithKline, Pfizer Canada and Sanofi-Aventis and has provided consulting services to and/or received research funding from Canyon Pharmaceuticals, Gen-Probe GTI Diagnostics, GlaxoSmithKline and Paringenix, and has provided expert witness testimonial relating to HIT. J. W. Eikelboom has received honoraria and/or research support from companies that develop/market antithrombotic drugs incl. AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Johnson&Johnson, Pfizer and Sanofi-Aventis. None of the other authors declares any conflict of interest.

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