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The association of anti-platelet factor 4/heparin antibodies with early and delayed thromboembolism after cardiac surgery

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Abstract

Background—Heparin induced thrombocytopenia (HIT) is a prothrombotic response to heparin therapy with platelet activating, anti-PF4/heparin antibodies leading to thrombocytopenia associated with thromboembolism.

Objective—We tested the hypothesis that anti-PF4/heparin antibodies are associated with thromboembolism after cardiac surgery.

Methods—This multi-center, prospective cohort study collected laboratory and clinical data up to 30 days after surgery and longer-term clinical follow up. The primary outcome variable combined new arterial or venous thrombotic complications (TEC) with all-cause death until 90 days after

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Trial registration: Duke IRB Protocol #00010736

ADDENDUM

I. J. Welsby was the site PI and prepared the manuscript. E. F. Krakow designed the study. J. A. Heit, E. C. Williams, S. Bar-Yosef, and S. Martinelli were site PIs. G. M. Arepally performed laboratory analysis. D. F. Kong was responsible for statistical design and interim analysis. I. Dhakal and W.-W. Liu were responsible for statistical analysis and data management. J. Kirscher was the PI for the data coordinating center and T. L. Ortel was the overall PI and was responsible for study design and manuscript preparation.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

surgery. Laboratory analyses included platelet counts and anti-PF4/heparin antibody tires (GTI ELISA, Waukesha, WI), with a confirmatory excess heparin step and serotonin release assay. Chi-squared testing was used to test the relationship between our outcome and HIT antibody seropositivity.

Results—Initially, 1021 patients enrolled between August 2006 and May 2009, follow-up was completed in December 2014. Seropositivity defined by OD > 0.4 was common, almost 20% preoperatively, over 30% by discharge and over 60% by Day 30. Death (1.7% within 30 days) or TEC (69 total) was more likely if seronegative (OD < 0.4), but defining positive by OD > 1.0 or including an excess heparin confirmatory step resulted in equal incidence of death or TEC whether seronegative or seropositive. Incorporating the serotonin release assay for platelet activating antibodies did not alter these findings.

Conclusions—Seropositivity for anti-PF4/heparin antibodies does not increase the risk of death or thromboembolism after cardiac surgery. Screening is not indicated and seropositivity should only be interpreted in the context of clinical evidence for HIT.

Keywords

Thrombocytopenia; heparin induced thrombocytopenia; thoracic surgery; thrombosis; thromboembolism

INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is one of the most clinically important drug-induced complications in hospitalized patients. This paradoxical, prothrombotic response to anticoagulant therapy is an immunologic condition in which antibodies to a complex of endogenous platelet factor 4 (PF4) and exogenous heparin activate platelets, leading to aggregation, thrombocytopenia, and, potentially, thromboembolic complications [1,2]. Treatment requires the cessation of heparin and initiation of an alternative anticoagulant, as symptomatic arterial or venous thrombosis associated with a high mortality may develop in a third to half of the patients with HIT who present with isolated thrombocytopenia [3–5].

Seropositivity to PF4/heparin complexes in cardiac surgery patients is common [6–9]. The actual incidence of HIT in patients undergoing cardiac surgery, however, is reportedly much lower, typically 0.5% to 1.8% [10–12]. Platelet count profiles may be helpful in determining the likelihood of HIT in a patient with thrombocytopenia following cardiopulmonary bypass surgery [13], but this has not been consistently observed [11]. This complicates the diagnosis of HIT and potentially exposes patients to hemorrhagic risks if they are treated with less familiar, non-heparin anticoagulants to treat false positive cases of HIT. However, anti-PF4/heparin antibodies in the absence of thrombocytopenia may not be entirely benign. For example, elevated antibody levels are associated with myocardial infarction at 30 days in non-thrombocytopenic patients presenting with acute coronary syndromes [14], arteriovenous fistula thrombosis in non-diabetic hemodialysis patients [15] and increased likelihood death or prolonged hospitalization after cardiac surgery, [16] although direct causality remains unproven. Still, heparin remains the anticoagulant of choice for over 250,000 cardiac surgeries performed in the US each year [17]. Up to half of these patients

will develop anti-PF4/heparin antibodies, and up to 4,500 are projected to develop HIT each year. While previous studies suggest an independent thrombotic risk from seropositivity [18], it remains essential to critically evaluate the relationship between anti-PF4/heparin antibodies and thromboembolism in a population that reflects current clinical and laboratory practice, and is adequately powered to evaluate uncommon thromboembolic events.

The overall aim of our study is to prospectively determine the time-course of anti-PF4/heparin antibody production and their relationship to thromboembolic events, from the day of surgery to 3 months after surgery, and long-term survival. These data will allow us to definitively test the hypothesis that anti-PF4/heparin antibodies are associated with thromboembolism and reduced survival after cardiac surgery.

METHODS

Study Population

All patients undergoing cardiac surgery requiring cardiopulmonary bypass with heparin anticoagulation were eligible for study. Exclusion criteria included planned post-operative anticoagulant therapy during the hospital stay with warfarin, therapeutic dose low-molecular weight heparin, or therapeutic unfractionated heparin. The study was approved at the Institutional Review Boards at each participating site, and written informed consent was obtained from all participants.

Study Design and Measurements

The multicenter, prospective cohort study was conducted through the Rare Thrombotic Diseases Consortium (ClinicalTrials.gov #NCT00237328), and patients were enrolled at five participating centers (Duke University Medical Center, Durham Veterans' Administration Medical Center, Mayo Clinic, the University of Wisconsin, and the University of North Carolina). Lysine analog anti-fibrinolytic agents were routinely used at all institutions.

Information collected at baseline included patient characteristics (including self-reported race and ethnicity), risk factors for thrombosis (including race), preoperative co-morbidities and operative details. Subsequently, information including all thrombotic events, transfusions, details of hospital readmissions, platelet counts, and utilization of antithrombotic medications in the postoperative setting was collected daily during hospitalization, then at the postoperative Day 30 and Day 90 follow-up time points. These collections were standardized by using a structured interview format with detailed questionnaires.

Collected data were transferred to an online data entry form by the staff member conducting the interview or test. Unique, de-identified study subject information was transmitted via encrypted virtual private network to a centralized, password protected database housed at the Data and Technology Coordinating Center (University of South Florida, Tampa, Florida) designed by the Rare Diseases Clinical Research Network. Online forms incorporated checks to minimize transcription and omission errors, including internal validity checks for reasonableness and consistency. Regular assessments of data quality were performed and automatically generated reminders helped keep follow-up evaluations within timeframe. All

outcome events were independently reviewed and coded by two independent reviewers to define and assign a date to an event. Strict case definitions were used to minimize reviewer discordance, which was arbitrated by the PI without knowledge of laboratory or other patient data.

All deaths and alternative anitcoagulant use in this period were independently adjudicated for their potential relationship to complications associated with anti-PF4/heparin antibodies.

Laboratory samples were collected at baseline, Day 5 (pre-discharge), and Day 30, processed, and stored at −80°C until testing was performed centrally at Duke University. The anti-PF4/heparin ELISA was performed using the Enhanced GTI kit, which detects IgG, IgM, and IgA anti-PF4/heparin antibodies (GTI, Waukesha, WI); specific IgG isotype assays were not commercially available at the time the study was open. A 'high-heparin' confirmatory test was performed on all samples with an absorbance optical density (OD) > 0.40, as previously described, and a positive result was defined as >50% inhibition of binding [19]. Data analysis was also performed using an OD cutoff of >1.0 units, which has been reported to increase the specificity of this assay [20]. Serotonin release assays were performed on samples from patients who were seropositive by both antibody titer and heparin confirmatory step, and reported as previously described [21].

Outcome Measures

The primary, combined end-point was all-cause death and/or new venous or arterial thromboembolic complications (TEC), including miscellaneous events compatible with HIT, occurring from the time of surgery up until 90 days after surgery. Informed consent included permission to interview next of kin/health care power of attorney and review the medical record to determine cause of death. Long-term follow-up was obtained from the Duke Death Registry that uses medical records and the National Social Security database as sources.

Statistical Analysis

A sample size of 800 patients was estimated to detect a 3% difference in thromboembolic events, assuming a 2 to 10-fold increased risk attributable to seropositivity and a 25–50% incidence of seropositivity. After the first 400 subjects had completed the protocol, an analysis blinded to antibody status determined outcome rate, re-estimated sample size and confirmed our original estimate of 800 patients requiring complete follow-up data. Assuming an attrition rate of 20%, we targeted enrollment of over 1000 patients.

Demographic data and other characteristics are described as numbers and percentages and their distribution as mean +/− standard deviation or median with interquartile range, as appropriate. The evolution of antibody status with time complicated a "time to event" analysis; therefore, the Chi square statistic was used to test the relationship between death or TEC, and antibody status, as defined by ELISA, OD, heparin confirmatory testing and the serotonin release assay. The laboratory value (positive/negative) preceding an event (if yes) or that preceding the last follow-up (if no) was related to outcome (yes/no). A p-value of 0.05 was considered statistically significant and no adjustment was made for multiple comparisons. Kaplan-Meier curves were drawn to demonstrate the effect of seropositivity on survival; Cox proportional hazards modeling, adjusted for Euroscore mortality risk, and

calculated the hazard ratio associated with seropositivity for those with available laboratory data at day 30 and evaluable data to calculate Euroscore.

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RESULTS

A total of 1030 eligible patients were enrolled between August 2006 and May 2009. Eight patients withdrew from the study, and data from one patient were missing. Complete demographic information was available for 990 patients (Table 1). Missing outcome (n=18) or laboratory (n=26) data resulted in a primary analysis dataset of 946 patients, which excluded 4 patients suffering death or TEC (Figure 1). The patient demographics differ little based on HIT antibody status, although seronegative patients had a higher incidence of previous arterial thrombosis, hormone replacement therapy or cardiac catheterization (Table 1). The average age of all patients with complete demographic data was 62 ± 12 years, and 74.6% of participants were male. Overall, 75% of patients underwent coronary artery bypass grafting (CABG). The remainder underwent more complex cardiac surgery; there were 6 reoperations, with 4 performed for internal bleeding. In the post-operative period, prophylactic heparin was administered to 39 patients (4.8%) and therapeutic heparin to 41 patients (5.1%).

Outcome measures

Up to 3 months after surgery, there were 17 deaths (1.7%) and 69 TECs affecting a total of 78 patients, as detailed in Table 2. One death was adjudicated as possibly HIT related and the remainder was considered unrelated. Using the standard, low titer cut-off (OD > 0.4), 8 of 17 patients who died were seropositive and the remaining 9 were seronegative. The Day 30 anti-heparin/PF4 antibody result in the patient who died with possible HIT was 0.46 and the two patients with confirmed thromboembolism who died were both seronegative prior to their deaths.

Of the 69 thromboembolic events, 3 (4.3%) occurred before postoperative day 5, classifying them as early complications. Four patients suffered pre- and post-discharge TECs and two suffered multiple TECs, one of whom died. While most patients (37/69 or 53.6%) with a TEC were seropositive, the high prevalence of a positive antibody titer led to no significant association between seropositivity and TEC (see Table S1).

Seven patients were treated with a parenteral, non-heparin anticoagulant in the postoperative setting (4 with bivalirudin, 2 with argatroban, and 1 with fondaparinux). Subsequent adjudication by study personnel of non-heparin anticoagulant use in these 7 patients (see Table S2) determined that 4 cases were unrelated, 1 was unlikely, 1 was probably, and 1 was definitely related to HIT. Day 30 ELISA optical densities for the latter 2 patients were 2.19 and 0.62, respectively.

Laboratory Testing

Seropositivity, when defined as an OD >0.4, was seen in the majority of patients by Day 30 (613 of 946, 65%). The more stringent definitions of OD > 1.0, OD > 0.4 with > 50% excess heparin confirmatory step, and OD > 1.0 with > 50% excess heparin confirmatory step generated a positive test result in 216 of 946 (23%), 466 of 927 (50%; 2% missing) and 184 of 942 (20%; 0.4% missing), respectively. The evolution of antibody status is illustrated in Figure 2, demonstrating how common a positive result is using the definition of OD > 0.4. The relationship between the 4 definitions of a positive anti-PF4/heparin antibody test and clinical events are detailed in Table S1

Based on TEC event timing, 26 patients sustained their TEC after Day 30, using Day 30 results as their index laboratory assay, 45 sustained their TEC between days 5 and 30, using Day 5 laboratory data, and 3 sustained their TEC before Day 5, using their preoperative laboratory data to test for an association between anti-heparin/PF4 antibodies and death or TEC. Of note, 127 patients who were missing the Day 30 results were included in the analysis dataset by evaluating Day 5 as index laboratory tests and the subsequent Day 5-Day 30 follow-up period for evaluation of events.

Baseline platelet counts were 287 (+/−102) $x10^9$/l with a postoperative nadir of 130 (+/−54) $x10^9$/l, a 54% decrease. Similar platelet count patterns were seen for seronegative and seropositive patients (supplemental data Fig S1). Patients experiencing a TEC displayed a similar platelet count pattern to the remainder (data not shown).

Chi-squared testing using 2×2 tables constructed from antibody status positive/negative and clinical event yes/no identified that 11% of those with an OD < 0.4 suffered death or TEC, while 6% of those with an OD > 0.4 suffered death or TEC (p = 0.013). In contrast, there were no significant relationships identified between events (death and/or TEC) and anti-PF4/heparin antibody test status when this was defined as high titer (OD > 1.0) or a heparin confirmatory step was added to a low or high positive titer (see Table S1). The serotonin release assay was performed on a sub-set of patients positive by both titer (OD > 0.4) and heparin confirmatory step and did not differentiate between those who subsequently suffered death and/or a TEC (data not shown).

Long Term Outcomes

This pattern persisted during follow-up. Post-hoc, long term follow-up data were available for 669 patients with D30 antibody titers, with matching Euroscores in 540 patients. The average duration of long-term follow up was 3.3 years for non-survivors and 6.7 years for survivors. Figure 3 illustrates reduced survival in seronegative patients with a hazard ratio [95% CI] for death of 1.77 [1.18–2.64] compared to those seropositive (OD > 0.4), after adjusting for Euroscore mortality risk (p=0.0053). This significant association between seronegativity (seropositive if OD > 0.4) and reduced survival was only present for this low titer definition (see Table S3).

DISCUSSION

We prospectively evaluated early and delayed thromboembolic events and long-term survival after cardiac surgery. Seropositivity was defined as either low titer (OD>0.4), high titer (OD > 1.0), heparin dependent (reduction in antibody/antigen binding following addition of excess heparin) or capable of activating platelets (SRA reactivity), yet the only association we found was with low titre ***seropositive*** status (OD > 0.4) and a ***lower*** incidence of death or thromboembolic events. This unexpected finding may be explained by the confounding effect of a greater incidence of prior arterial thrombosis, actively treated cancer and hormonal therapy usage in the seronegative group, and was not investigated further. Therefore, in the absence of a clinical suspicion for HIT, we reject the hypothesis that early or late thromboembolism is associated with the development of anti-PF4/heparin antibodies after cardiac surgery.

This is currently the largest prospective series designed to relate pre-defined thromboembolic events to the evolution of the perioperative anti-PF4/heparin antibody response. In keeping with our findings, smaller, prospective series (n > 200 but < 500) have described a similar incidence of preoperative and early postoperative anti-PF4/heparin antibodies [6,7,9,22] that are also unrelated to all-cause thromboembolism. Later in the postoperative period, the 70% seropositivity incidence we describe after 4 weeks is consistent with the 52% incidence of anti-PF4/heparin antibodies previously measured 6 weeks after surgery reported by Gluckman, et al [9]. They found no relationship between antibodies and evidence of early saphenous vein graft thrombosis that they observed in a third of the 368 patients.

Notably, a prospective study by Mattioli et al reported that anti-PF4/heparin antibodies in the early postoperative period conferred considerably increased risk of thrombotic events for up to one year [18]. However, the rates of thromboembolism and mortality in that series greatly exceeded those we report, complicating comparison of the two studies. Retrospective series have also reported an increase in thrombotic complications associated with HIT limited to pulmonary embolism [23] or intracardiac thrombosis diagnosed by echocardiography [10], but anti-PF4/heparin antibodies were only measured if clinically indicated in these studies. In contrast, we systematically tested for anti-PF4/heparin antibodies in all patients regardless of clinical suspicion for HIT.

Antibody status

The definition of a “positive” anti-PF4/heparin antibody test remains controversial. Antibodies represent a polyclonal response to the complex antigen formed by the binding of the cationic platelet factor 4 protein, released from the alpha granules of activated platelets, and the glycosoaminoglycan moieties of heparin, producing IgA, IgG and IgM isotypes. Most commercially available anti-PF4/heparin antibody ELISA kits detect all 3 isotypes, while antibodies capable of activating platelets are typically of the IgG isotype [24–27]. Lack of isotype specificity may reduce the overall specificity of a positive test [27,28], although Selleng, et al [22] noted no association between pre- or post-operative IgG antibodies and thromboembolism but rather an association between IgM antibodies and non-thrombotic complications after cardiac surgery. Larger studies to confirm this relationship

between IgG antibodies and outcomes would still be worthwhile. This possible pro-inflammatory link seems plausible, as trauma, and the accompanying inflammatory response, promotes anti-PF4/heparin antibody production in the postoperative period [29]. The intense inflammatory stimulus of cardiopulmonary bypass may act as an adjuvant, promoting the formation of non-pathologic antibodies that neither activate platelets nor lead to HIT but, rather, are a non-specific epiphenomenon of a pro-inflammatory state.

The serotonin release assay identifies only platelet activating antibodies and is regarded as a gold standard test for pathologically relevant anti-PF4/heparin antibodies [30,31]. A positive serotonin release assay is associated with a high likelihood of true HIT, including thrombotic complications, when clinical suspicion of HIT exists, but is typically unavailable to clinicians in a timely manner [32,33]. However, in asymptomatic patients recovering from cardiac surgery, we found no association between a positive serotonin release assay and all-cause death or thromboembolism.

Thrombocytopenia Incidence rates of HIT up to 5%, have been described after retrospective study [34], but we observed a lower incidence of HIT, similar to recent, prospective studies [11,23,35]. We did not combine patterns of postoperative thrombocytopenia [36,37] with anti-PF4/heparin antibody results to diagnose HIT retrospectively; the HIT episodes we report were diagnosed by the clinical team, as study related ELISA results were not available at the time of hospitalization. However, we found that platelet counts did not differ between those who did or did not develop either all-cause thromboembolism or anti-PF4/heparin antibodies. (Fig S1).

Limitations

One limitation of our study design and analysis was the relatively low incidence of thromboembolism requiring caution when extrapolating our findings to higher risk cases or those requiring obligatory, postoperative anticoagulation. Determination of thromboembolic events relied on clinical diagnoses by the attending physicians, not by sensitive imaging such as duplex ultrasound or transesophageal echocardiography [10]. While only used in this study if clinically indicated, routine imaging may have detected more thrombotic complications, some of which may have only become clinically evident after our 90 day follow-up, or remained occult. Direct thrombin inhibitor use was infrequent (0.8%) and unlikely to substantially reduce event rates; only one of these patients experienced HIT related thromboembolism. However, the possibility of Type II error from a low event rate does not negate our findings, as gross underpowering of the study is unlikely. Evaluation of over 800 patients approximates the annual caseload of a major cardiac surgery program, yet not even a trend towards an association between anti-PF4/heparin antibodies and thromboembolism was seen.

The pathogenesis of HIT has been extensively studied and well described [5,38]; our data do not question that anti-PF4/heparin antibodies are the agent of HIT and can lead to thrombosis. However, it seems evident that the anti-PF4/heparin antibodies commonly observed after cardiac surgery are not associated with early or delayed thromboembolism. They do not, therefore, stand alone as a risk factor for thromboembolism, in contrast to associations described after acute coronary syndrome [14] or during dialysis [15]. It is

plausible that the almost ubiquitous use of aspirin [39] after cardiac surgery interrupts the pathogenesis of HIT by altering platelet factor 4 release, anti-PF4/heparin antibody binding or platelet activation [40,41]. While antiplatelet agents do not universally prevent HIT [42], their use may explain why anti-PF4/heparin antibodies do not predict graft thrombosis during dialysis [43] or after peripheral vascular surgery [44] and are also not associated with thromboembolism after cardiac surgery.

The American College of Chest Physicians Consensus Conference Guidelines (9th edition) recommends that routine testing for anti-PF4/heparin antibodies before cardiac surgery should be avoided and that a diagnosis of HIT should be considered if the platelet count falls by more than 50% between days 5 and 14 following initiation of heparin therapy [30]. Our data confirm that anti-PF4/heparin antibody seropositivity is common in the postoperative period. Because postoperative thrombocytopenia is also common after cardiac surgery, careful clinical evaluation of platelet profile and the timing of HIT antibody testing is needed to avoid a false positive diagnosis of HIT [11,23,33,45].

In conclusion, a positive polyclonal anti-PF4/heparin antibody ELISA following cardiac surgery is common but does not predict future thromboembolism. Treating an incidental positive test is, therefore, unnecessary in the absence of a clinical diagnosis of HIT and screening all thrombocytopenic cardiac surgery patients for anti-PF4/heparin antibodies is not warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

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Essentials

- We evaluated antibody status, thromboembolism and survival after cardiac surgery.
- Positive antibody tests are common – over 50% are seropositive at 30 days.
- Seropositivity did not increase thromboembolism or impair survival after cardiac surgery.
- Results show heparin induced thrombocytopenia antibody screening after surgery is not warranted.

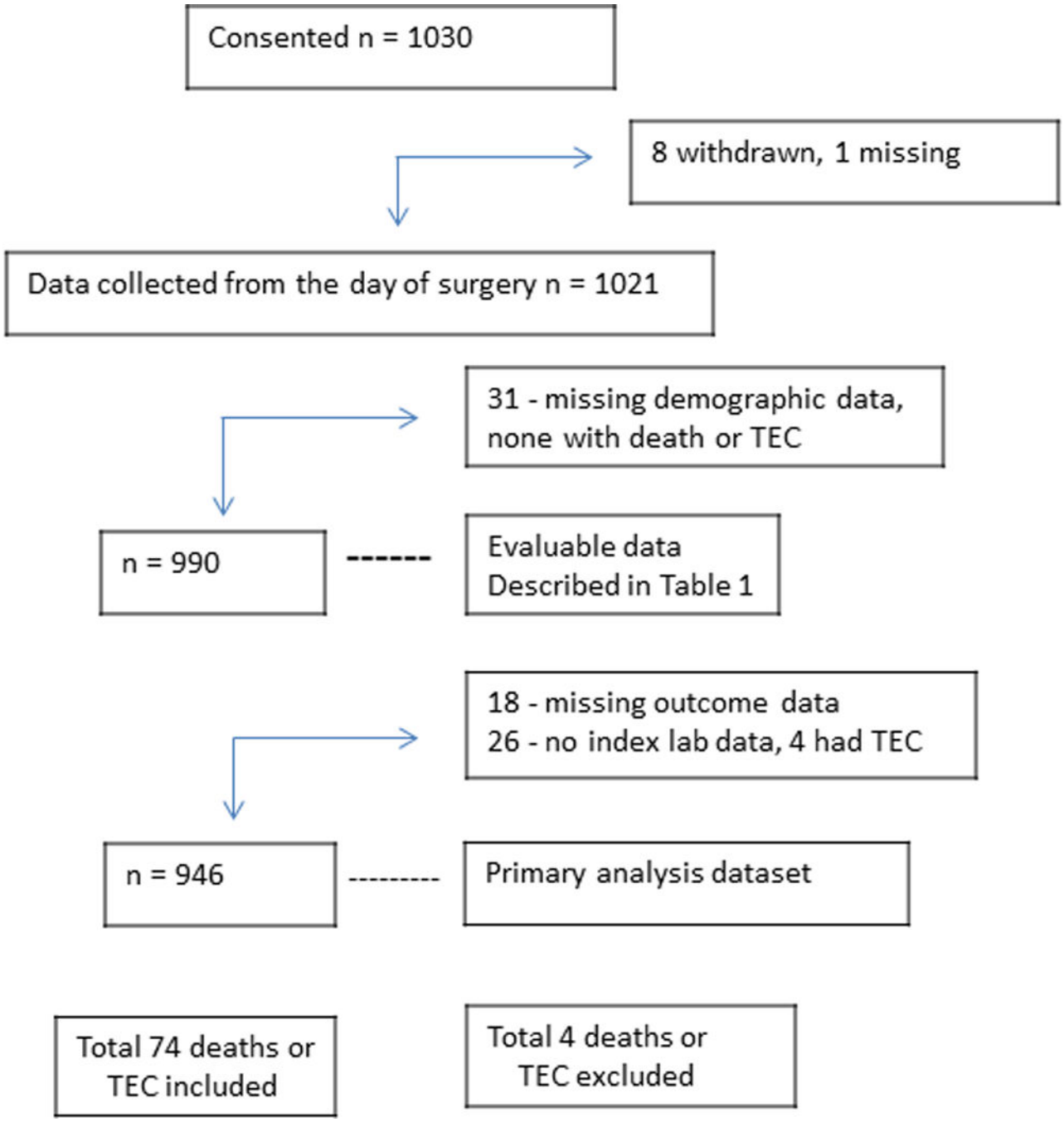

Figure 1.

The primary analysis dataset included only patients with evaluable demographic, laboratory and outcome data (n=946). The index value is the laboratory test preceding an event, or the D30 blood draw, if no event occurred. Note that if a patient had one or more TEC, this is counted as 1 event in this figure.

Abbreviations: TEC, Thromboembolic complication; D30, The study timepoint approximately thirty days after surgery; D5, The study timepoint approximately five days after surgery; PRE-OP, The preoperative study timepoint.

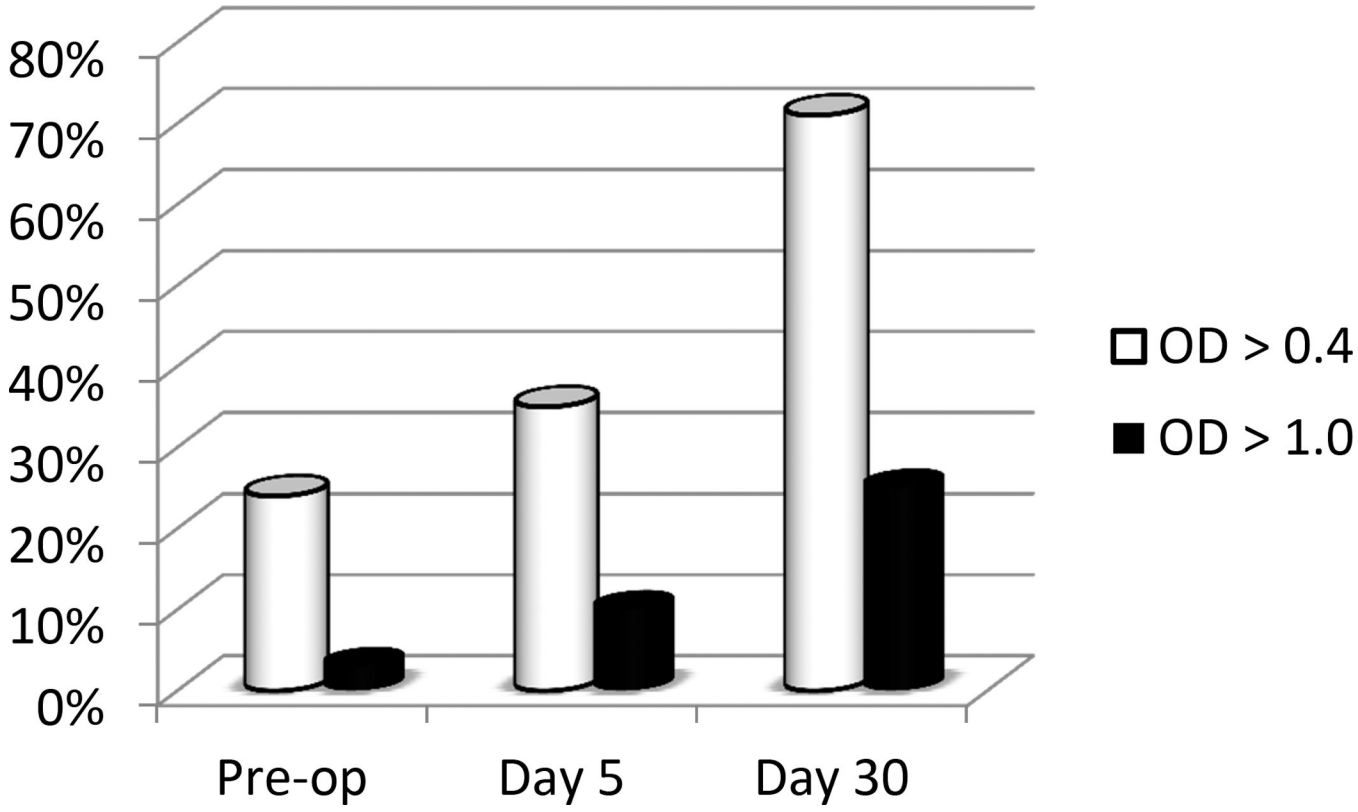

Figure 2.

This figure depicts the percentages of patients testing seropositive by low titre (OD > 0.4) and high titre (OD > 1.0) anti-PF4/heparin antibody definitions at preoperative, postoperative day 5 and postoperative day 30 timepoints. Adding a confirmatory step of heparin dependent binding (>50% reduction in optical density after the addition of excess heparin) reduces the number of seropositive patients by approximately one third in the low titre and one quarter in the high titre columns.

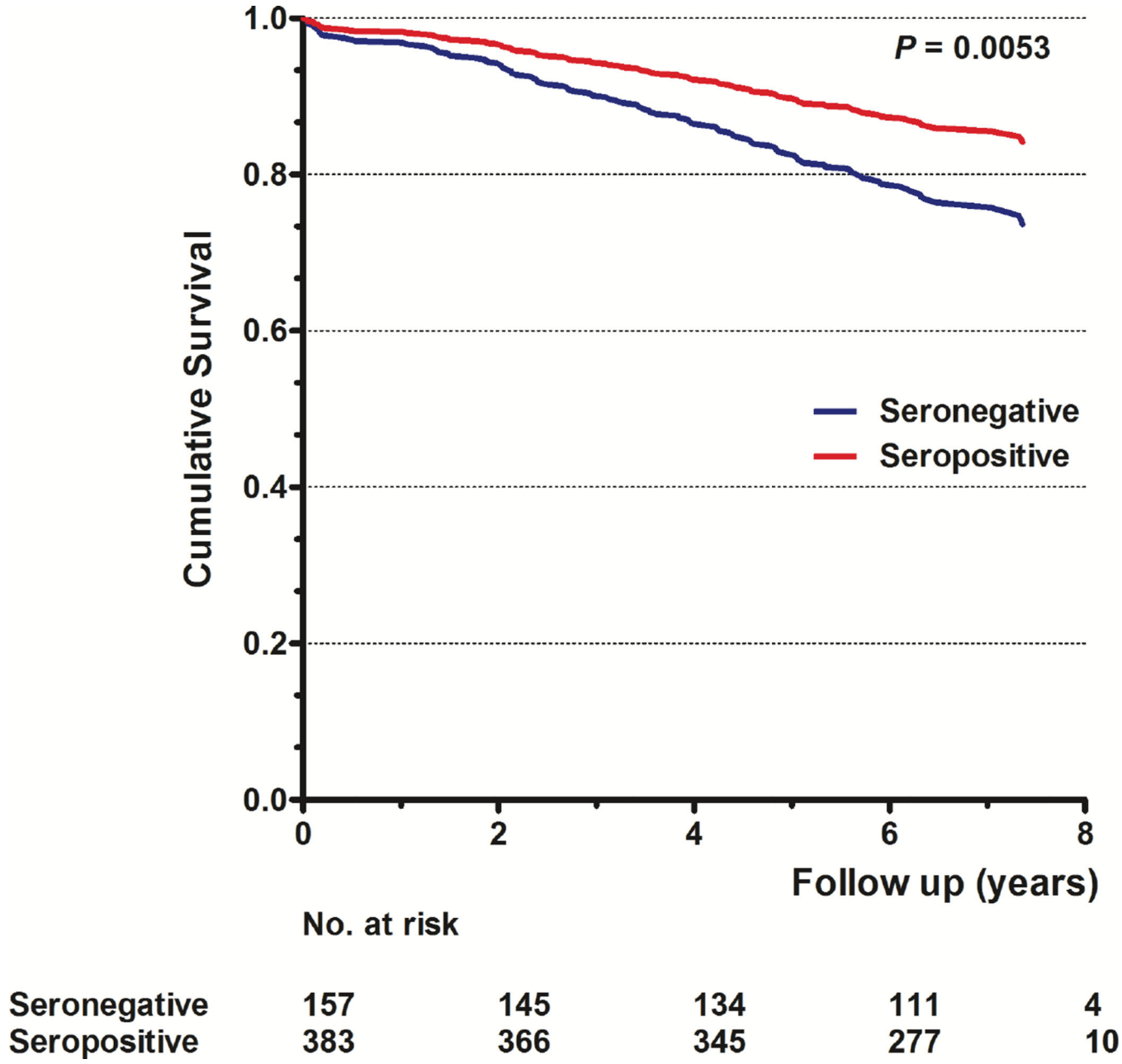

Figure 3.

This survival curve is based on the Cox proportional hazards model, adjusted for the Euroscore mortality risk, and illustrates the improved survival in patients seropositive (OD > 0.4) after surgery.

Table 1
Patient characteristics by anti-PF4/heparin antibody status

Characteristics of the study population, including prior anticoagulant exposure, mostly expressed as the number and percentage of the total with the listed characteristic. Positive antibody status is defined as an OD > 0.4 either pre-event or at the follow-up visit 30 days after surgery.

Demographics	**Negative (n=363)**	**Positive (n=627)**	**P value**
Age (mean+/− SD)	62.5 (11.7)	60.7 (11.8)	0.06
Gender (% female)	25.1	28.6	0.24
Race			
African American	11.0	13.6	0.25
Native American	3.9	4.9	0.43
White	85.4	81.5	0.11
Hispanic ethnicity	1.4	1.4	0.94
Body mass index (kg/m^2)	28.8 (6.2)	29.4 (5.8)	0.15
Co-morbidities/risk factors			
Diabetes	35.2	36.1	0.79
Hypertension	73.7	71.9	0.55
History of cancer	19.3	15.8	0.16
In remission	16.5	14.8	0.48
Undergoing therapy	2.8	1.0	0.03
Smoker			
Current	11.6	11.2	0.85
Former	55.1	53.6	0.64
Hypercholesterolemia	72	69	0.33
End stage renal disease (kidney failure)	11.1	9.9	0.57
Prior hemodialysis graft thrombosis	33.3	0	0.94
Hormone replacement or oral contraceptive*	9.9	3.9	0.05
Miscarriage	25.3	22.7	0.64
Previous MI	42.0	36.1	0.07
Previous stroke	9.9	9.1	0.67
Previous HIT diagnosis	0	0.5	0.19
Enoxaparin or dalteparin	8.0	7.7	0.85
Intravenous heparin	41.3	38.3	0.34
Any prior venous thrombosis	5.0	3.5	0.26
Any prior arterial thrombosis	47.1	39.2	0.02
Current warfarin use	2.5	2.2	0.80
Preoperative			
Prior cardiac surgery	6.1	6.1	0.99
Prior cardiac catheterization	96.4	92.4	0.01

Demographics	Negative (n=363)	Positive (n=627)	P value
Prophylactic anticoagulant use	21.6	19.0	0.32

Abbreviations used include: SD, Standard deviation; MI, Myocardial infarction; HIT, Heparin induced thrombocytopenia; LMWH, Low molecular weight heparin; UFH, Unfractionated heparin; OD, Optical density.

Table 2

Deaths and thromboembolic events

During the study period, a total of 17 deaths (Section A) and 69 thromboembolic events (Section B) were sustained by 78 patients. Events are segregated into the segments of the study during which they occurred (from enrollment to Day 5; from Day 5 to Day 30; and from Day 30 to Day 90).

A. Deaths	
Timing	**Cause of Death**
Before Day 30 (n=6)	Cardiac arrest (n=1) Cardiac failure (n=1) Complications of diabetes (n=1) Renal failure (n=1) Trauma-induced subarachnoid hemorrhage (n=1) Unknown (n=1)
Days 30–90 (n=11)	Cardiac arrest (n=1) Cardiac failure (n=1) Myocardial infarction (n=1) Malignancy, respiratory failure (n=1) Sepsis (n=2) Ruptured thoracic aortic aneurysm (n=1) Unknown (n=4)
B. Thromboembolic Events	
Before Day 5 (n=3)	Peripheral arterial thrombosis and VTE (n=1) Thrombotic stroke/TIA (n=1) VTE (n=1)
Days 5–30 (n=46)	HIT/HITT (n=5) VTE (n=21) Acute coronary syndrome/MI/graft thrombosis (n=5) Thrombotic stroke/TIA (n=10) Left atrial appendage thrombosis (n=1) Peripheral arterial thromboembolism (n=2) Unspecified thrombosis/IVC filter placement (n=2)
Days 30–90 (n=20)	HITT (n=1) VTE (n=8) Acute coronary syndrome/MI/graft thrombosis (n=7) Thrombotic stroke/TIA (n=3) Peripheral arterial thromboembolism (n=1)

Abbreviations used include: VTE, venous thromboembolism; TIA, transient ischemic attack; HIT, heparin induced thrombocytopenia; HITT, heparin induced thrombocytopenia and thrombosis; IVC, inferior vena cava.