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Objective—To determine the most important inflammatory and hematologic predictors of thromboembolism (TE) in patients undergoing valve replacement (VR) to be used in conjunction with clinical risk factors for preoperative risk profiling.

Methods and Results—Preoperative and immediately postoperative clinical, echocardiographic, hematologic, biochemical and microbiological parameters were examined prospectively in 370 patients undergoing VR (249 AVR, 93 MVR, 28 DVR). Mean follow-up was 4.4 years (max 6.6 years; total 1566 pt/yrs), and 96 TE events were documented (28 major and 68 minor). INR data were collected on all patients. Laboratory values were considered elevated if they exceeded the 80th percentile of those of 70 controls with the same distribution of age and gender. IgA antibody to Chlamydia pneumoniae (CP)≥1:64 was considered indicative of significant infection. Predictors of TE on multivariate analysis following AVR were (hazard ratios): CP infection (2.6), previous TE (2.5), raised eosinophils (2.4), cancer history (2.1), postoperative infection (2.0), hypertension (2.0), CABG × 3/4 (2.0), and diabetes (1.9). Predictors of TE following MVR/DVR were raised mean platelet volume (4.0), raised factor VII (3.1), CP infection (2.7), previous mitral valvotomy (2.5), raised fibrinogen (2.2), and raised reticulocytes (2.0). These risk factors were additive when present in the same patient, enabling a scoring system to be developed that accurately predicted risk of TE based on number of risk factors.

Conclusions—Selected blood tests and clinical risk factors provide a scoring system that accurately predicts TE risk and may guide prosthesis choice and antithrombotic management. **(*Circulation*. 2003;108[suppl II]:II-68-II-74.)**

Key Words: heart valve prosthesis ■ embolism ■ risk factors

Thromboembolism and serious bleeding events together account for about 75% of the events reported as complications after mechanical valve replacement.[1] The guidelines for reporting these events recommend that all such events should be attributed to the prosthesis,[2] even though many are almost certainly not prosthesis-related and simply part of the background incidence of stroke, TIA and major bleeding in the general population.[3] This has led to the publication of comparisons of one prosthesis versus another based on thromboembolic (TE) rates in particular and has led some manufacturers to claim in their advertising material that their prosthesis has a lower TE rate than their competitors' products. Yet examination of large numbers of published series shows that there is as much variation in TE rates between different series of the same type of prosthesis as there is between one prosthesis and another.[4]

Three major factors are likely to account for these differences in TE rates with the same type of prosthesis: the method of data collection, the antithrombotic management and the effect of patient risk factors. It has been shown for example that different methods of collecting data in the same cohort of patients yield TE rates that differ by a factor of greater than 2;[5] patients submitted to questionnaire at the end of a long period of follow-up tend to forget many minor events and this type of analysis therefore always underestimates event rates. Different intensity of anticoagulation also yields different TE rates for the same prosthesis, particularly in the mitral position.[6] The greatest influence on TE rates, however, probably comes from individual patient factors and in particular factors that increase stroke risk.[3] It is self-evident that **patients** suffer TE events, not prostheses, and to speak of a prosthesis having a 'TE rate' makes no sense. Nor is it meaningful to attempt meta-analyses on published series, which differ widely in their methods of data collection and in their patient populations, for the purposes of either comparing one prosthesis with another or comparing one antithrombotic regime with another.

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In an attempt to unravel the complex interplay of factors responsible for thromboembolism after valve replacement, a prospective study was initiated in 1995 with the aim of identifying pre-operative clinical and laboratory variables that would identify patients at risk of thromboembolism during follow-up.

Methods

Selection of Patients

All patients undergoing elective valve replacement between June 1995 and July 1998 were eligible. Exclusion criteria were previous valve replacement, valve replacement for complications of infective endocarditis, emergency operations, and concomitant aortic root replacement. The Local Research Ethics Committee approved the protocol, and all patients gave informed consent. We recruited 370 patients (199 female), with a mean age (SD) of 66[9] years, who underwent 249 aortic (AVR), 93 mitral (MVR), and 28 double (aortic and mitral—DVR) valve replacement operations. The valves used were bileaflet (St. Jude Standard—70 AVR, 35 MVR, 11 DVR, and St. Jude Silzone—32 AVR, 13 MVR, 6 DVR), or single tilting disc (Medtronic Hall—68 AVR, 27 MVR, 10 DVR, and Ultracor—34 AVR, 18 MVR, 1 DVR) mechanical valves, or bioprostheses (Carpentier Edwards porcine or pericardial valves—45 AVR). A comparison of the St. Jude Standard and St. Jude Silzone valves used in this study, in terms of incidence of embolism and paravalvular leak, will be reported separately.

Clinical and Laboratory Data

Medical history and current status were documented on admission by interview and by examining the patients and their medical records. Venous blood obtained a few days before the operation was tested for hematologic, biochemical, and microbiological abnormalities. IgA antibodies against Chlamydia pneumoniae (CP) were assayed using a commercial indirect immunofluorescence method (MRL Diagnostics). A titer of ≥ 1 in 64 was considered indicative of significant infection. Routine blood counts, including hemoglobin measurements, white cell differential counts, platelet parameters, and reticulocyte counts were estimated using Advia 120 hematology analysers (Bayer). Hemostasis assays were performed on blood collected with minimum venous stasis using 21 gauge needles and evacuated blood collection tubes containing 0.1vol 108 mmol/L sodium citrate (Becton Dickenson). Platelet poor plasma was obtained after centrifugation at 2000 $\times$ *g* for 15 minutes at 4°C. The thrombin time (TT), prothrombin time (PT), activated partial thromboplastin time (aPTT), factor VII (FVII), factor VIII (FVIII), and fibrinogen assays (Clauss technique) were performed using standard laboratory procedures.[7,8] Von Willebrand factor antigen (vWFAg) was measured by enzyme-linked immunoassay (ELISA) as described by Giddings[9] using commercially available antisera (Dako Ltd, UK).

Other investigations performed were transesophageal echocardiography (TEE), carotid Doppler and transcranial Doppler (TCD) to document high intensity transient signals (HITS).

Control Subjects

Healthy age- and sex-matched control subjects were recruited among patients undergoing minor outpatient surgical procedures or attending an ophthalmology outpatient clinic, who had no history of cardiovascular disease, no long-term medications, and a normal physical examination. Current smokers were excluded. Control subjects had the same blood tests as patients.

Follow-Up

Patients attended the outpatient clinic at 6 weeks and between 6 and 12 months after their operation for clinical examination and a structured interview. The following events were documented: ischemic stroke, reversible ischemic neurological deficit (RIND), transient ischemic attack (TIA), and peripheral embolism. Ischemic or hemorrhagic stroke was diagnosed with imaging studies at the time of neurological events leading to hospital admission. International normalized ratio (INR) levels were documented from patient-held charts. Adequacy of anticoagulation was estimated by the percentage of INRs within the target range (2.5 to 3.5). Beyond 1 year, patients had annual interviews to document embolism and other end-points until final follow-up in February 2002. Additional information was obtained from patient charts. Copies of death certificates were obtained from the UK Office of National Statistics.

TABLE 1. Baseline Characteristics

Patient Demographics	No Events (n=285)	Events (n=75)	Univariate HR	*P*
AGE	66.2±9.6	64.1±8.8	0.9	0.17
Female sex	52	60	1.3	0.26
Mitral or double valve	31	41	1.6	0.04
Current smoking	11	12	1.1	0.75
Systemic hypertension	22	29	1.3	0.20
Diabetes	6	12	2.3	0.02
Previous TE event	10	19	2.1	0.01
Non sinus rhythm	34	36	1.2	0.39
NYHA class 3 or 4	61	64	1.3	0.25
Cancer history	4	8	2.0	0.09
Previous mitral valvotomy	5	8	2.1	0.09
Previous MI	6	8	1.4	0.42
CAD at angiography	41	49	1.4	0.14
3 or 4 CABG	5	9	1.8	0.14
Postoperative infection	4	9	1.9	0.10

Mean±SD, or (%). Abbreviations: CABG, coronary artery bypass grafts; CAD, coronary artery disease; HR, hazard ratio on univariate analysis; MI, myocardial infarction; NYHA, New York Heart Association; TE, thromboembolic.

Statistical Methods

Continuous data were described by mean (SD) and compared by analysis of variance. Categorical data were described by percentages and compared by Chi-square tests. Hematologic or biochemical data were considered elevated if the value was greater than the 80th percentile of normal, as determined from 70 control patients. Univariate and multivariate Cox regression analyses were performed to identify factors that were significantly associated with an increased risk of TE events.[10] The total number of multivariate risk factors present in a single patient determined that patient's 'risk score'. True hazard ratios from the Cox regression vary for patients in the same count-group, depending on which particular set of risk factors they have, but for simplification, counts rather than hazard ratios were used to develop this risk score. Event free curves were constructed using the actuarial method of Kaplan-Meier (KM).[11] Statistical analysis was performed using SPSS for Windows, version 10.0.7 (SPSS, Chicago, IL) and the SPLUS software package, version 2000 (Insightful, Inc, Seattle, WA).

Results

Baseline characteristics and hematology at entry into the study are given for the whole group (Tables 1 and 2) and by valve position (Tables 3 and 4). There were 70 controls (33 F), with a mean age (SD) of 63;[11] they had none of the risk factors described in Table 1, with the exception of previous smoking (3% had stopped within the last 5 years and 34% had stopped more than 5 years previously).

During follow-up for 0 to 6.6 years (mean 4.4, SD 1.6, total follow-up 1567 patient-years, completeness of follow-up

TABLE 2. Laboratory Values

	No Events (n=285)	Events (n=75)	Univariate HR	P
IgA antibodies to CP≥1:64 (%)	14	35	2.9	<0.001
FVII despite warfarin (%)	5	15	2.5	<0.01
Reticulocytes (%)	14	23	2.0	0.02
Eosinophils (%)	11	21	1.9	0.03
Mean platelet volume (%)	38	51	1.7	0.03
Fibrinogen (%)	35	45	1.6	0.04
Lymphocytes (%)	7	14	1.6	0.17
Factor VIII (%)	16	21	1.4	0.20

Data show the percentage of patients with an elevated level. Abbreviations: CP, chlamydia pneumoniae; FVII, factor 7; HR, hazard ratio on univariate analysis.

97.3%), 96 thromboembolic events occurred: 28 were major (25 strokes and 3 peripheral emboli), and 68 minor (67 transient ischemic attacks and one reversible ischemic neurologic deficit).

On univariate analysis, clinical and hematologic factors significantly associated with TE, in order of their hazard ratios, were: IgA antibodies to Chlamydia pneumoniae (CP)≥1 in 64, factor VII>90 iu/dL despite warfarin, diabetes, previous event, previous valvotomy, cancer history, reticulocyte count $>86\times10^9$/L, eosinophils $>0.23\times10^9$/L, mean platelet volume >9.2fL, fibrinogen >3.5 g/L, and mitral position. There was also a strong trend for an association with postoperative infection, 3 or 4 CABG grafts, CAD at angiography, lymphocytes $>2.4\times10^9$/L, and factor VIII iu/dL >190 (Tables 1 and 2). Established stroke risk factors (diabetes, previous event, and hypertension) were significantly associated with an increase risk of TE events in patients with aortic valve disease but not mitral or double valve disease (Table 3), whereas elevations in hematologic factors including mean platelet volume, factor VII, factor VIII, and fibrinogen were more associated with events in patients with mitral or double valve disease (Table 4).

On multivariate analysis, factors significantly associated with TE in AVR patients were (hazard ratios): IgA antibodies against CP≥1 in 64 (2.6), previous TE event (2.5), elevated eosinophils (2.4), cancer history (2.1), postoperative infection (2.0), hypertension (2.0), 3 or 4 CABG grafts (2.0), and diabetes (1.9). For MVR/DVR patients, IgA antibodies against CP≥1 in 64 (2.7), previous mitral valvotomy (2.5), and elevations in mean platelet volume (4.0), factor VII despite warfarin (3.1), fibrinogen (2.2), and reticulocytes (2.0) were associated with an increased risk of TE.

Patients risk scores, which were calculated as the total number of multivariate risk factors (as listed in Table 5), ranged from 0 to 8 in this study. Freedom from all TE and from major TE (ischemic stroke or peripheral embolism) by risk score are shown in Figures 1 and 2, respectively. A score of 0 to 6+ risk factors effectively stratified patients and permitted estimates of long-term TE risk to be created both in terms of freedom from TE at 4 years and linearized rates (Table 6).

Factors assessed as possible risk factors in this analysis, which subsequently had no association with TE events, included echocardiographic measurements (aortic atheroma score, left atrial size, left ventricular dysfunction including regional wall motion abnormalities), previous myocardial infarction, internal carotid artery stenosis >60%, postoperative HITS count, percentage of INR values outside the target range, platelet aggregability, abnormalities of fibrinolytic function, and abnormalities of lipid and homocysteine metab-

TABLE 3. Baseline Characteristics by Valve Position

	Events in Patients with AVR				Events in Patients with MVR			
	No	Yes	HR	P	No	Yes	HR	P
n	197	44			88	31		
AGE	66±10	66±8	1.0	0.72	66±8	61±9	0.9	<0.01
Female sex	44	48	1.1	0.67	72	77	1.2	0.65
Current smoking	11	11	1.1	0.92	9	13	1.3	0.64
Systemic hypertension	26	41	1.8	0.07	13	13	1.0	0.95
Diabetes	7	18	3.0	<0.01	5	3	1.3	0.81
Previous TE event	7	21	2.8	<0.01	16	16	1.3	0.56
Non sinus rhythm	13	5	0.4	0.20	81	81	1.2	0.76
NYHA class 3 or 4	55	50	1.0	0.95	76	84	1.7	0.26
Cancer history	4	9	2.3	0.11	3	7	1.7	0.46
Previous mitral valvotomy	1	0	0.05	0.95	13	19	2.0	0.13
Previous MI	7	7	1.2	0.76	3	10	1.7	0.38
CAD at angiography	45	57	1.7	0.08	33	39	1.2	0.65
3 or 4 CABG	6	9	2.0	0.19	5	10	1.4	0.59
Postoperative infection	5	14	2.7	0.03	3	3	0.9	0.91

Mean±SD, or (%). Abbreviations: AVR, aortic valve replacement; CABG, coronary artery bypass grafts; CAD, coronary artery disease; HR, hazard ratio on univariate analysis; MI, myocardial infarction; MVR, mitral or double valve replacement; NYHA, New York Heart Association; TE, thromboembolic.

TABLE 4. Laboratory Values by Valve Position

	Events in Patients with AVR				Events in Patients with MVR			
	No	Yes	HR	*P*	No	Yes	HR	*P*
n	197	44			88	31		
IgA to CP≥1:64 (%)	15	37	2.9	<0.01	14	32	3.2	<0.01
FVII despite warfarin (%)	3	2	1.0	0.97	10	32	2.5	0.02
Reticulocytes (%)	12	20	1.9	0.10	18	28	2.1	0.10
Eosinophils (%)	11	30	2.9	<0.01	12	7	0.8	0.69
Mean platelet volume (%)	38	39	1.1	0.83	38	68	3.1	<0.01
Fibrinogen (%)	35	41	1.4	0.31	38	52	1.9	0.10
Lymphocytes (%)	7	14	1.7	0.28	8	14	1.5	0.49
Factor VIII (%)	15	16	1.0	0.96	18	29	1.9	0.09

Data show the percentage of patients with an elevated level. Abbreviations: AVR, aortic valve replacement; CP, chlamydia pneumoniae; FVII, factor 7; HR, hazard ratio on univariate analysis; MVR, mitral valve replacement.

olism. Genetic abnormalities of coagulation (factor V Leiden and prothrombin) and homocysteine metabolism (MTHFR) were also not predictive. On univariate analysis there was a trend for an increased number of TE events in patients who received a mechanical valve (n=325) compared with those who received a tissue valve (n=45). However, on multivariate analysis, this factor was displaced by other variables in the model.

Discussion

This is the first study that has attempted to stratify the risk of TE events after valve replacement based on a detailed analysis of pre- and peri-operative variables. The addition of a large number of laboratory variables to the more widely acknowledged clinical variables in the analysis has enabled many new factors to be identified that are related to an increased risk of subsequent thromboembolism. These factors appear to be additive in terms of risk prediction when they occur in combination.

TABLE 5. Variables Used in the Risk Score for Thromboembolism

Previous TE event
Hypertension
Diabetes
3 or 4 CABG grafts
Cancer history
Postoperative infection
Previous mitral valvotomy
IgA antibodies against CP≥1 in 64
Mean platelet volume >9.2 fL
Eosinophils >0.23×10^9/L
Factor VII despite warfarin >90 iu/dL
Fibrinogen >3.5 g/L
Reticulocytes >86×10^9/L

Abbreviations: CABG, coronary artery bypass grafts.

Among the clinical factors identified on multivariate analysis, 3 have not been described before; a past history of cancer, previous closed mitral valvotomy, and postoperative infection. Malignant disease in general and many individual cancers in particular have been shown to be associated with an increased risk of thrombosis through several different prothrombotic mechanisms,[12] but it is widely assumed that the risk of thrombosis returns to 'normal' following effective treatment of the cancer. The results of this study, with a 2-fold increased risk of TE events, suggest that this is not the case, as none of the patients in the study were known to have residual or recurrent malignant disease at the time of surgery. The explanation may be that prothrombotic abnormalities persist even after effective cancer treatment or that these abnormalities are long-standing and predate the cancer also, as it is known that coagulation abnormalities are involved in tumor cell growth and metastasis and may be related to long-term prognosis.[12,13] A raised eosinophil count sometimes occurs in occult[14] and overt cancer[15] and may be

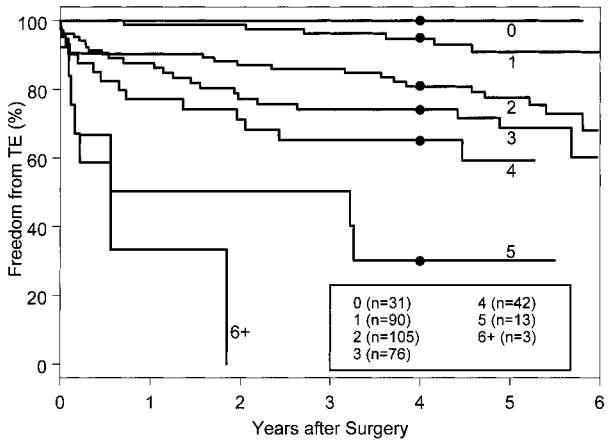

Figure 1. Kaplan Meier curve of event-free period for all thromboembolism by Risk Score (total number of risk factors) for patients who underwent aortic, mitral or double valve replacement. For each curve, freedom from TE at 4 years is indicated by (●).

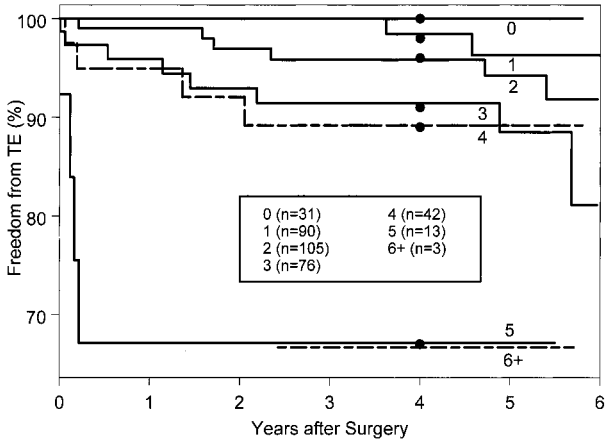

Figure 2. Kaplan Meier curve of event-free period for major thromboembolism (stroke or peripheral embolism) by Risk Score (total number of risk factors) for patients who underwent aortic, mitral or double valve replacement. The vertical axis goes from 65% to 100%. For each curve, freedom from TE at 4 years is indicated by (●).

involved in the pathogenesis of cancer-associated thrombosis.[14] In this study, 28% of patients with a cancer history had a raised eosinophil count versus 13% of patients without ($P=0.06$), and a raised eosinophil count was also an independent risk factor for TE.

Previous closed mitral valvotomy may be a direct risk factor or may be a surrogate for rapid progression of rheumatic disease in the mitral valve, leading to the necessity for mitral valvotomy at an early stage. Closed mitral valvotomy involves ligation and amputation of the left atrial appendage that can leave a rather corrugated irregular surface within the left atrium but this usually becomes smoothed out with time and does not appear irregular or thrombogenic at subsequent operation for mitral valve replacement many years later. Therefore, it is possible that whatever causes rapid progression to mitral stenosis also makes the patient more susceptible to thromboembolism. Some support for this hypothesis comes from histologic examination of rheumatic mitral valves that has shown that the progression of valve thickening is because of repeated deposition of microthrombus with subsequent organization.[16]

Postoperative infections in this study included 13 wound infections, 2 pulmonary infections, 1 urinary-tract infection, 1 case of mediastinitis, and 1 intravenous line infection. Seven patients with postoperative infections had 10 TE events (7 ischemic stroke in 5 patients and 3 TIA). On multivariate analysis, considering time to first event in all patients, they doubled the risk of subsequent TE. This suggests that stimulation of an inflammatory response also activated the coagulation system, as the two are known to be closely linked,[17] and that this effect persisted following discharge from the hospital. First events occurred within 6 months in 4 patients, 2 years in 2 patients, and within 6 years in 1 patient suggesting that the effect, if present, was predominantly related to the early postoperative months.

Some traditional risk factors for TE had little or no impact on event rates in this study. Age in itself was not a risk factor, suggesting that biological factors were more important than mere chronological age. Similarly, nonsinus rhythm had little impact probably because relatively few AVR patients and a very high percentage of all MVR/DVR patients were in atrial fibrillation (Table 3).

Among the laboratory variables identified as risk factors, evidence of chronic infection with Chlamydia pneumoniae emerged as the strongest predictor of future TE events with a hazard ratio of 2.9. Chronic Chlamydial infection as a risk factor for TE events after valve replacement is consistent with similar data for stroke in the general population.[18,19] Interestingly Chlamydial infection was present in 5 out of 7 patients who had both postoperative infection and subsequent TE events and the hazard ratio for the combination of Chlamydial infection and a postoperative infection was 8.3.

Of the other laboratory variables, most are known to be prothrombotic when present in the circulation at raised concentrations[20] or, in the case of platelets, when platelet volume is increased.[21] However, none has previously been shown to be a risk factor for TE events after valve replacement. Factor VII usually falls to very low levels in patients on warfarin. The discovery that absence of this response is a risk factor is also a new finding and may have implications for the monitoring of patients on warfarin. It is possible that warfarin may have been stopped prior to acquisition of preoperative venous blood in some patients, but despite this factor VII

TABLE 6. Freedom from TE and Linearized Rates by Risk Score

Risk Score	0	1	2	3	4*	5*	6+*
Sample size	31	90	105	76	42	13	3
Patient years	140.2	400.3	486.1	329.4	154.2	44.2	12.1
All Thromboembolic events:							
Number of events	0	6	33	29	16	8	4
Freedom from event at 4 years (%)	100	95	81	74	65	30	0
Linearised Rate (%/yr)	0	1.5	6.8	8.8	10.4	18.1	33.1
Major Thromboembolic events:							
Number of events	0	2	7	10	4	4	1
Freedom from event at 4 years (%)	100	98	96	91	89	67	67
Linearised Rate (%/yr)	0	0.5	1.4	3.0	2.6	9.0	8.3

*Estimates may be imprecise due to small sample sizes.

remained elevated in patients with events [66(SD 37) v 55,[25] $P<0.05$] while preoperative INR measured at the same time was not different between patients with and without events [2.1 (SD 0.7) for both].

When patients with AVR and MVR or DVR were assessed separately in terms of their risk factors for TE, some differences emerged. Traditional 'arterial' risk factors such as diabetes and systemic hypertension were more predictive after AVR, whereas previous mitral valvotomy was only predictive after MVR/DVR. The effect of postoperative infection as a risk factor was confined to AVR patients. Of the laboratory variables, evidence of chronic Chlamydial infection was a strong predictor of TE in both AVR and MVR/DVR patients. A raised eosinophil count was a strong predictor only in AVR patients, in keeping with the effect of eosinophil activation on platelet activation,[22] which is the dominant mechanism of thrombogenesis in the high shear stress conditions associated with AVR.[3] In contrast, the effect of inappropriately high levels of factor VII while on warfarin, raised factor VIII, and raised fibrinogen, occurred only or mainly in MVR/DVR patients, in keeping with the dominant effect of the coagulation system in determining the risk of TE in the conditions of relative stasis in the left atrium often associated with MVR.[3] Increased platelet size was also only a risk factor in association with MVR. Large platelets are known to be more reactive[21] and therefore, more 'sticky' and it is likely that this effect is more pronounced in conditions of relative stasis, allowing platelets to adhere more readily.

The finding that 'arterial' risk factors increase the risk of TE in patients undergoing AVR is in keeping with previous data we have published from a large prospective study based on a single prosthesis (Medtronic Hall valve).[23] However, in that study, smoking also emerged as a risk factor, particularly in patients who continued to smoke postoperatively, whereas in this study smoking was not an independent risk factor. In this smaller study, postoperative smoking was strongly discouraged, but it is possible that the dominant effect of chronic Chlamydial infection displaced pre-operative smoking per se as a risk factor. This infection is known to be more prevalent in smokers[24] and in this study 41% of patients with chronic Chlamydial infection were current or recent (<5 years) smokers whereas only 22% were nonsmokers ($P=0.001$). Recently it has been shown that atheroma in the carotid artery develops or progresses among smokers only if they also have evidence of chronic infection, including chronic Chlamydial infection.[25]

Most of the blood tests found to be predictive of TE events in this study are performed routinely in all hospitals at minimal cost. The only test which is not routinely performed and which is more expensive is that for IgA antibodies to Chlamydia pneumoniae. However, because of its high predictive power, the cost seems justifiable.

The use of a scoring system based on pre-operative and peri-operative variables should allow more accurate risk stratification to inform discussions with patients about their long-term risks after valve replacement. Knowledge of likely long-term outcomes may also facilitate decisions about choice of prosthesis (eg, mechanical versus biological), antithrombotic management and the closeness of follow-up required. However, the scoring system proposed here needs to be tested further in other large prosthetic valve databases before introduction to clinical practice.

The finding that patient variables make a huge difference to the risk of TE events after valve replacement provides further emphasis for the need to use caution in interpreting unstratified TE rates after valve replacement reported in the literature, particularly as a measure of prosthesis performance. Common sense dictates that cerebrovascular events, the most common manifestation of 'thromboembolism', are likely to be multifactoral in their etiology and related not only to the presence of a prosthetic valve and antithrombotic management but also to factors associated with atherosclerosis, inherent diverse mechanisms of hypercoagulability and pre-existing intracardiac flow conditions.

The findings of this study also have implications for the future management of patients with prosthetic valves in terms of reducing their risk of thromboembolism. In the case of risk factors that are amenable to modification, further prospective studies are required to test the hypothesis that amelioration or abolition of these factors will reduce the incidence of thromboembolism.

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