ORIGINAL ARTICLE

Preexisting Morbidity as an Independent Risk Factor for Perioperative Acute Thromboembolism Syndrome

Mutsuhito Kikura, MD, PhD; Tomosue Takada, MD; Shigehito Sato, MD, PhD

Hypothesis: Preexisting morbidities are risk factors for perioperative arterial or venous thromboembolic events and subsequent death within 30 postoperative days.

Design: Prospective cohort study.

Setting: University-affiliated general hospital.

Patients: A total of 21 903 surgery patients treated from January 1, 1991, through December 31, 2002.

Main Outcome Measures: Independent risk factors for perioperative arterial or venous thromboembolic events.

Results: History of atrial fibrillation and coronary artery disease increased the risk of myocardial infarction (odds ratio [95% confidence interval], 4.3 [2.8-6.7]). History of stroke increased the risk of stroke (2.4 [1.4-4.1]) and death (4.7 [1.3-17.3]). Diabetes mellitus increased the risk of myocardial infarction (2.1 [1.3-3.2]), and hyperuricemia increased the risk of stroke (3.5 [1.2-9.8]), and both increased the risk of death (4.3 [1.3-14.1] and 11.8 [2.2-63.5], respectively). History of myocardial infarction increased the risk of deep vein thrombosis (7.7 [1.7-34.7]). Cancer increased the risk of all thromboembolism (2.4 [1.9-3.2]). Trend analysis showed that preexisting morbidities will increase 1.5-fold and thromboembolic events will increase 3-fold during the next decade.

Conclusion: Cardiac and cerebrovascular diseases, metabolic diseases, and cancer are becoming increasingly high-risk comorbidities for perioperative acute thromboembolism syndrome.

Arch Surg. 2005;140:1210-1217

Author Affiliations:
Department of Anesthesiology and Pain Clinic, Seirei-Mikatabara General Hospital (Drs Kikura and Takada), Department of Anesthesiology and Intensive Care, Hamamatsu University School of Medicine (Dr Sato), and Department of Anesthesiology and Intensive Care, Hamamatsu Medical Center (Dr Kikura), Hamamatsu, Japan.

CARDIAC AND CEREBROVASCULAR diseases are the leading causes of death worldwide and represent a critical health problem.[1,2] They are accelerated by preexisting risk factors such as coronary artery disease, hypertension, diabetes mellitus, hyperlipidemia, and hyperuricemia, which exacerbate the progression of atherosclerotic disease, trigger atherothrombotic complications, and are associated with poor outcomes.[3,4] Patients undergoing surgery are especially prone to perioperative myocardial infarction[5,6] and stroke,[7,8] because they tend to have atherosclerotic disease. Surgical patients are also vulnerable to perioperative deep vein thrombosis and pulmonary embolism, which are also major health problems and common causes of death.[9,10] Although the incidences of ischemic heart disease, cerebrovascular disease, diabetes mellitus, and cancer are increasing worldwide,[1,2,11,12] how these preexisting morbidities, as risk factors for perioperative arterial or venous thromboembolism, will influence future morbidity and mortality rates is unknown.

Perioperative myocardial infarction, ischemic stroke, deep vein thrombosis, and pulmonary embolism appear to share a common pathophysiology that includes perioperative hemodynamic disturbance,[5-8] bed rest,[9,10] and a state described by a cell-based

See Invited Critique at end of article

model of vascular thrombosis.[13] This state is characterized by the Virchow triad: endothelial injury and dysfunction, disturbed blood flow, and hypercoagulability and reduced fibrinolysis. Thus, thrombin generation is induced, promoted by inflammatory cytokines and tissue factor, and results in thrombosis from adherence of activated neutrophils and platelets to activated endothelial cells.[13-16] Surgical patients are predisposed to these proinflammatory and prothrombotic processes and are particularly vulnerable to myocardial infarction and pulmonary embolism during week 1 after surgery, and to stroke, deep vein thrombosis, and cardiac or cerebrovascular death during weeks 1 and 2 after surgery. These

events have been referred to collectively as a perioperative acute thromboembolism syndrome that is a multifactorial thromboembolic disorder rather than merely a combination of the separate individual diseases.[17]

Comprehensive study of preexisting morbidities as risk factors for perioperative thromboembolic events is necessary for informed patient consent, patient counseling, surgical treatment decisions, and prophylactic antithromboembolic medications.

We conducted a prospective cohort study during a 12-year period to identify which preexisting morbidities are risk factors for perioperative acute thromboembolism syndrome, including myocardial infarction, ischemic stroke, deep vein thrombosis, pulmonary embolism, and subsequent cardiac or cerebrovascular death within 30 postoperative days, and to test the hypothesis that the incidence of this syndrome will increase because of an increase in the incidence of preexisting morbidities during the next decade.

METHODS

STUDY PARTICIPANTS

The study protocol was approved by the institutional review board (Sei-rei Mikatabara General Hospital, Hamamatsu, Japan), and consecutive patients who underwent elective general surgery, orthopedic surgery, or thoracic or peripheral vascular surgery between January 1, 1991, and December 31, 2002, were enrolled in the study. Written informed consent for medical care and procedures in the clinic and hospital was obtained from all patients. Patients undergoing surgery on the head, neck, or thoracic aorta were not included to exclude thromboembolic accidents that are directly related to surgical procedures. All patients were monitored for new onset of myocardial infarction, pulmonary embolism, deep vein thrombosis, ischemic stroke, and death from cardiovascular causes for 30 days postoperatively. Diagnosis of myocardial infarction was confirmed if symptoms met the World Heath Organization criteria and the event was associated with abnormal levels of cardiac enzymes and met diagnostic electrocardiographic criteria. Ischemic stroke was diagnosed if the patient showed new neurologic deficits that persisted for more than 24 hours. Computed tomographic scans or magnetic resonance images were available for most events and were used to distinguish hemorrhagic from ischemic events. Pulmonary embolism was diagnosed if a pulmonary angiogram, computed tomographic scan, magnetic resonance image, echocardiogram, or pathologic characteristics of a thrombus removed at surgery or autopsy confirmed pulmonary embolism. Deep vein thrombosis was diagnosed if a duplex ultrasonogram, venous angiogram, computed tomographic scan, magnetic resonance image, or pathologic characteristics of a thrombus removed at surgery or autopsy confirmed deep vein thrombosis. Deaths from cardiovascular causes were confirmed by review of the death certificates, medical records, and autopsy reports.

PREEXISTING MORBIDITIES

All patients in this study underwent preoperative evaluation of preexisting morbidities. Preexisting morbidities in surgical patients recorded in the hospital database included hypertension (defined as a systolic blood pressure of ≥140 mm Hg, a diastolic blood pressure of ≥90 mm Hg, or both), diabetes mellitus (defined as a blood glucose level of ≥126 mg/dL [6.93 mmol/L] after an overnight fast, a glycosylated hemoglobin value of ≥6.5%, or both), hyperlipidemia (serum total cholesterol level of ≥220 mg/dL [5.72 mmol/L], low-density lipoprotein cholesterol level of ≥140 mg/dL [2.8 mmol/L], or both), and hyperuricemia (serum uric acid level of ≥7.0 mg/dL [0.42 mmol/L]). Preexisting morbidities also included cardiovascular disease diagnosed by board-certified cardiologists, including atrial fibrillation confirmed by electrocardiography, stable angina (symptoms of frequent chest pain, dyspnea on exertion, or nuclear imaging abnormalities), unstable angina (increased frequency, intensity, or duration of chest pain, or decreased response to nitrates in the previous 2 months), myocardial infarction (as described in the previous section), valvular disease (diagnosed on the basis of symptoms, echocardiographic findings, cardiac catheterization findings, or angiographic findings), pulmonary hypertension (diagnosed via cardiac catheterization, mean pulmonary arterial pressure ≥25 mm Hg, or echocardiographic or angiographic findings), ischemic stroke diagnosed by board-certified neurologists (as described in the previous section), and cancer. The computerized medical database file of each patient in the study was prospectively collected and secured in the Division of Medical Records and Information of our institution.

STATISTICAL ANALYSIS

The preexisting specific incidences and risks of myocardial infarction, pulmonary embolism, deep vein thrombosis, ischemic stroke, and death were calculated. Correlation between the year of surgery and the percentage of patients with a preexisting morbidity or with a perioperative arterial or venous thromboembolic event within 30 postoperative days was determined by linear regression analysis.

The potential association of age, sex, and histories of cardiac and cerebrovascular disease, metabolic disease, and cancer with the occurrence of any perioperative thromboembolic event was analyzed by χ^2 test and Fisher exact test for trend. To estimate odds ratios and 95% confidence intervals by multivariate logistic regression analysis, age category (<50 years, 50-69 years, and ≥70 years), sex, and history of cardiac or cerebrovascular disease, metabolic disease, and cancer were treated as independent categorical variables. Type of thromboembolic event (myocardial infarction, pulmonary embolism, deep vein thrombosis, ischemic stroke, or death) was treated as a dependent categorical variable. All independent variables that were significant (2-tailed nominal $P<.1$) in univariate analyses were entered into a multivariate logistic analysis by the proportional odds model. Stepwise logistic regression was performed, and variables that were significant (2-tailed nominal $P<.05$) were retained. Statistical analysis was performed with SAS statistical software (SAS Institute Inc, Cary, NC).

RESULTS

STUDY PARTICIPANTS

The study population consisted of 21 903 surgical patients (**Table 1**). General surgery included lower (19.1% of patients) or upper (16.0%) abdominal surgery and other general procedures (4.4%); orthopedic surgery included total knee (4.7%) or hip (4.0%) replacement, spinal surgery (10.4%), and other orthopedic procedures (29.1%); thoracic or vascular surgery included lung and mediastinal surgery (10.6%), peripheral vascular surgery (1.5%), and other related operations (0.2%). A total of 255 patients (1.16%) experienced thromboembolic complications within 30 postoperative days, 105 patients (0.48%) had myocardial infarction, 30 (0.14%) had pulmonary embolism, 23 (0.11%) had deep vein thrombosis, 97 (0.44%) had ischemic stroke, and 13 (0.06%)

Table 1. Incidence of Perioperative Arterial and Venous Thromboembolism in Relation to Preexisting Comorbidities

	No. (%)			
		Thromboembolic Events		
	All Patients (N = 21 903)	No (n = 21 648)	Yes (n = 255)	*P* Value*
Age, y				
>50	8093 (36.9)	8073 (37.3)	20 (7.8)	
50-69	7403 (33.8)	7346 (33.9)	57 (22.4)	
≥70	6407 (29.3)	6229 (28.8)	178 (69.8)	<.001†
Sex, M	12 243 (55.9)	12 108 (55.9)	135 (52.9)	.34
History of comorbidity				
Cardiovascular disease				
Atrial fibrillation	331 (1.5)	315 (1.5)	16 (6.3)	<.001
Angina pectoris	846 (3.9)	817 (3.8)	29 (11.4)	<.001
Myocardial infarction	287 (1.3)	267 (1.2)	20 (7.8)	<.001
Valvular disease	22 (0.1)	0	22 (8.6)	NA
Hypertension	2447 (11.2)	2425 (11.2)	22 (8.6)	.23
Pulmonary hypertension	13 (0.1)	13 (0.1)	0	NA
Varix	238 (1.1)	227 (1.0)	11 (4.3)	.001
Cerebrovascular disease				
Ischemic stroke	881 (4.0)	849 (3.9)	32 (12.5)	<.001
Metabolic disease				
Diabetes mellitus	2220 (10.1)	2162 (10.0)	58 (22.7)	<.001
Hyperuricemia	169 (0.8)	164 (0.8)	5 (2.0)	.02
Hyperlipidemia	638 (2.9)	632 (2.9)	6 (2.4)	.59
Cancer	3896 (17.8)	3806 (17.6)	90 (35.3)	<.001

Abbreviation: NA, not applicable.
**P* values for comparison between no events and thromboembolic events.
†*P* values for trend.

died of cardiac or cerebrovascular causes. The mortality was 13 patients (5.1%) in the 255 patients with any thromboembolic complications, 7 patients (6.7%) in the 105 patients with myocardial infarction, 5 patients (5.2%) in the 97 patients with ischemic stroke, and 1 patient (3.3%) in the 30 patients with pulmonary embolism.

The incidences of all thromboembolic events and of myocardial infarction, ischemic stroke, pulmonary embolism, deep vein thrombosis, and subsequent death are shown in **Tables** 1, **2**, and **3** in relation to age, sex, and preexisting morbidities. The incidence of perioperative thromboembolism was higher in patients who had a history of atrial fibrillation, angina pectoris, myocardial infarction, ischemic stroke, diabetes mellitus, hyperuricemia, and cancer.

INDEPENDENT RISK FACTORS

The risk and incidence of all arterial or venous thromboembolic events increased with age, particularly for patients 70 years or older ($P<.001$), with a history of atrial fibrillation ($P=.005$), myocardial infarction ($P<.001$), ischemic stroke ($P=.001$), diabetes mellitus ($P<.001$), or cancer ($P<.001$) as determined by multivariate logistic regression analysis and summarized in **Table 4** and **Table 5**.

Men had an increased risk of myocardial infarction ($P=.03$), and women had an increased risk of pulmonary embolism ($P=.01$) and deep vein thrombosis ($P=.004$). The risk and incidence of myocardial infarction increased with age ($P<.001$), and with a history of atrial fibrillation ($P=.02$), angina pectoris ($P=.01$), myocardial infarction ($P<.001$), or diabetes mellitus ($P=.001$). The risk and incidence of ischemic stroke increased with age ($P<.001$) and with a history of ischemic stroke ($P=.002$) or hyperuricemia ($P=.01$). The risk and incidence of deep vein thrombosis increased with age ($P<.001$) and with a history of myocardial infarction ($P=.008$). The risk and incidence of postoperative death increased with a history of ischemic stroke ($P=.02$), diabetes mellitus ($P=.01$), or hyperuricemia ($P=.004$). Patients with cancer had an increased risk of myocardial infarction ($P<.001$), ischemic stroke ($P=.03$), pulmonary embolism ($P=.001$), deep vein thrombosis ($P=.02$), and subsequent death ($P=.01$).

TREND ANALYSIS

There was a correlation between the year of surgery (x variable) and the percentages of patients with preexisting comorbidities (y variables) (**Figure 1**A). We estimate from these trends that the percentage of surgical patients with any preexisting cardiac or cerebrovascular disease, metabolic disease, or cancer will increase to 44.0% in 2015, a 1.5-fold increase from the mean percentage during the 12 years of the present study.

There was a correlation between the year of surgery (x variable) and the percentages of patients experiencing a thromboembolic event, myocardial infarction, ischemic stroke, deep vein thrombosis, pulmonary embolism, and subsequent death (y variables) (Figure 1B). We estimate from these trends that the percentage of surgical patients experiencing any thromboembolic event will increase to 4.0% in 2015, a 3-fold increase from the mean percentage during the 12 years of our study.

Table 2. Incidence of Myocardial Infarction and Ischemic Stroke in Relation to Preexisting Comorbidities

	Myocardial Infarction, No. (%)			Ischemic Stroke, No. (%)		
	No (n = 21 798)	Yes (n = 105)	*P* Value*	No (n = 21 806)	Yes (n = 97)	*P* Value*
Age, y						
>50	8081 (37.1)	12 (11.4)		8089 (37.1)	4 (4.1)	
50-69	7377 (33.8)	26 (24.8)		7387 (33.9)	16 (16.5)	
≥70	6340 (29.1)	67 (63.8)	<.001	6330 (29.0)	77 (79.4)	<.001
Sex, M	12 174 (55.8)	69 (65.7)	.04	12 192 (55.9)	51 (52.6)	.5
History of comorbidity						
Cardiac and cerebrovascular disease						
Atrial fibrillation	322 (1.5)	9 (8.6)	<.001	325 (1.5)	6 (6.2)	<.001
Angina pectoris	826 (3.8)	20 (19.0)	<.001	838 (3.8)	8 (8.2)	.02
Myocardial infarction	270 (1.2)	17 (16.2)	<.001	286 (1.3)	1 (1.0)	.06
Hypertension	2435 (11.2)	12 (11.4)	.88	2438 (11.2)	9 (9.3)	.55
Pulmonary hypertension	13 (0.1)	0	NA	13 (0.1)	0	.06
Ischemic stroke	867 (4.0)	14 (13.3)	<.001	864 (4.0)	17 (17.5)	<.001
Varix	237 (1.1)	1 (1.0)	.89	238 (1.1)	0	.63
Metabolic disease						
Diabetes mellitus	2188 (10.0)	32 (30.5)	<.001	2201 (10.1)	19 (19.6)	.002
Hyperuricemia	168 (0.8)	1 (1.0)	.83	165 (0.8)	4 (4.1)	<.001
Hyperlipidemia	635 (2.9)	3 (2.9)	.97	635 (2.9)	3 (3.1)	.01
Cancer	3851 (17.7)	45 (42.9)	<.001	3871 (17.8)	25 (25.8)	.04

Abbreviation: NA, not applicable.
**P* values for comparison between no events and each thromboembolic event.

Table 3. Incidence of Pulmonary Embolism, Deep Vein Thrombosis, and Death in Relation to Preexisting Comorbidities

	Pulmonary Embolism, No. (%)			Deep Vein Thrombosis, No. (%)			Death, No. (%)		
	No (n = 21 873)	Yes (n = 30)	*P* Value*	No (n = 21 880)	Yes (n = 23)	*P* Value*	No (n = 21 890)	Yes (n = 13)	*P* Value*
Age, y									
>50	8090 (37.0)	3 (10.0)		8092 (37.0)	1 (4.3)		8091 (37.0)	2 (15.4)	
50-69	7395 (33.8)	8 (26.7)		7396 (33.8)	7 (30.4)		7402 (33.8)	1 (7.7)	
≥70	6388 (29.2)	19 (63.3)	.001	6392 (29.2)	15 (65.2)	<.001	6397 (29.2)	10 (76.9)	<.001
Sex, M	12 232 (55.9)	11 (36.7)	.33	12 239 (55.9)	4 (17.4)	<.001	12 233 (55.9)	10 (76.9)	.13
History of comorbidity									
Cardiac and cerebrovascular disease									
Atrial fibrillation	330 (1.5)	1 (3.3)	.41	331 (1.5)	0	.55	329 (1.5)	2 (15.4)	<.001
Angina pectoris	845 (3.9)	1 (3.3)	.88	846 (3.9)	0	.34	846 (3.9)	0	.47
Myocardial infarction	287 (1.3)	0	.53	285 (1.3)	2 (8.7)	.002	286 (1.3)	1 (7.7)	.04
Hypertension	2447 (11.2)	0	.05	2446 (11.2)	1 (4.3)	.3	2446 (11.2)	1 (7.7)	.69
Pulmonary hypertension	13 (0.1)	0	.89	13 (0.1)	0	.9	13 (0.1)	0	.93
Ischemic stroke	881 (4.0)	0	.26	880 (4.0)	1 (4.3)	.93	877 (4.0)	4 (30.8)	<.001
Varix	234 (1.1)	4 (13.3)	<.001	232 (1.1)	6 (26.1)	<.001	238 (1.1)	0	.71
Metabolic disease									
Diabetes mellitus	2217 (10.1)	3 (10.0)	.98	2216 (10.1)	4 (17.4)	.25	2214 (10.1)	6 (46.2)	<.001
Hyperuricemia	169 (0.8)	0	.63	169 (0.8)	0	.67	167 (0.8)	2 (15.4)	<.001
Hyperlipidemia	638 (2.9)	0	.34	638 (2.9)	0	.41	637 (2.9)	1 (7.7)	.31
Cancer	3884 (17.8)	12 (40.0)	.001	3888 (17.8)	8 (34.8)	.03	3890 (17.8)	6 (46.2)	.008

**P* values for comparison between no events and each thromboembolic event.

RELATIONSHIP OF RISK FACTORS TO THROMBOEMBOLIC EVENTS

The relationship of preexisting morbidities to perioperative risk of myocardial infarction, ischemic stroke, pulmonary embolism, deep vein thrombosis, and subsequent cardiac and cerebrovascular death is summarized in **Figure 2**.

COMMENT

This large, contemporary, prospective 12-year study of consecutive surgical patients offers physicians important, clinically relevant information about the relationship of patients' preexisting morbidity to perioperative morbidity, mortality, and risk of a perioperative acute thromboem-

Table 4. Summary of Multivariate Logistic Regression Analysis of Independent Risk Factors for Preexisting Comorbidities for a Perioperative Thromboembolism Syndrome: All Thromboembolism, Myocardial Infarction, and Ischemic Stroke

	All Thromboembolism		Myocardial Infarction		Ischemic Stroke	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age, y						
>50	1.0		1.0		1.0	
50-69	2.0 (1.2-3.3)	.008	NA		3.7 (1.2-11.1)	.02
≥70	7.5 (4.8-11.9)	<.001	4.0 (2.0-7.6)	<.001	20.2 (7.3-56.2)	<.001
Sex						
Male	1.1 (0.8-1.4)	.59	1.6 (1.0-2.4)	.03	NA	
Female	1.0		1.0		NA	
History of comorbidity						
Cardiovascular disease						
Atrial fibrillation	2.1 (1.2-3.4)	.005	2.4 (1.1-5.0)	.02	NA	
Angina pectoris	1.2 (0.8-1.8)	.44	1.9 (1.1-3.4)	.01	NA	
Myocardial infarction	2.9 (1.8-4.8)	<.001	5.7 (3.1-10.3)	<.001	NA	
Hypertension	0.7 (0.4-1.1)	.1	NA		NA	
Varix	7.2 (3.8-13.7)	<.001	1.8 (0.2-13.1)	.57	NA	
Cerebrovascular disease						
Ischemic stroke	1.8 (1.3-2.7)	.001	NA		2.4 (1.4-4.1)	.002
Metabolic disease						
Diabetes mellitus	1.7 (1.2-2.2)	<.001	2.1 (1.3-3.2)	.001	NA	
Hyperuricemia	1.9 (0.8-4.2)	.12	NA		3.5 (1.2-9.8)	.01
Hyperlipidemia	0.9 (0.4-1.9)	.77	NA		NA	
Cancer	2.4 (1.9-3.2)	<.001	3.0 (2.0-4.6)	<.001	1.6 (1.0-2.5)	.03

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

Table 5. Summary of Multivariate Logistic Regression Analysis of Independent Risk Factors for Preexisting Comorbidities for a Perioperative Thromboembolism Syndrome: Pulmonary Embolism, Deep Vein Thrombosis, and Death

	Pulmonary Embolism		Deep Vein Thrombosis		Death	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age, y						
>50	1.0		1.0		NA	
50-69	NA		NA		NA	
≥70	7.0 (2.0-24.1)	.002	12.8 (1.7-99.1)	.01	NA	
Sex						
Male	1.0		1.0		NA	
Female	2.7 (1.3-5.9)	.01	5.1 (1.7-15.2)	.004	NA	
History of comorbidity						
Cardiovascular disease						
Atrial fibrillation	NA		NA		NA	
Angina pectoris	NA		NA		NA	
Myocardial infarction	NA		7.7 (1.7-34.7)	.008	NA	
Hypertension	NA		NA		NA	
Varix	22.1 (7.0-69.6)	<.001	53.5 (17.7-161.3)	<.001	NA	
Cerebrovascular disease						
Ischemic stroke	NA		NA		4.7 (1.3-17.3)	.02
Metabolic disease						
Diabetes mellitus	NA		NA		4.3 (1.3-14.1)	.01
Hyperuricemia	NA		NA		11.8 (2.2-63.5)	.004
Hyperlipidemia	NA		NA		NA	
Cancer	3.5 (1.7-7.4)	.001	2.8 (1.2-6.9)	.02	4.3 (1.3-13.7)	.01

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

bolism syndrome (Figure 2). Our data on arterial and venous thromboembolic events have serious implications. The incidence of these events (1.2%) is projected to increase more than 3-fold, accelerated by a predicted 1.5-fold increase in preexisting morbidity during the next decade, creating a more severe health care problem.

MYOCARDIAL INFARCTION

The present study showed atrial fibrillation and cancer to be independent risk factors for perioperative myocardial infarction, in addition to traditional risk factors such as aging or a history of myocardial infarction, an-

gina pectoris, and diabetes mellitus.[5,6] Atrial fibrillation, the most common sustained arrhythmia seen in clinical practice, is associated with a 2-fold increase in total and cardiovascular mortality.[18] C-reactive protein level, an indicator of systemic inflammation and coronary risk,[16] increases in patients with atrial fibrillation,[19] and increased levels of C-reactive protein predict increased risk for future myocardial infarction and thromboembolic stroke.[20] In addition to an irregular heart rate and the resulting turbulent flow in the systemic vessels, proinflammatory and prothrombotic status could be related to the association between atrial fibrillation and the risk of perioperative myocardial infarction.[16,18-20] A relatively lower risk observed in our study compared with the previous studies[5,6] is probably a result of the noncardiac surgery and Asian population of the present study.

STROKE

A history of hyperuricemia was shown to be an independent risk factor for perioperative stroke, as are aging and history of stroke.[7,8] An increased level of serum uric acid has been identified as an independent risk factor for stroke in the general medical population.[21,22] Increased uric acid level may play a pathogenetic role in stroke by promoting hypertension, atherosclerotic change and subsequent endothelial dysfunction,[23] or activation of platelets and inflammatory cytokines.[24] The uric acid level reflects the degree of circulating xanthine oxidase activity, an important source of oxygen free radicals.[25]

DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM

A history of myocardial infarction was also shown to be an independent risk factor for perioperative deep vein thrombosis, as are aging and a history of varix and deep vein thrombosis.[9,10] The risk of deep vein thrombosis in patients hospitalized with acute myocardial infarction is moderate and is comparable to that in general surgical patients.[26] Recent study indicates that atherosclerosis can induce deep vein thromboembolism, and atherosclerosis and deep vein thrombosis share a common prothrombotic pathophysiology, such as activated platelets and upregulated blood coagulation.[27] Our results support the relationship between history of coronary atherosclerotic disease and perioperative deep vein thrombosis. A relatively lower perioperative incidence in our study compared with the other studies[10,28] might be due to lower prevalence of deep venous thromboembolism in the Asian population.

CARDIAC AND CEREBROVASCULAR DEATH

Diabetes mellitus, hyperuricemia, stroke, cancer, and age of 70 years and older were also shown to be independent risk factors for perioperative cardiac or cerebrovascular death. Diabetes mellitus and hyperuricemia increase cardiac and cerebrovascular mortality in the general population by promoting atherosclerosis, endothelial dysfunction, and activation of platelets and inflammatory cytokines.[4,21,22,29,30] The present study findings indicate that surgical stress enhances the prothrombotic pathophysiology and inhibits the fibrinolytic pathophysiology in diabetes mellitus and hyperuricemia, thus increasing the risk of perioperative cardiac or cerebrovascular death.

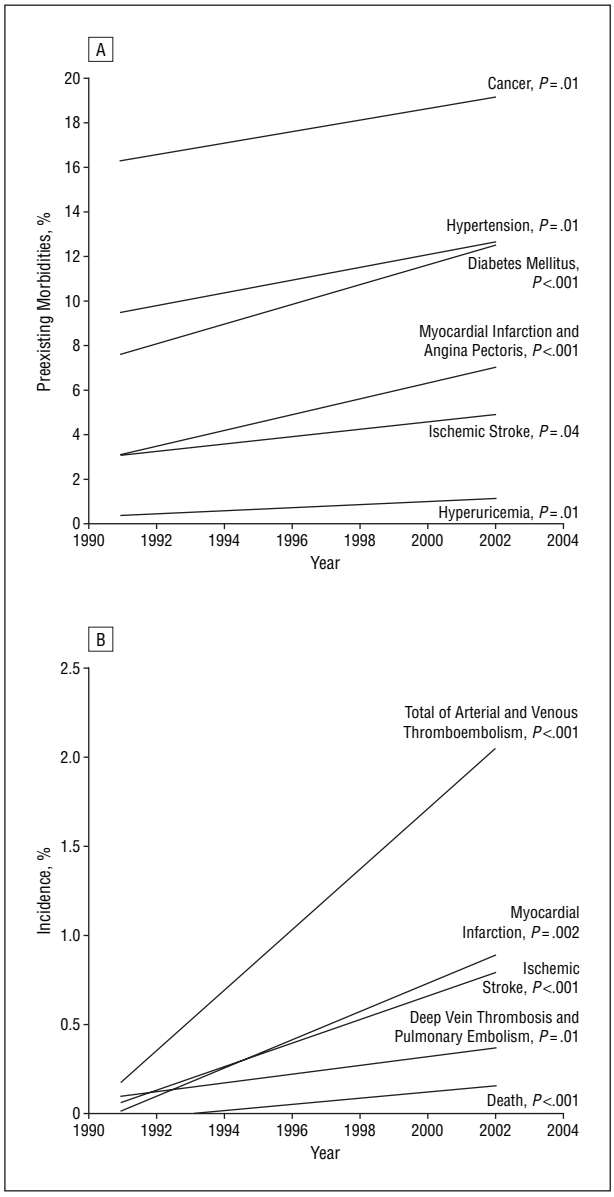

Figure 1. Increases in percentages of patients with preexisting comorbidities (A) and thromboembolic events (B) by year of surgery.

CANCER

Cancer was shown to be an independent risk factor for perioperative arterial and venous thromboembolism. A critical component of cancerous tumor progression is inflammation, in which abundant proinflammatory cytokines such as tumor necrosis factor α and interleukin 1 are produced.[31] The mechanisms explaining the association between preexisting cancer and perioperative myocardial infarction and stroke are unknown. Perhaps the elevated levels of D dimers and serum angiogenic factors that promote the proinflammatory and prothrom-

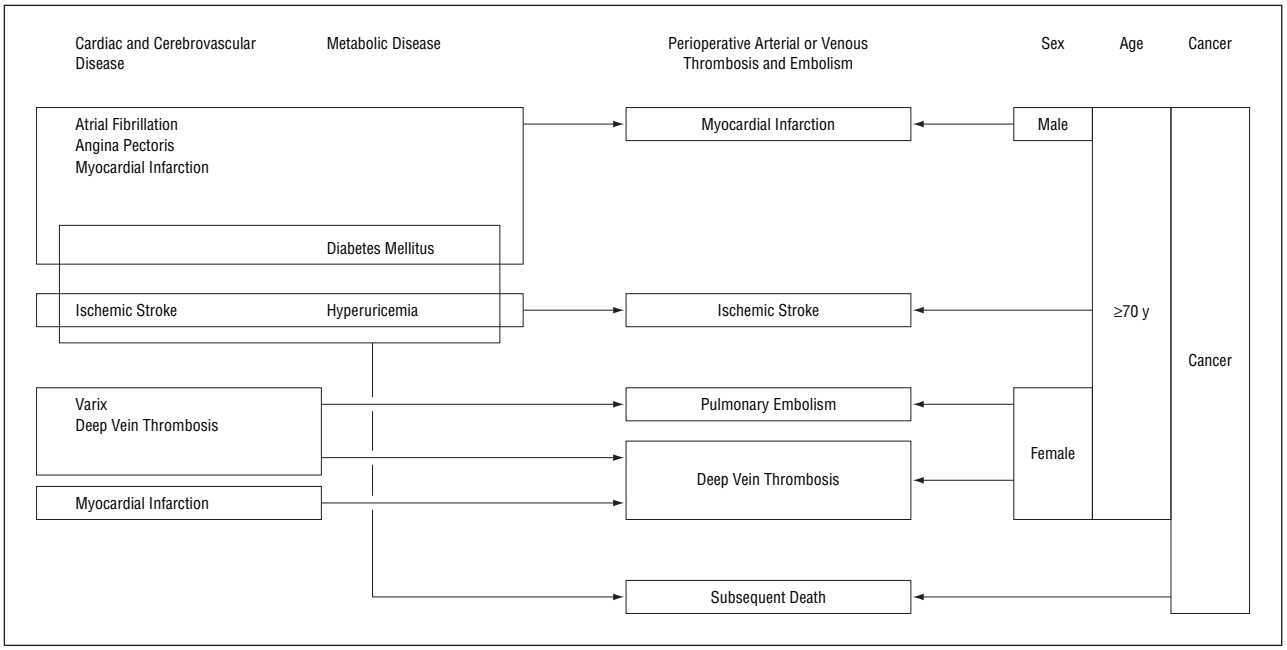

Figure 2. Independent risk factors for perioperative acute thromboembolism syndrome. Preexisting morbidities as risk factors for perioperative arterial or venous thrombosis and embolism are summarized, and cardiac and cerebrovascular thrombotic diseases and metabolic diseases produce a cross-linkage, causing perioperative acute thromboembolism syndrome and subsequent death.

botic state increase the risk of arterial thrombosis.[31-33] Cancer increases the risk of deep vein thrombosis and pulmonary embolism in the general medical population.[10,34] Endothelial dysfunction, alterations in procoagulant and anticoagulant protein levels, and deregulation of cytokine activities have been proposed as underlying mechanisms.[31,33,34]

THROMBOEMBOLIC PROPHYLAXIS

Perioperative administration of aspirin reduces the incidence of myocardial infarction and stroke by one half[35] and the risk of pulmonary embolism and deep vein thrombosis by one third and two thirds, respectively.[28] An orally active direct thrombin inhibitor, ximelagatran, has been shown to prevent stroke in patients with atrial fibrillation,[36] major cardiovascular events following acute myocardial infarction,[37] and venous thromboembolism in patients undergoing elective hip or knee replacement surgery.[38] Its further usefulness in perioperative prophylaxis is anticipated, in addition to the traditional antithromboembolic prophylaxis by warfarin, low-dose heparin, and low-molecular-weight heparin.

Recent evidence supports a role of inflammatory stimulation in the pathogenesis of atherosclerosis.[16] Serum markers of inflammation such as C-reactive protein have proven remarkably robust as markers of cardiac and cerebrovascular risk, and targeting inflammation has become a focal point for understanding and treating atherosclerosis.[16,20,39] Aspirin, β-adrenergic blocking agents, statins (inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase), angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and fibric acid derivatives have emerged as new pharmacologic strategies for preventing perioperative myocardial infarction, stroke, and subsequent death, thus complementing traditional antiplatelet and anticoagulant therapies.[16,28,35,39,40]

STUDY LIMITATIONS

We should address the limitations of the present study. First, we did not identify the patients with asymptomatic arterial and venous thromboembolic events such as silent myocardial ischemia, cerebrovascular transient ischemic attack, or asymptomatic deep vein thromboembolism. Therefore, the numbers of surgical patients exposed to the risk of perioperative arterial and venous thromboembolic events should be greater than those we estimated in this study. Second, hypertension and hyperlipidemia, traditional atherothrombotic risk factors, were not identified as risk factors for any thromboembolic events in this study. The reason might be that the Asian population has less severe atherosclerotic disease. In addition, perioperative surgical stress itself is a more influential and detrimental factor for thromboembolic events than hypertension and hyperlipidemia in surgical patients, and the risk of hypertension and hyperlipidemia might not be demonstrated in this study. Third, we estimated an increase in a perioperative arterial or venous thromboembolic events by linear regression analysis. However, the increases in comorbidities associated with the expanding elderly population might increase the incidence of a perioperative acute thromboembolism syndrome more than we expected in the present study.

CONCLUSIONS

The results of the present study permit identification of patients at risk of perioperative acute thromboembolism syndrome, thus indicating the need for prophylactic anti-

thromboembolic treatment. Our findings underscore the importance of minimizing risk of perioperative acute thromboembolism syndrome arising from comorbid diseases. We hope to reduce its incidence and thereby reduce associated costs as well as improve patient outcomes.

Accepted for Publication: March 23, 2005.
Correspondence: Mutsuhito Kikura, MD, PhD, Department of Anesthesia and Intensive Care, Hamamatsu Medical Center, 328 Tomizuka-cho, Hamamatsu, Japan 432-8580 (mkikura@hotmail.com).

REFERENCES

1. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet*. 1997;349:1498-1504.
2. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet*. 1997;349:1269-1276.
3. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA*. 2002;288: 2709-2716.
4. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA*. 2002;287:2570-2581.
5. Mangano DT. Perioperative cardiac morbidity. *Anesthesiology*. 1990;72:153-184.
6. Eagle KA, Berger PB, Calkins H, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation*. 2002;105:1257-1267.
7. Limburg M, Wijdicks EF, Li H. Ischemic stroke after surgical procedures: clinical features, neuroimaging, and risk factors. *Neurology*. 1998;50:895-901.
8. Wong GY, Warner DO, Schroeder DR, et al. Risk of surgery and anesthesia for ischemic stroke. *Anesthesiology*. 2000;92:425-432.
9. Goldhaber SZ. Pulmonary embolism. *N Engl J Med*. 1998;339:93-104.
10. Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. *Chest*. 2001;119(suppl)1:132S-175S.
11. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care*. 1998;21:1414-1431.
12. Antunes JL, Toporcov TN, de Andrade FP. Trends and patterns of cancer mortality in European countries. *Eur J Cancer Prev*. 2003;12:367-372.
13. Hoffman M, Monroe DM III. A cell-based model of hemostasis. *Thromb Haemost*. 2001;85:958-965.
14. Dahl OE. Mechanisms of hypercoagulability. *Thromb Haemost*. 1999;82:902-906.
15. McEver RP. Adhesive interactions of leukocytes, platelets, and the vessel wall during hemostasis and inflammation. *Thromb Haemost*. 2001;86:746-756.
16. Libby P. Inflammation in atherosclerosis. *Nature*. 2002;420:868-874.
17. Kikura M, Takada T, Sato S. Age- and sex-specific incidence, risk, and latency period of a perioperative acute thromboembolism syndrome (PATS). *Thromb Haemost*. 2004;91:725-732.
18. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98:946-952.
19. Chung MK, Martin DO, Sprecher D, et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. *Circulation*. 2001;104:2886-2891.
20. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med*. 2000;342:836-843.
21. Weir CJ, Muir SW, Walters MR, Lees KR. Serum urate as an independent predictor of poor outcome and future vascular events after acute stroke. *Stroke*. 2003; 34:1951-1956.
22. Lehto S, Niskanen L, Ronnemaa T, Laakso M. Serum uric acid is a strong predictor of stroke in patients with non–insulin-dependent diabetes mellitus. *Stroke*. 1998;29:635-639.
23. Nieto FJ, Iribarren C, Gross MD, Comstock GW, Cutler RG. Uric acid and serum antioxidant capacity: a reaction to atherosclerosis? *Atherosclerosis*. 2000;148: 131-139.
24. Leyva F, Anker SD, Godsland IF, et al. Uric acid in chronic heart failure: a marker of chronic inflammation. *Eur Heart J*. 1998;19:1814-1822.
25. Terada LS, Guidot DM, Leff JA, et al. Hypoxia injures endothelial cells by increasing endogenous xanthine oxidase activity. *Proc Natl Acad Sci U S A*. 1992; 89:3362-3366.
26. Simmons AV, Sheppard MA, Cox AF. Deep venous thrombosis after myocardial infarction: predisposing factors. *Br Heart J*. 1973;35:623-625.
27. Prandoni P, Bilora F, Marchiori A, et al. An association between atherosclerosis and venous thrombosis. *N Engl J Med*. 2003;348:1435-1441.
28. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet*. 2000;355:1295-1302.
29. Luscher TF, Creager MA, Beckman JA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part II. *Circulation*. 2003;108:1655-1661.
30. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992: National Health and Nutrition Examination Survey. *JAMA*. 2000;283:2404-2410.
31. Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002;420:860-867.
32. Cestari DM, Weine DM, Panageas KS, Segal AZ, DeAngelis LM. Stroke in patients with cancer: incidence and etiology. *Neurology*. 2004;62:2025-2030.
33. Salgado R, Benoy I, Weytjens R, et al. Arterio-venous gradients of IL-6, plasma and serum VEGF and D-dimers in human cancer. *Br J Cancer*. 2002;87:1437-1444.
34. Lee AY, Levine MN. Venous thromboembolism and cancer: risks and outcomes. *Circulation*. 2003;107(suppl 1):I17-I21.
35. Mangano DT. Aspirin and mortality from coronary bypass surgery. *N Engl J Med*. 2002;347:1309-1317.
36. Olsson SB. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet*. 2003;362:1691-1698.
37. Wallentin L, Wilcox RG, Weaver WD, et al; ESTEEM Investigators. Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomised controlled trial. *Lancet*. 2003;362:789-797.
38. Francis CW, Berkowitz SD, Comp PC, et al; EXULT A Study Group. Comparison of ximelagatran with warfarin for the prevention of venous thromboembolism after total knee replacement. *N Engl J Med*. 2003;349:1703-1712.
39. Gorelick PB. Stroke prevention therapy beyond antithrombotics: unifying mechanisms in ischemic stroke pathogenesis and implications for therapy: an invited review. *Stroke*. 2002;33:862-875.
40. Poldermans D, Bax JJ, Kertai MD, et al. Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. *Circulation*. 2003;107:1848-1851.