ORIGINAL RESEARCH

Thrombotic/Thrombolytic Balance as a Cardiac Treatment Determinant in Patients With Diabetes Mellitus and Coronary Artery Disease

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***Background*—**This study aimed to assess whether the plasminogen activator inhibitor-1/tissue plasminogen activator (PAI-1/tPA) ratio as a prothrombotic state is useful for optimizing cardiac treatment strategy.

***Methods and Results*—**Using BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial data, we used a Cox proportional hazard model to calculate hazard ratios with 95% CIs for cardiac events in patients receiving early revascularization (percutaneous coronary intervention or coronary artery bypass grafting) or medical therapy, separately in patients with low (n=1276) and high (n=894) PAI-1/tPA ratios. The primary outcome was major cardiac events, which was a composite end point including cardiac death and nonfatal myocardial infarction. The mean±SD follow-up period was 4.1±1.7 years. The risk of major cardiac events in patients with high PAI-1/tPA ratio was significantly higher when receiving percutaneous coronary intervention (hazard ratio, 1.84; 95% CI, 1.16–2.93; *P*=0.01) than when receiving medical therapy, whereas that in patients with low PAI-1/tPA ratio did not differ significantly between the groups (hazard ratio, 0.95; 95% CI, 0.66–1.36; *P*=0.77); the interaction between the cardiac treatment strategy and PAI-1/tPA ratio was significant (*P*=0.02). However, regardless of the PAI-1/tPA ratio, major cardiac event risk seemed to be lower in patients receiving coronary artery bypass grafting than in those receiving medical therapy.

***Conclusions*—**In patients with type 2 diabetes mellitus and coronary artery disease, this study demonstrated that those with high PAI-1/tPA ratio were at higher risks of major cardiac events when treated with percutaneous coronary intervention than when treated with intensive medical therapy. **(*J Am Heart Assoc*. 2019;8:e011207. DOI: 10.1161/JAHA.118.011207.)**

Key Words: coronary artery bypass graft surgery • coronary artery disease • diabetes mellitus • percutaneous coronary intervention • plasminogen activator inhibitor-1 • tissue plasminogen activator • type 2 diabetes mellitus

The number of patients with type 2 diabetes mellitus is increasing worldwide.[1,2] Glycemic control alone may not prevent major cardiovascular events in such patients,[3–5] and some experience coronary artery disease (CAD) despite good glycemic control. However, the optimal treatment strategy for patients with type 2 diabetes mellitus and CAD remains unknown. The BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial indicated that the risk of cardiovascular events in patients with type 2 diabetes mellitus and CAD did not differ significantly between those patients receiving early revascularization and those receiving only intensive medical therapy.[6] However, detailed analyses revealed that the risk of a composite cardiac outcome, including cardiac death and myocardial infarction, was significantly higher in patients receiving percutaneous coronary intervention (PCI) than in those receiving intensive medical therapy.[7] A recent study reported that patients with diabetes mellitus are still at higher risks of adverse events after PCI than those without diabetes mellitus.[8]

Because hypercoagulability is common in patients with diabetes mellitus,[9,10] further consideration of imbalance of plasminogen activator inhibitor-1 (PAI-1) to tissue plasminogen activator (tPA) as a prothrombotic state may be useful for selecting the optimal cardiac treatment strategy in patients with diabetes mellitus and CAD. Therefore, we aimed to evaluate the association between the cardiac

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Accompanying Table S1 and Figures S1 through S4 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011207

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Clinical Perspective

What Is New?

- In patients with type 2 diabetes mellitus and coronary artery disease, those with high plasminogen activator inhibitor-1/tissue plasminogen activator ratio were at higher risks of major cardiac events, major adverse cardiovascular event, and myocardial infarction when treated with percutaneous coronary intervention than when treated with intensive medical therapy.
- In contrast, patients with type 2 diabetes mellitus and coronary artery disease receiving coronary artery bypass grafting tended to have lower risks than those receiving intensive medical therapy, regardless of the plasminogen activator inhibitor-1/tissue plasminogen activator ratio.

What Are the Clinical Implications?

- The plasminogen activator inhibitor-1/tissue plasminogen activator ratio as a prothrombotic state may be useful for optimizing cardiac treatment strategy.
- Further studies are required to assess whether additional cardiac treatment beyond intensive medical therapy is beneficial in patients with type 2 diabetes mellitus and stable coronary artery disease.

treatment strategy and risk of cardiac events in patients with type 2 diabetes mellitus and CAD on the basis of the PAI-1/tPA ratio.

Methods

The anonymized data from the BARI 2D trial have been made publicly available at the National Heart, Lung, and Blood Institute and can be accessed.[11]

Study Design and Participants

We analyzed the BARI 2D trial data, which included 2368 patients with type 2 diabetes mellitus and CAD, recruited from 49 clinical sites in the United States, Canada, Mexico, Brazil, Austria, and the Czech Republic, who were followed up from January 1, 2001, to March 31, 2005. The BARI 2D trial protocol, design, and participant characteristics have been reported previously.[6,12–15] The BARI 2D trial was a multicenter, international, randomized clinical trial using patients with type 2 diabetes mellitus and CAD. Using a 2×2 factorial design, the participants were randomly assigned to 1 of 2 treatment strategy groups: (1) early revascularization combined with intensive medical therapy versus intensive medical therapy alone, and (2) providing more endogenous or exogenous insulin versus reducing insulin resistance, with a target glycated hemoglobin level <7.0%. Randomization was stratified according to the optimal revascularization method (PCI or coronary artery bypass grafting [CABG]), which was determined a priori by the attending physician.[6,12–15] The inclusion criteria for patients were as follows: (1) aged ≥25 years and (2) a diagnosis of type 2 diabetes mellitus and CAD. Type 2 diabetes mellitus was diagnosed on the basis of patient records and either the need for treatment with oral hypoglycemic drugs or insulin or elevated levels of fasting plasma glucose (≥126 mg/dL [≥7.0 mmoL/L]). CAD was diagnosed on the basis of angiography records, using criteria of ≥50% stenosis of a major epicardial coronary artery associated with a positive stress test result or ≥70% stenosis of a major epicardial coronary artery and classic angina. Patients were excluded if they had undergone revascularization within 12 months of their inclusion to this study, required immediate coronary revascularization, had congestive heart failure of functional class III or IV (New York Heart Association), had serum creatinine levels >2 mg/dL, had hepatic disease, had stenosis ≥50% of the left main coronary artery, or had glycated hemoglobin >13.0%. Studies have recommended revascularization rather than medical therapy for patients with stenosis ≥50% of the left main coronary artery.[16,17] After randomization, all patients underwent intensive treatment to manage hypertension (blood pressure <130/80 mm Hg) and dyslipidemia (low-density lipoprotein cholesterol level <100 mg/dL). In addition, all patients received advice about weight loss, physical exercise, and smoking cessation. Because data from patients aged ≥80 years were trimmed in the BARI 2D trial data, they were excluded from the present analyses (n=38). Furthermore, patients without PAI-1 or tPA data were excluded (n=160); the final sample comprised 2170 individuals. Participants provided written informed consent before enrollment in the BARI 2D trial. The present study was approved by the institutional review board of the National Center for Global Health and Medicine. The National Heart, Lung, and Blood Institute approved our use of the BARI 2D trial data.

PAI-1 and tPA

PAI-1 activity (AU/mL) and tPA antigen (ng/mL) in the blood samples were measured at baseline.[18] Baseline tPA activity is undetectable and was not measured.[18] The BARI 2D Fibrinolysis and Coagulation Systems Core Laboratory at the University of Vermont provided kits for both proteins to all clinical sites. The site personnel were carefully trained to perform the venipuncture technique by the core personnel to minimize both trauma to patients and sample variability. The tPA antigen levels were determined with commercially available enzyme-linked immunoassay kits (Trinity Biotech PLC, Bray, Wicklow, Ireland).[19] The PAI-1 activity was assessed using a modified chromogenic substrate enzymatic assay developed by

Chmielewska and Wiman, as previously described.[19,20] Detailed information about biomarker assays has been previously reported.[18]

Outcome Measurements

Detailed analyses of the BARI 2D trial outcomes were reported previously.[6,7] An independent Mortality and Morbidity Classification Committee performed the adjudication and classification of the end point data. Patients were evaluated monthly during the first 6 months and every 3 months thereafter, up to a maximum of 6 years (until November 30, 2008). The primary outcome was major cardiac events, which was a composite end point including cardiac death and nonfatal myocardial infarction. Cardiac death included death from cardiogenic shock, congestive heart failure, myocardial infarction, and sudden cardiac death within 60 minutes of the onset of cardiac symptoms. It also included death within 30 days or within the same hospitalization for a cardiac procedure such as diagnostic angiography, PCI, or CABG. Myocardial infarction included spontaneous, silent, and procedure-related events.[6,7] Spontaneous myocardial infarction was diagnosed on the basis of doubled cardiac biomarkers (eg, creatine kinase MB or troponin) and evidence of ischemia evaluated from symptoms, electrocardiography, or imaging.[6,7] Silent myocardial infarction was diagnosed on the basis of a 2-grade Q-wave change on routine electrocardiography, according to the Minnesota code.[6,7] The secondary outcomes included major adverse cardiovascular events (MACEs), myocardial infarction, stroke, all-cause death, and cardiac death. MACE was a composite end point that included cardiovascular death, myocardial infarction, and stroke.

Statistical Analysis

Demographic data are presented as means±SDs or proportions. Continuous variables were compared using the *t* test, and categorical variables were compared using the χ^2 test or Fisher's exact test. Patients were divided into 2 groups (low and high ratio), according to a cutoff PAI-1/tPA ratio of 2 (low ratio, <2; high ratio, ≥2), which approximated the overall mean value. For a sensitivity analysis, we divided patients equally into tertile groups according to their PAI-1/tPA ratio levels (low ratio, <1.33; middle ratio, 1.33–2.20; and high ratio, ≥2.21) to assess the association between the PAI-1/tPA ratio and the risk of major cardiac events. Kaplan-Meier survival curves for primary and secondary outcomes were constructed, and the event rates were calculated in patients grouped by whether they received early revascularization or intensive medical therapy. Using the randomized design of the BARI 2D trial, a Cox proportional hazard model was used to calculate hazard ratios (HRs) for primary and secondary outcomes with 95% CIs. A comparison between the early revascularization and medical therapy cohorts was performed separately for patients with low and high PAI-1/tPA ratios. These analyses were primarily performed to assess the HRs for primary or secondary outcomes after PCI and CABG relative to those in the medical therapy group. The interaction between the cardiac treatment strategy and PAI-1/tPA ratio was also assessed. To confirm the results, we performed further analyses to assess the risk of major cardiac events in the early revascularization (PCI or CABG) group relative to the medical therapy group, according to PAI-1 activity and tPA antigen levels. The PAI-1 activity levels were divided into 2 categories according to a cutoff PAI-1 activity level of 20 AU/mL; tPA antigen levels were divided similarly according to a cutoff tPA antigen level of 10 ng/mL. Cutoff levels approximated the overall mean values. We tested the proportional hazards assumption using scaled Schoenfeld residual methods and graphical tests.[21] The proportional hazards assumption was met for almost all analyses. Because large differences in the cardiac outcomes were noted within 1 year between the PCI and medical therapy groups in patients with high PAI-1/tPA ratio, the assumption may be potentially violated. Considering the periprocedural complications of PCI, such as stent thrombosis, perforation, and distal embolization,[22] the risk in patients with high PAI-1/tPA ratio was assessed by comparing the incidence of cardiac events within 1 year and after 1 year of the follow-up in the PCI groups with the medical therapy group.

In addition, we performed a Cox proportional hazard analysis to assess the association between the PAI-1/tPA ratio and subsequent cardiovascular events in patients with type 2 diabetes mellitus and CAD.

$P<0.05$ was considered statistically significant. All statistical analyses were performed using Stata software, version 14.1 (Stata Corp, College Station, TX).

Results

Characteristics of the Study Participants

The baseline characteristics of the patient group with the low (n=1276) and high (n=894) PAI-1/tPA ratios are presented in Table 1. The mean±SD ages of patients with the low and high PAI-1/tPA ratios were 62.8±8.4 and 60.1±8.5 years, and the proportions of women were 28.4% and 32.6%, respectively. The baseline characteristics of each condition were not significantly different between the early revascularization and medical therapy groups. Similar results were observed in the PCI and CABG strata.

Primary and Secondary Outcomes

The overall mean±SD follow-up period was 4.1±1.7 years: 4.0±1.8 and 4.1±1.7 years for patients with low and high PAI-1/tPA ratios, respectively. The Kaplan-Meier survival

Table 1. Baseline Characteristics of Patients With Low and High Ratios of PAI-1/tPA

Characteristics	Low PAI-1/tPA Ratio			High PAI-1/tPA Ratio		
	Medical Therapy (N=665)	Revascularization (N=611)	*P* Value	Medical Therapy (N=429)	Revascularization (N=465)	*P* Value
Age, y	62.9±8.5	62.7±8.2	0.71	60.0±8.5	60.3±8.5	0.53
Female sex, %	29.0	27.7	0.59	31.5	33.6	0.50
Race and ethnicity (white), %	71.1	67.6	0.17	77.4	78.5	0.69
Smoking status, %						
Never	33.7	34.1	0.87	29.2	35.1	0.06
Former	55.7	53.8	0.48	56.6	51.5	0.12
Current	10.6	12.1	0.38	14.2	13.4	0.71
Education level, %						
Less than high school	36.5	39.6	0.25	33.6	31.0	0.41
High school	23.6	20.2	0.14	21.0	25.2	0.13
More than high school	39.9	40.2	0.91	45.4	43.8	0.62
Physical activity, %						
Sedentary	18.8	19.1	0.89	23.5	21.5	0.46
Mild	40.0	42.7	0.31	42.7	43.4	0.82
Moderate/strenuous	41.2	38.1	0.26	33.8	35.1	0.67
Body mass index, kg/m^2*	31.2±5.7	31.0±5.7	0.48	33.4±5.6	32.8±6.0	0.13
Duration of diabetes mellitus ≥5 y, %	71.6	69.5	0.41	62.5	61.2	0.69
Hypertension, %	82.4	82.5	0.96	83.9	84.0	0.98
Hypercholesterolemia, %	82.5	82.2	0.88	82.0	86.3	0.08
History of MI, %	32.1	31.6	0.87	30.0	29.1	0.84
History of stroke/TIA, %	11.5	10.7	0.62	9.1	8.2	0.63
History of chronic heart failure, %	6.5	8.7	0.14	6.1	5.2	0.54
Medications, %						
ACE-I/ARB	80.2	76.7	0.12	79.5	76.1	0.22
Calcium channel blocker	31.4	29.1	0.38	35.9	32.4	0.27
β Blockers	75.4	72.8	0.30	70.2	75.2	0.09
Diuretics	40.5	41.9	0.60	37.5	38.4	0.79
Statin	76.4	75.1	0.58	75.5	76.2	0.80
Aspirin	89.3	86.1	0.08	89.2	89.2	0.99
Biguanides	52.8	49.4	0.23	60.4	61.1	0.81
Sulfonylureas	54.0	51.4	0.35	53.2	52.7	0.89
Insulin	32.0	30.3	0.51	25.4	25.2	0.94
Glycated hemoglobin, %	7.6±1.6	7.7±1.6	0.60	7.7±1.5	7.6±1.6	0.21
Estimated GFR, mL/min per 1.73 m^2	70.2±20.8	71.7±36.8	0.33	75.0±21.8	73.5±20.9	0.28
Glycemic treatment assignment						
Insulin providing, %	49.6	51.9	0.42	49.2	48.0	0.71

Data are presented as percentage of participants or mean±SD. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; GFR, glomerular filtration rate; MI, myocardial infarction; PAI-1/tPA, plasminogen activator inhibitor-1/tissue plasminogen activator; TIA, transient ischemic attack.
*Body mass index was calculated as weight in kilograms divided by the square of height in meters.

curves for major cardiac events in patients with low and high PAI-1/tPA ratios are shown in Figure 1. The risk of major cardiac events in patients with low or high PAI-1/tPA ratios did not differ significantly between the early revascularization and medical therapy groups (HR in the early revascularization group compared with the medical therapy group in patients

with low PAI-1/tPA ratio: 0.83; 95% CI, 0.63–1.10; *P*=0.19 [Figure 1A]; and HR in those with high PAI-1/tPA ratio: 1.30; 95% CI, 0.90–1.88; *P*=0.16 [Figure 1B]). In the PCI stratum, the risk of major cardiac events in patients with low PAI-1/tPA ratio did not differ between patients receiving PCI and those receiving medical therapy (HR, 0.95; 95% CI, 0.66–1.36; *P*=0.77; Figure 1C); however, in patients with high PAI-1/tPA ratio, the risk was significantly higher in the PCI group than in the medical therapy group (HR, 1.84; 95% CI, 1.16–2.93; *P*=0.01; Figure 1D). A significant interaction was observed between the cardiac treatment strategy (PCI or medical therapy) and the PAI-1/tPA ratio (*P* value for interaction=0.02). The incidence of major cardiac events within 1 year of follow-up in patients with high PAI-1/tPA ratio was significantly higher in the PCI group than in the medical therapy group (10.1% versus 3.2%, respectively [*P*=0.001]), whereas the risk after 1 year of follow-up did not significantly differ between the 2 groups (HR, 1.22; 95% CI, 0.66–2.26; *P*=0.53). Conversely, in the CABG stratum, although there was no significant difference, risk of major cardiac events in both patients with low and high PAI-1/tPA ratios was lower in the CABG group than in the medical therapy group (HR in those with low PAI-1/tPA ratio: 0.66; 95% CI, 0.42–1.05; *P*=0.08 [Figure 1E]; and HR in those with high PAI-1/tPA ratio: 0.62; 95% CI, 0.32–1.22; *P*=0.16 [Figure 1F]). No significant interaction was observed between the cardiac treatment strategy (CABG or medical therapy) and the PAI-1/tPA ratio (*P* value for interaction=0.87).

Figure 2 and Figure S1 show the Kaplan-Meier survival curves for MACE, myocardial infarction, and stroke in the PCI and CABG strata, respectively. The event rates and HRs for cardiovascular events and death in the PCI and CABG strata are shown in Table 2. In the PCI stratum, the risk of MACE in patients with low PAI-1/tPA ratio did not differ significantly between the PCI and medical therapy groups (HR, 1.06; 95% CI, 0.77–1.47; *P*=0.72; Figure 2A). However, in patients with high PAI-1/tPA ratio, the risk of MACE was significantly higher in the PCI group than in the medical therapy group (HR, 1.77; 95% CI, 1.14–2.76; *P*=0.01; Figure 2B). Similarly, the risk of myocardial infarction in patients with low PAI-1/tPA ratio did not differ significantly between the 2 groups (HR, 0.76; 95% CI, 0.50–1.15; *P*=0.55; Figure 2C), whereas that in patients with high PAI-1/tPA ratio was significantly higher in the PCI group than in the medical therapy group (HR, 1.87; 95% CI, 1.13–3.09; *P*=0.01; Figure 2D). There was a significant interaction between the cardiac treatment strategy (PCI or medical therapy) and the PAI-1/tPA ratio (*P* value for interaction=0.006). The incidence of MACE within 1 year of follow-up in patients with high PAI-1/tPA ratio was significantly higher in the PCI group than in the medical therapy group (10.4% versus 3.9%, respectively [*P*=0.003]), whereas the risk after 1 year of follow-up was not significantly different between the 2 groups (HR, 1.19; 95% CI, 0.66–2.15; *P*=0.56). Similar findings were observed in the analysis for myocardial infarction. The risk of stroke was not significantly different between the PCI and medical therapy groups regardless of the PAI-1/tPA ratio (Figure 2E and 2F).

In the CABG stratum, the risks of both MACE and myocardial infarction in patients with low PAI-1/tPA ratio were significantly lower in the CABG group than in the medical therapy group (HR for MACE: 0.64; 95% CI, 0.41–0.98; *P*=0.03; Figure S1A; HR for myocardial infarction: 0.46; 95% CI, 0.26–0.80; *P*=0.006; Figure S1C). However, there were no significant differences in the risks of MACE and myocardial infarction in patients with high PAI-1/tPA ratio (HR for MACE: 0.66; 95% CI, 0.36–1.23; *P*=0.19; Figure S1B; HR for myocardial infarction: 0.72; 95% CI, 0.72–1.56; *P*=0.40; Figure S1D). For MACE and myocardial infarction, no significant interaction was observed between the cardiac treatment strategy (CABG or medical therapy) and the PAI-1/tPA ratio (*P* values for interaction=0.90 and 0.34, respectively). There were no significant differences in the risks of stroke between the CABG and medical therapy groups, regardless of the PAI-1/tPA ratio (Figure S1E and S1F).

Sensitivity analyses using tertile groups according to the PAI-1/tPA ratio levels found that the risk of major cardiac events was significantly higher in the PCI group than in the medical therapy group only in the patients with a high ratio (HR, 2.05; 95% CI, 1.20–3.49; *P*=0.008; Figure S2).

Major Cardiac Events According to PAI-1 Activity and tPA Antigen Levels

The Kaplan-Meier survival curves for major cardiac events in the revascularization and medical therapy groups are shown in Figures S3 and S4, respectively. The risks of major cardiac events were not significantly different between the revascularization and medical therapy groups, regardless of PAI-1 activity level (Figure S3A and S3B). In the PCI stratum, the risk of major cardiac events in patients with low PAI-1 activity levels was not significantly different between the PCI and medical therapy groups (HR, 1.04; 95% CI, 0.73–1.48; *P*=0.83; Figure S3C), whereas the risk in patients with high PAI-1 activity levels was significantly higher in the PCI group than in the medical therapy group (HR, 1.66; 95% CI, 1.04–2.65; *P*=0.03; Figure S3D). In the CABG stratum, the risk of major cardiac events in patients with low PAI-1 activity levels was significantly lower than that in the medical therapy group (HR, 0.63; 95% CI, 0.39–0.99; *P*=0.04; Figure S3E), but not significantly different in patients with high PAI-1 activity levels (HR, 0.71; 95% CI, 0.37–1.36; *P*=0.30; Figure S3F). The risks of major cardiac events were not significantly different between the revascularization and medical therapy groups, regardless of tPA antigen level (Figure S4).

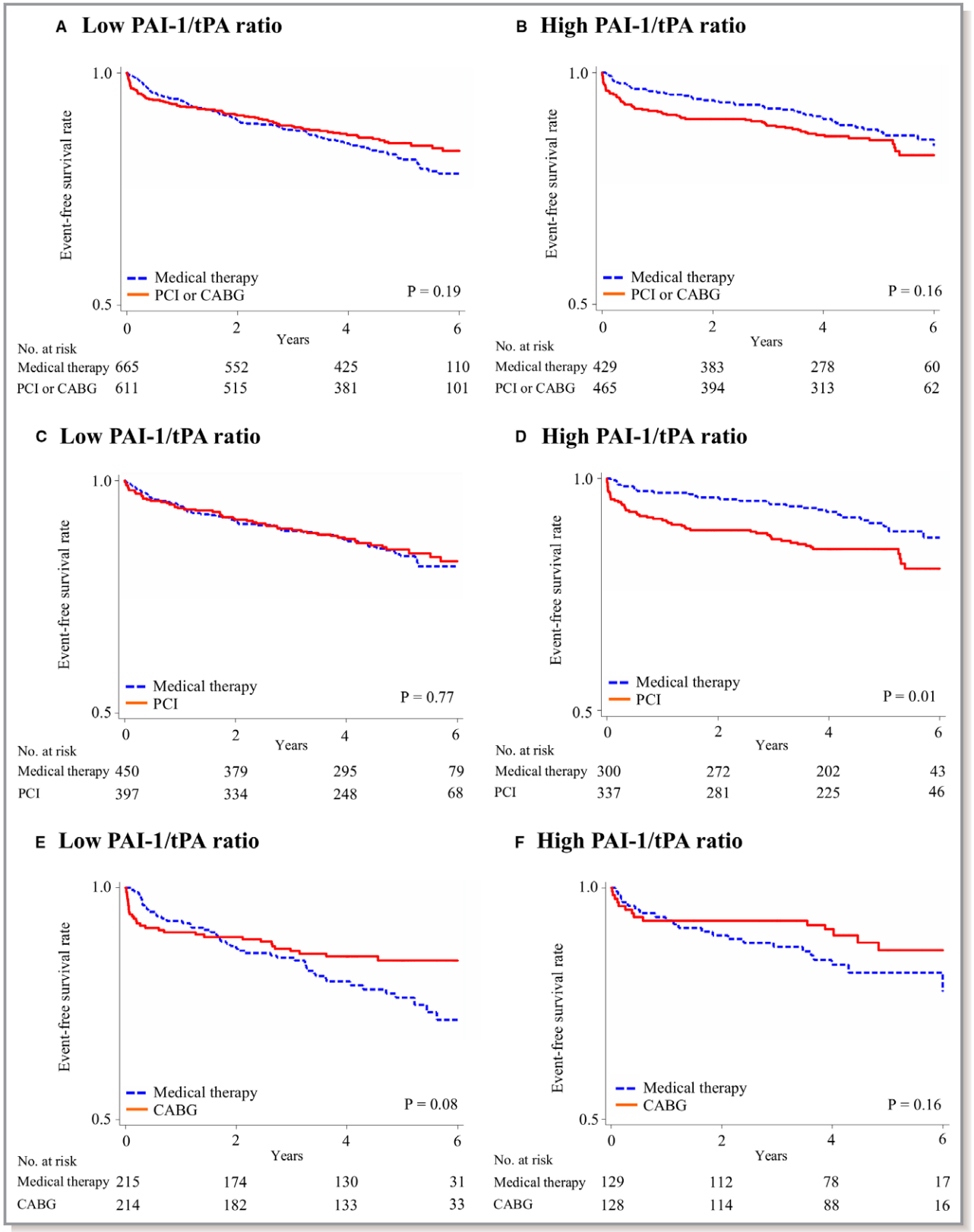

Figure 1. Kaplan-Meier survival curves for major cardiac events in patients with low and with high plasminogen activator inhibitor-1/tissue plasminogen activator (PAI-1/tPA) ratio. Rates of freedom from major cardiac events: early revascularization vs medical therapy (**A** and **B**), percutaneous coronary intervention (PCI) vs medical therapy (**C** and **D**), and coronary artery bypass grafting (CABG) vs medical therapy (**E** and **F**). Major cardiac events include cardiac death and nonfatal myocardial infarction.

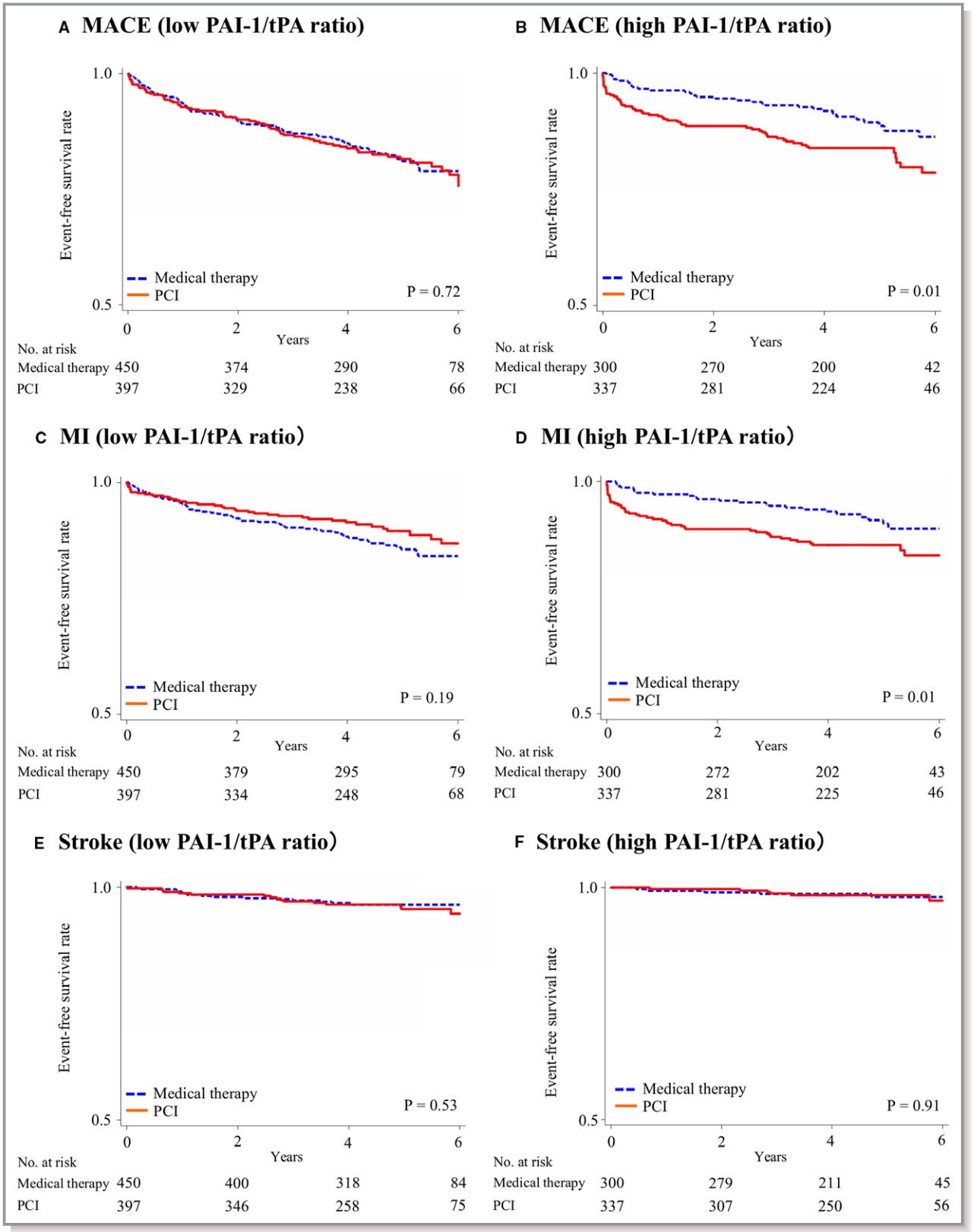

Figure 2. Cardiovascular events in patients receiving percutaneous coronary intervention (PCI) or intensive medical therapy, according to low and high plasminogen activator inhibitor-1/tissue plasminogen activator (PAI-1/tPA) ratio. Rates of freedom from major adverse cardiovascular events (MACEs; **A** and **B**), myocardial infarction (MI; **C** and **D**), and stroke (**E** and **F**). MACE includes cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

Table 2. Cardiac Events and Mortality in Patients With and Without History of Myocardial Infarction

Variable	Low PAI-1/tPA Ratio			High PAI-1/tPA Ratio		
	Medical Therapy (N=450)	PCI (N=397)	*P* Value	Medical Therapy (N=300)	PCI (N=337)	*P* Value
Event						
Major cardiac events						
No. of patients	65	54		27	53	
Event rate (per 1000 person-years)	35.3	33.6		21.1	39.2	
Hazard ratio (95% CI)	1.00 (Reference)	0.95 (0.66–1.36)	0.77	1.00 (Reference)	1.84 (1.16–2.93)	0.01
Major adverse cardiovascular events						
No. of patients	76	70		30	57	
Event rate (per 1000 person-years)	41.8	44.6		23.6	42.2	
Hazard ratio (95% CI)	1.00 (Reference)	1.06 (0.77–1.47)	0.72	1.00 (Reference)	1.77 (1.14–2.76)	0.01
Myocardial infarction						
No. of patients	57	38		23	46	
Event rate (per 1000 person-years)	30.9	23.6		17.9	34.0	
Hazard ratio (95% CI)	1.00 (Reference)	0.76 (0.50–1.15)	0.55	1.00 (Reference)	1.87 (1.13–3.09)	0.01
Stroke						
No. of patients	15	16		5	6	
Event rate (per 1000 person-years)	7.7	9.7		3.8	4.0	
Hazard ratio (95% CI)	1.00 (Reference)	1.25 (0.62–2.53)	0.53	1.00 (Reference)	1.06 (0.32–3.49)	0.91
All-cause death						
No. of patients	57	47		26	32	
Event rate (per 1000 person-years)	25.6	24.8		17.7	19.4	
Hazard ratio (95% CI)	1.00 (Reference)	0.97 (0.66–1.43)	0.88	1.00 (Reference)	1.10 (0.65–1.84)	0.72
Cardiac death						
No. of patients	19	20		10	14	
Event rate (per 1000 person-years)	8.5	10.6		6.8	8.5	
Hazard ratio (95% CI)	1.00 (Reference)	1.23 (0.65–2.30)	0.52	1.00 (Reference)	1.25 (0.55–2.81)	0.59
	Medical Therapy (N=215)	CABG (N=214)	*P* Value	Medical Therapy (N=129)	CABG (N=128)	*P* Value
Event						
Major cardiac events						
No. of patients	47	31		22	14	
Event rate (per 1000 person-years)	56.8	36.8		43.2	26.5	
Hazard ratio (95% CI)	1.00 (Reference)	0.66 (0.42–1.05)	0.08	1.00 (Reference)	0.62 (0.32–1.22)	0.16
Major adverse cardiovascular events						
No. of patients	54	34		25	17	
Event rate (per 1000 person-years)	66.0	40.8		49.7	32.5	
Hazard ratio (95% CI)	1.00 (Reference)	0.64 (0.41–0.98)	0.03	1.00 (Reference)	0.66 (0.36–1.23)	0.19
Myocardial infarction						
No. of patients	40	18		15	11	
Event rate (per 1000 person-years)	51.4	16.9		29.4	20.8	

Continued

Table 2. Continued

	Medical Therapy (N=215)	CABG (N=214)	*P* Value	Medical Therapy (N=129)	CABG (N=128)	*P* Value
Hazard ratio (95% CI)	1.00 (Reference)	0.46 (0.26–0.80)	0.006	1.00 (Reference)	0.72 (0.33–1.56)	0.40
Stroke						
No. of patients	7	3		4	3	
Event rate (per 1000 person-years)	7.6	3.4		7.5	5.5	
Hazard ratio (95% CI)	1.00 (Reference)	0.45 (0.11–1.76)	0.25	1.00 (Reference)	0.75 (0.17–3.37)	0.71
All-cause death						
No. of patients	33	32		21	11	
Event rate (per 1000 person-years)	32.2	32.5		35.3	18.3	
Hazard ratio (95% CI)	1.00 (Reference)	1.01 (0.62–1.64)	0.96	1.00 (Reference)	0.51 (0.25–1.06)	0.07
Cardiac death						
No. of patients	15	17		13	6	
Event rate (per 1000 person-years)	14.6	17.3		21.9	10.0	
Hazard ratio (95% CI)	1.00 (Reference)	1.18 (0.59–2.36)	0.64	1.00 (Reference)	0.45 (0.17–1.19)	0.11

CABG indicates coronary artery bypass grafting; PAI-1/tPA, plasminogen activator inhibitor-1/tissue plasminogen activator; PCI, percutaneous coronary intervention.

To assess the impact of PAI-1 activity and tPA antigen levels on major cardiac events, we subdivided patients into 4 categories, as follows: (1) high PAI-1 activity and high tPA antigen levels, (2) high PAI-1 activity and low tPA antigen levels, (3) low PAI-1 activity and high tPA antigen levels, and (4) low PAI-1 activity and low tPA antigen levels. As shown in Figure 3, only patients in category 2 had a significant difference in the risk of major cardiac events; risk was significantly higher in the PCI group than in the medical therapy group (HR, 6.28; 95% CI, 1.44–27.5; *P*=0.01; Figure 3B).

Association Between the PAI-1/tPA Ratio and Subsequent Cardiovascular Events

As seen in Table S1, after multivariable adjustment, the risks of major cardiac events, MACE, myocardial infarction, stroke, all-cause death, and cardiac death were not significantly different between patients with low and high PAI-1/tPA ratios.

Discussion

This study revealed that the risks of major cardiac events, MACE, and myocardial infarction in patients with high PAI-1/tPA ratio were significantly higher in those receiving PCI than in those receiving intensive medical therapy, with large differences within 1 year of the follow-up. However, the risks in patients with low PAI-1/tPA ratio were not significantly different between those receiving PCI and intensive medical therapy. This difference represents a significant interaction between the cardiac treatment strategy and the PAI-1/tPA ratio. Furthermore, in patients with high PAI-1 activity and low tPA antigen levels, the risk of major cardiac events was significantly higher in those receiving PCI than in those receiving intensive medical therapy. In contrast, regardless of the PAI-1/tPA ratio, these risks seemed to be lower in patients receiving CABG than in those receiving intensive medical therapy. No significant association was observed between the PAI-1/tPA ratio and subsequent cardiovascular events in patients with type 2 diabetes mellitus and stable CAD.

Thrombotic/Thrombolytic Balance and Adverse Cardiac Events

The coagulation and fibrinolytic pathways are composed of a complicated cascade. When activated, the coagulation proteins lead to thrombin and fibrin generation. On the other hand, plasmin is an important enzyme within the fibrinolytic cascade. Plasmin is regulated by plasminogen activators, such as tPA, and indirectly by plasminogen-activator inhibitors, such as PAI-1.tPA is secreted by endothelial cells,[23] and elevated tPA levels are associated with endothelial cell dysfunction and damage.[24] Elevated tPA levels can generate plasmin and thus degrade fibrin; this may be beneficial because endothelial dysfunction is associated with an increased risk of thrombosis.[9,10] Conversely, elevated PAI-1 activity levels reflect impaired fibrinolysis and are associated with an increased risk of coronary events and reinfarction after myocardial infarction.[25–29] Increased PAI-1 concentrations are observed in patients with type 2 diabetes mellitus.[30–33] Insulin and

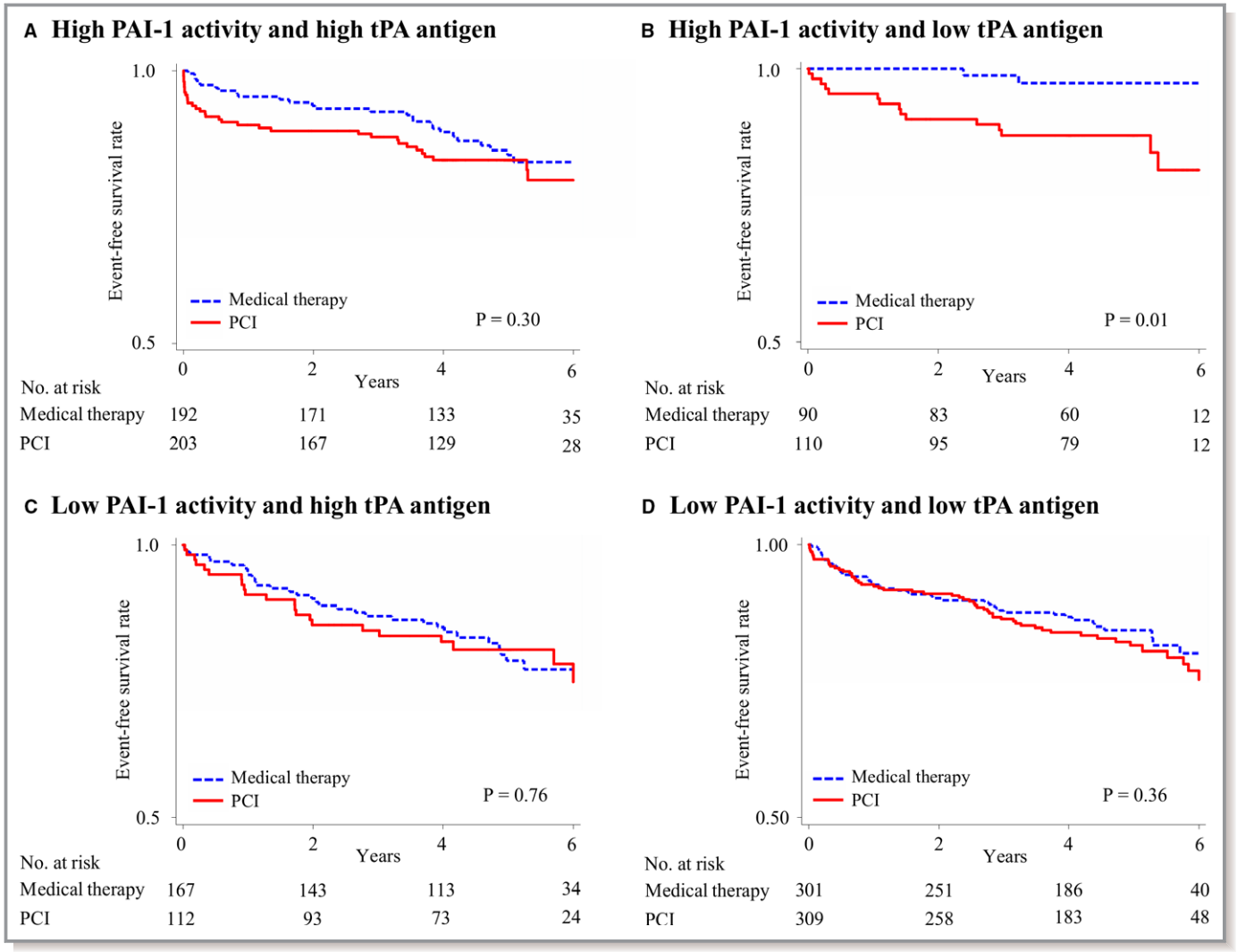

Figure 3. Major cardiac events in patients receiving percutaneous coronary intervention (PCI) or intensive medical therapy, according to categorization by plasminogen activator inhibitor-1 (PAI-1) activity and tissue plasminogen activator (tPA) antigen levels. Rates of freedom from major cardiac events in patients with high PAI-1 activity and high tPA antigen levels (**A**), high PAI-1 activity and low tPA antigen levels (**B**), low PAI-1 activity and high tPA antigen levels (**C**), and low PAI-1 activity and low tPA antigen levels (**D**).

precursors of insulin were shown to directly augment the expression of PAI-1.[34,35] A previous study demonstrated higher PAI-1 levels in obese and diabetic patients than in lean control subjects despite the lack of significant differences in plasma concentrations of tPA.[30] The impaired fibrinolysis in patients with diabetes mellitus can result in an increased risk of cardiovascular events.[36] Although data are limited, higher PAI-1 levels after PCI may also result in a higher incidence of all-cause mortality or acute coronary syndrome.[37] A study suggested that increased PAI activity and reduced tPA antigen are associated with CAD.[38] Moreover, a high PAI-1/tPA ratio was significantly associated with an increased risk of myocardial infarction.[39] Further studies are warranted to reveal the association between the PAI-1/tPA ratio and coronary events after revascularization in patients with type 2 diabetes mellitus.

The present study demonstrated that patients with high PAI-1/tPA ratio had an increased risk of major cardiac events when they received PCI than when they received intensive medical therapy, with a large difference of cardiac event rates between PCI and medical therapy groups at an early period after the follow-up. Stent thrombosis, which can cause luminal occlusion and myocardial infarction, is a major problem after PCI. PCI using stent in patients with high PAI-1/tPA ratio, which represents prothrombotic state, may have higher risk of stent thrombosis. A recent report suggested that death within the 30-day period after PCI may be attributed to PCI-related complications, particularly stent thrombosis.[40] Thus, PCI for patients with high PAI-1/tPA ratio can be potentially dangerous. To reveal the association between the PAI-1/tPA ratio and PCI-related complications, such as stent thrombosis and in-

stent restenosis, further studies are warranted. Conversely, no significant interaction between cardiac treatment strategy (CABG or medical therapy) and the PAI-1/tPA ratio was observed, suggesting that CABG may be beneficial in patients with type 2 diabetes mellitus and stable CAD. The risk of stroke was not significantly different between patients receiving early revascularization (PCI or CABG) combined with intensive medical therapy and those receiving intensive medical therapy alone, regardless of the PAI-1/tPA ratio. In patients receiving intensive medical therapy, vascular events (excluding coronary events) may not be associated with the cardiac treatment strategy. Moreover, the small number of stroke events may have introduced some bias to our results. In addition, the PAI-1/tPA ratio itself was not significantly associated with subsequent cardiovascular events. Although the exact reasons remain unknown, the favorable effects of intensive medical therapy for all participants in the BARI 2D trial may suppress the higher risks of an imbalanced PAI-1/tPA ratio. Further studies are required to assess whether additional cardiac treatment beyond intensive medical therapy is beneficial in patients with type 2 diabetes mellitus and stable CAD.

Limitations

The present study has several limitations. First, this study is a secondary analysis of a randomized controlled trial. Consequently, the definition of myocardial infarction used in the present study was different from the current definition, including acute myocardial injury with the detection of an increase and/or decrease of cardiac troponin values with at least 1 value above the 99th percentile upper reference limit.[41] In addition, the results may reflect the type II errors because of insufficient statistical power resulting from a small number of subjects. Furthermore, uncontrolled or residual confounding may be present. Therefore, our results need to be confirmed by newly randomized controlled trials applying the updated definition. Second, some patients in the BARI 2D trial underwent PCI with a bare-metal stent or no stent.[6] Whether the PAI-1/tPA ratio affects the major cardiac event risk in patients receiving PCI with current drug-eluting stent remains unknown. Because stent thrombosis is still a serious problem in patients with drug-eluting stents, further studies are required to evaluate whether the status of the PAI-1/tPA ratio affects the cardiac outcomes in patients receiving PCI with drug-eluting stent. Third, the type of revascularization (PCI or CABG) was assigned at the physician's discretion, and the number of patients in each stratum was small. Although the patients were randomly assigned to revascularization and medical therapy in both PCI and CABG strata, further large-scale studies are required for patients with type 2 diabetes mellitus and CAD considering the PAI-1/tPA ratio. Fourth, our PAI-1/tPA ratio cutoff may not be an optimal indicator for cardiac treatment determinant. Further studies are needed to reveal the optimal cutoff value for the best selection of the cardiac treatment.

Conclusion

This study demonstrated that in patients with type 2 diabetes mellitus and stable CAD, those with high PAI-1/tPA ratios were at higher risks of major cardiac events, MACE, and myocardial infarction when treated with PCI than when treated with intensive medical therapy. However, patients receiving CABG tended to have lower risks than those receiving intensive medical therapy, regardless of the PAI-1/tPA ratio. These results indicate that PCI should not be recommended in favor of intensive medical therapy or CABG in patients with type 2 diabetes mellitus and stable CAD who have a high PAI-1/tPA ratio. No current treatment is known to lower the PAI-1/tPA ratio itself. Further studies are warranted to assess whether the PAI-1/tPA ratio can be an indicator for cardiac treatment determinant and a treatment target to improve outcomes.

Author Contributions

Study concept and design: Tsujimoto. Data acquisition: Tsujimoto. Analysis and data interpretation: Tsujimoto and Kajio. Drafting the manuscript: Tsujimoto and Kajio. Statistical analysis: Tsujimoto. Tsujimoto had full access to all data in the study and takes responsibility for the integrity and accuracy of data analysis. This article was prepared using BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) Research Materials obtained from the National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the BARI 2D trial or the NHLBI.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Cardiovascular events according to the PAI-1/tPA ratios.

	PAI-1/tPA ratio		P value
	Low	High	
	(n = 1,276)	(n = 894)	
Major cardiac events			
No. of patients	197	116	
Event rate (per 1,000 person-year)	38.5	31.6	
Unadjusted HR	1.00 [ref]	0.82 (0.66–1.04)	0.10
Multivariable-adjusted HR, model 1*	1.00 [ref]	0.89 (0.69–1.14)	0.34
Multivariable-adjusted HR, model 2†	1.00 [ref]	0.91 (0.71–1.17)	0.46
Major adverse cardiovascular events			
No. of patients	234	129	
Event rate (per 1,000 person-year)	46.5	35.4	
Unadjusted HR	1.00 [ref]	0.77 (0.62–0.95)	0.01
Multivariable-adjusted HR, model 1	1.00 [ref]	0.81 (0.64–1.02)	0.11
Multivariable-adjusted HR, model 2	1.00 [ref]	0.82 (0.65–1.04)	0.11

Myocardial infarction			
No. of patients	153	95	
Event rate (per 1,000 person-year)	29.9	25.9	
Unadjusted HR	1.00 [ref]	0.87 (0.67–1.12)	0.28
Multivariable-adjusted HR, model 1	1.00 [ref]	0.90 (0.69–1.19)	0.47
Multivariable-adjusted HR, model 2	1.00 [ref]	0.93 (0.70–1.23)	0.60
Stroke			
No. of patients	41	18	
Event rate (per 1,000 person-year)	7.6	4.6	
Unadjusted HR	1.00 [ref]	0.61 (0.35–1.07)	0.08
Multivariable-adjusted HR, model 1	1.00 [ref]	0.61 (0.32–1.15)	0.13
Multivariable-adjusted HR, model 2	1.00 [ref]	0.61 (0.32–1.16)	0.13
All-cause death			
No. of patients	169	90	
Event rate (per 1,000 person-year)	27.6	20.9	
Unadjusted HR	1.00 [ref]	0.76 (0.59–0.98)	0.03

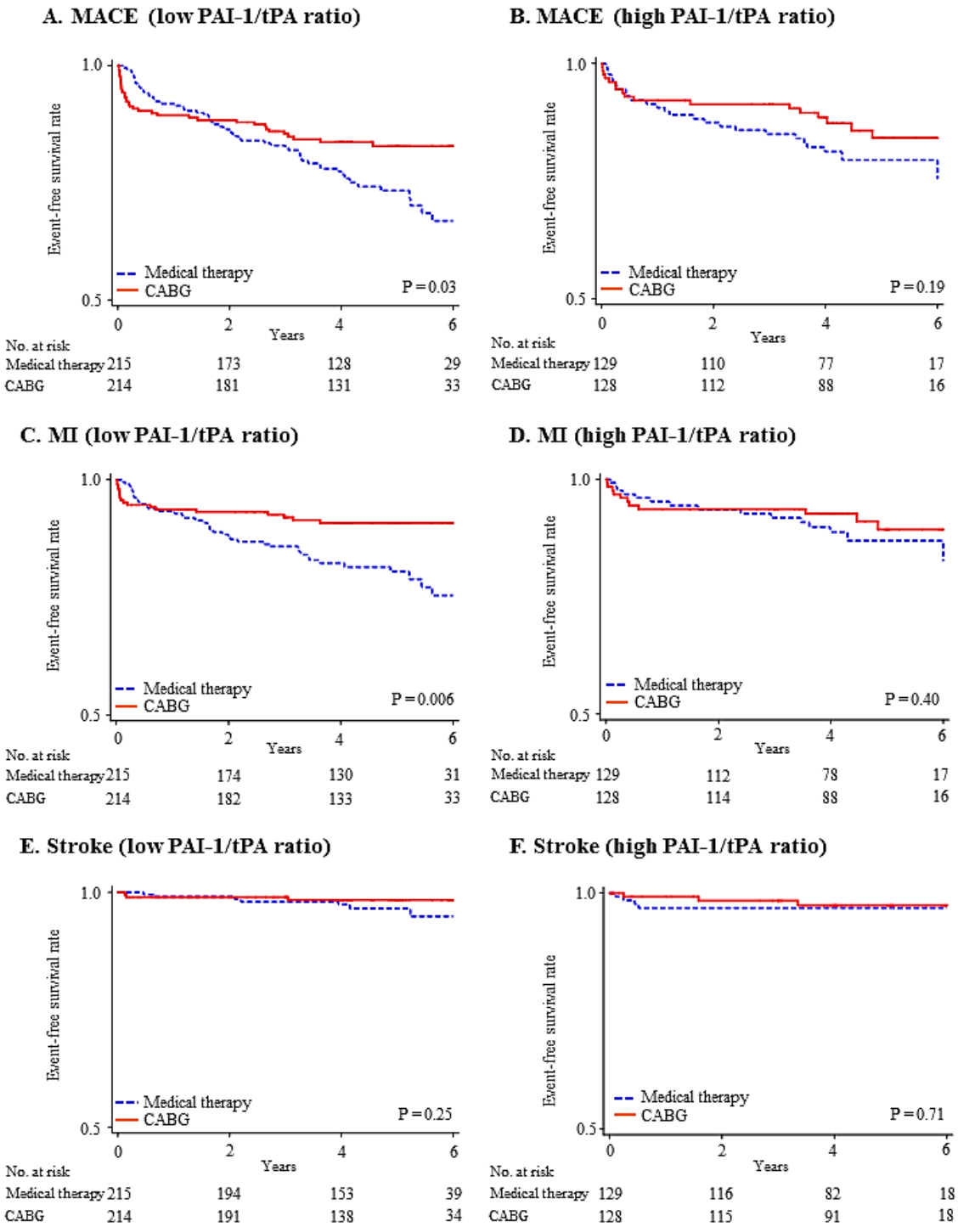
Multivariable-adjusted HR, model 1	1.00 [ref]	0.96 (0.73–1.26)	0.75
Multivariable-adjusted HR, model 2	1.00 [ref]	0.97 (0.74–1.28)	0.83
Cardiac death			
No. of patients	71	43	
Event rate (per 1,000 person-year)	11.6	10.0	
Unadjusted HR	1.00 [ref]	0.86 (0.59–1.25)	0.42
Multivariable-adjusted HR, model 1	1.00 [ref]	1.07 (0.71–1.61)	0.75
Multivariable-adjusted HR, model 2	1.00 [ref]	1.10 (0.73–1.66)	0.65

Data are presented as number or hazard ratio (95% CI).

*In model 1, the following confounders were adjusted: age, sex, race and ethnicity, educational status, physical activity, smoking status, body mass index, duration of diabetes, hypertension, hypercholesterolemia, previous history of myocardial infarction, previous history of stroke/transient ischemic attack, previous history of chronic heart failure, glycated hemoglobin levels, estimated glomerular filtration rate levels, glycemic treatment assignment (insulin sensitizing or insulin providing), and cardiac treatment assignment (early revascularization or medical therapy).

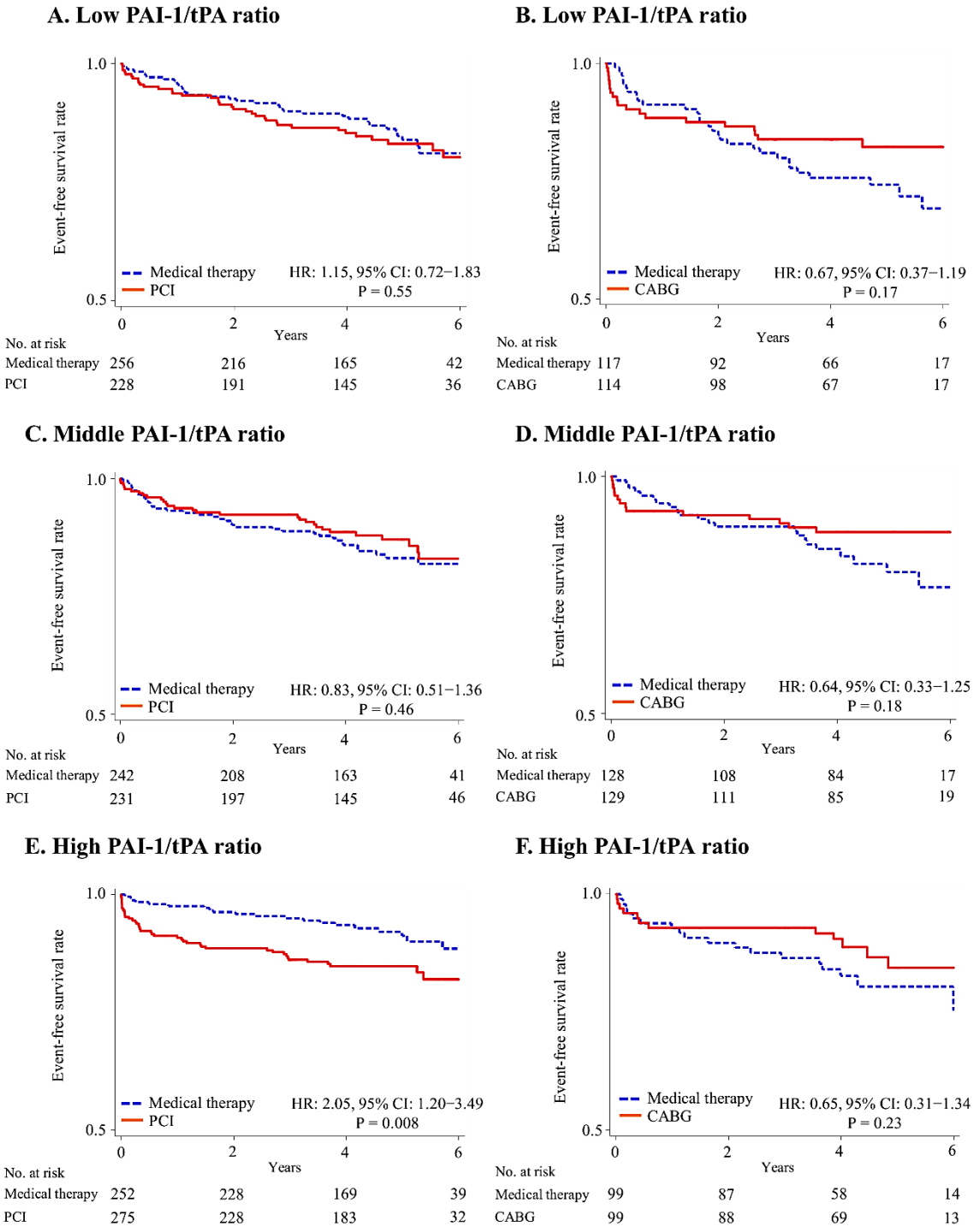
†In model 2, the following confounders were adjusted: age, sex, race and ethnicity, educational status, physical activity, smoking status, body mass index, duration of diabetes, hypertension, hypercholesterolemia, previous history of myocardial infarction, previous history of stroke/transient ischemic attack, previous history of chronic heart failure, glycated hemoglobin levels, estimated glomerular filtration rate levels, use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, use of beta blockers, use of diuretics, use of statins, use of aspirin, use of insulin, glycemic treatment assignment (insulin sensitizing or insulin providing), and cardiac treatment assignment (early revascularization or medical therapy).

Figure S1. Cardiovascular events in patients receiving CABG or intensive medical therapy, according to low and high PAI-1/tPA ratio.



Rates of freedom from MACE (A and B), MI (C and D), and stroke (E and F). MACE includes cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. PAI-1, plasminogen activator inhibitor-1; tPA, tissue plasminogen activator; MACE, major adverse cardiovascular events; MI, myocardial infarction; CABG, coronary artery bypass graft surgery.

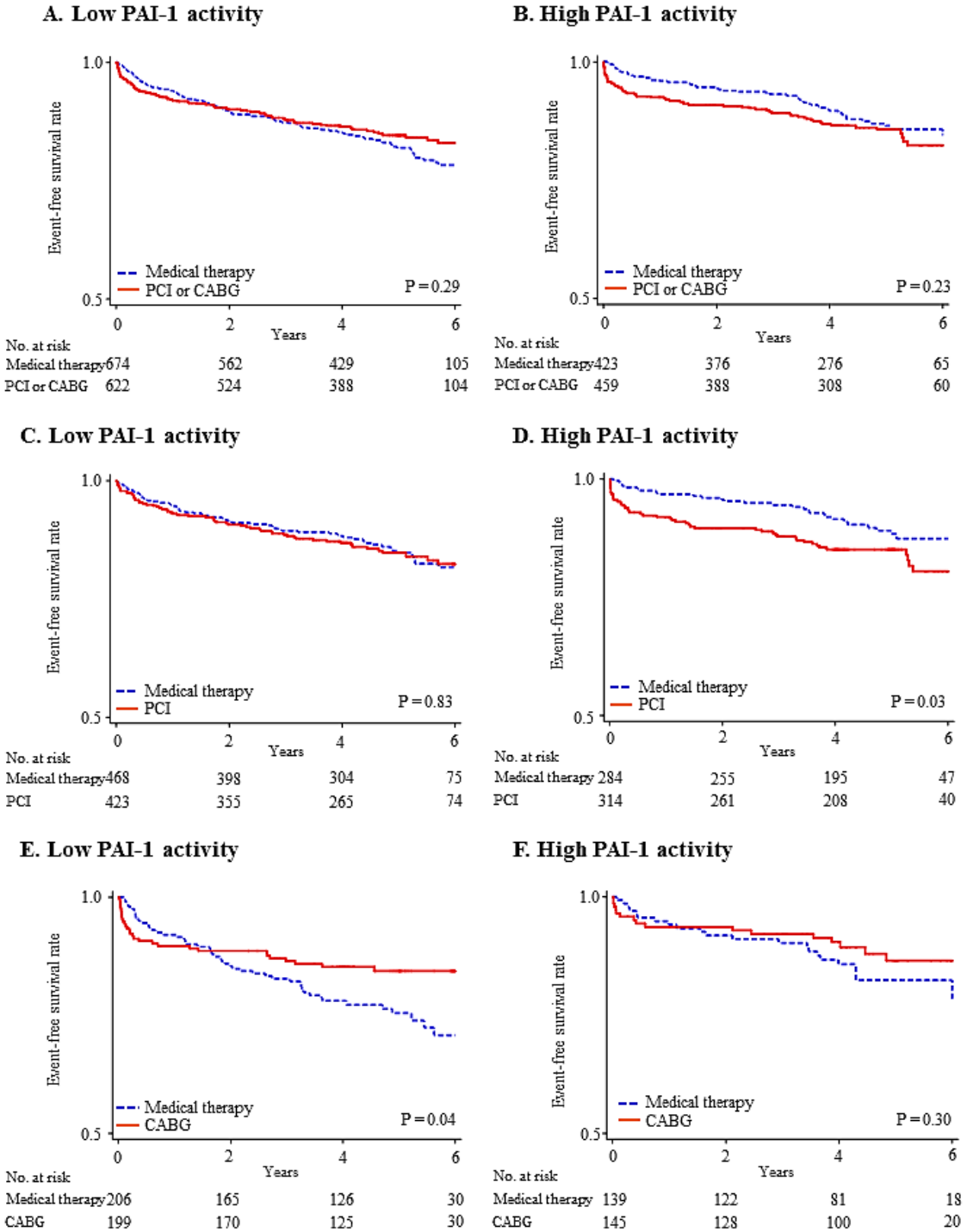
Figure S2. Major cardiac events in patients receiving revascularization or intensive medical therapy, according to low, middle, and high PAI-1/tPa ratio activity levels.



Rates of freedom from major cardiac events in the low (A and B), middle (C and D), and high (E and F) PAI-1/tPA ratio patients. PAI-1, plasminogen activator inhibitor-1;

tPA, tissue plasminogen activator; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery.

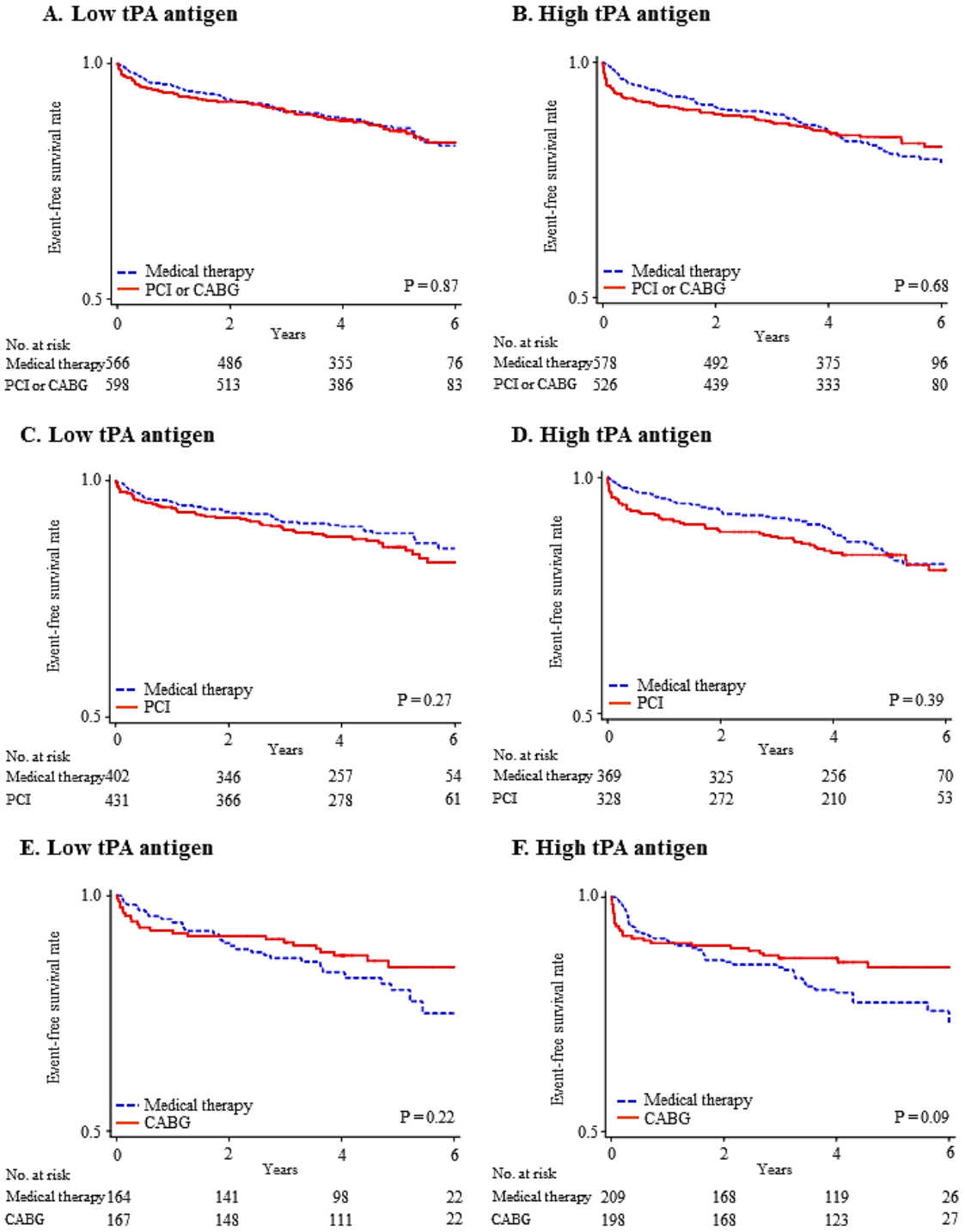
Figure S3. Major cardiac events in patients receiving revascularization or intensive medical therapy, according to low and high PAI-1 activity levels.



Rates of freedom from major cardiac events in all patients (A and B), in the PCI stratum (C and D), and in the CABG stratum (E and F). PAI-1, plasminogen activator inhibitor-

1; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery.

Figure S4. Major cardiac events in patients receiving revascularization or intensive medical therapy, according to low and high tPA antigen levels.



Rates of freedom from major cardiac events in all patients (A and B), in the PCI stratum (C and D), and in the CABG stratum (E and F). tPA, tissue plasminogen activator; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery.