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Comparison of Levels of Plasminogen Activator Inhibitor-1, Tissue Type Plasminogen Activator Antigen, Fibrinogen, and D-Dimer in Various Age Decades in Patients with Type-2 Diabetes Mellitus and Stable Coronary Artery Disease (From the BARI 2d Trial)

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Abstract

Advancing age is associated with down-regulation of fibrinolysis in normal subjects reflecting high concentrations of plasminogen activator inhibitor-1 (PAI-1) in blood implicated in increasing cardiovascular morbidity and mortality. We sought to delineate the relation of PAI-1 to several factors including age, sex, and ethnicity in patients with type 2 diabetes mellitus (DM) and stable coronary artery disease (CAD) enrolled in the BARI 2D trial: 2,321 patients with DM and stable CAD in BARI 2D were grouped by age (<50; 50–59; 60–69; and ≥70 years). Tissue-type plasminogen activator (t-PA) antigen, PAI-1 antigen and activity, fibrinogen, and D-dimer were quantified at baseline. PAI-1 antigen (p<0.001), activity (p<0.001) and their ratios to t-PA (p<0.001) were all paradoxically lower with advancing age whereas D-dimer (p<0.0001) was elevated. Fibrinogen was highest in the oldest age group (p 0.01). t-PA antigen did not vary with age. These age related differences were observed primarily in men and in non-Hispanic white and Asian/other participants. In conclusion, PAI-1 is inversely related to age in diabetic patients with stable CAD and associated with elevation of D-dimer reflecting augmented fibrinolysis. The unexpected profibrinolytic state seen with advancing age and DM may reflect a protective phenomenon resulting from enhanced survival of some older patients with DM that endowed the older patients with longevity sufficient to enable them to participate in BARI 2D. Targeting factors that lead to the downregulation of PAI-1 in patients with type 2 DM may offer an attractive strategy for reduction of cardiovascular risk.

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[¶]A list of BARI 2D participants has been published (Baseline characteristics of patients with diabetes and coronary artery disease enrolled in the Bypass Angioplasty Revascularization Investigation 2 Diabetes [BARI 2D] trial)

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Keywords

Plasminogen activator inhibitor-1; Tissue type plasminogen activator antigen; Fibrinogen; D-dimer; Diabetes mellitus; Advanced age

INTRODUCTION

The BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial enrolled patients with type 2 diabetes mellitus (DM) and stable coronary artery disease (CAD). It was designed to determine: 1) the efficacy of initial elective coronary revascularization combined with aggressive medical therapy compared with initial, aggressive medical therapy alone with deferred revascularization as needed and, 2) the efficacy of a strategy of providing more insulin (endogenous or exogenous) compared with a strategy of increasing sensitivity to insulin (reducing insulin resistance) in the management of hyperglycemia with a target hemoglobin A1c level of < 7.0% for each strategy (1–3). In the present study, we sought to delineate the relationship of PAI-1 to several factors including age, sex, and ethnicity in patients with DM and stable CAD enrolled in the BARI 2D trial.

METHODS

The BARI 2D study was designed to identify optimal long-term treatment for patients with type 2 DM and documented stable CAD coupled with uniform glycemic control and intensive risk factor modification (2). Patients were eligible for enrollment in BARI 2D if they had type 2 DM and angiographically documented CAD in at least one artery for which revascularization was not imminently required for control of symptoms. The design of BARI 2D has been published previously in detail (2). The study was approved by Institutional Review Boards at each participating institution. Each study participant provided written, informed consent before enrollment.

Between January 1, 2001 and March 31, 2005, 2,321 patients with type 2 DM were enrolled in 49 medical centers. In a 2X2 factorial design, patients were randomized to facilitate testing of 2 hypotheses. The first randomization addressed the hypothesis that coronary revascularization added to aggressive medical therapy is superior to aggressive medical therapy alone for the treatment of patients with DM with chronic CAD. The second randomization addressed the hypothesis that insulin sensitization is superior to insulin provision in patients in whom a targeted hemoglobin A1c of < 7% was reached. Exclusion criteria included: coronary revascularization within 12 months, class III or IV heart failure, renal insufficiency (creatinine > 2.0), uncontrolled DM, severe peripheral arterial occlusive disease, liver disease, alcohol abuse or corticosteroid therapy. The primary end point was 5-year mortality. A major secondary combined end point was death, myocardial infarction, or stroke. All patients entered into BARI 2D were identified after clinically indicated noninvasive screening and coronary angiography.

At recruitment, fasting blood samples were collected without vacuum into 3.2% sodium citrate solution from an antecubital vein with use of a 2 syringe technique. Within 15 minutes of collection, the plasma was separated by centrifugation at 3000 g at 4°C for 10 minutes to remove all platelets thus eliminating a source of contamination of samples with PAI-1 liberated from platelets artifactually *in vitro*. Plasma samples were then maintained at –70°C until assay. Tissue-type plasminogen activator (t-PA) antigen and plasminogen activator inhibitor type-1 (PAI-1) antigen were determined with the use of commercially available enzyme-linked immuno assay kits (Trinity Biochech Plc., Bray, Co., Wicklow, Ireland). PAI-1 activity was assessed with the use of a modified chromogenic substrate enzymatic assay developed by

Chmielewska and Wiman as previously described (4). Fibrinogen was measured by the Claus method. D-dimer was measured immunoturbidimetrically with the use of STA-Liatest D-Dimer reagents (Diagnostica Stago) on a STA Compact.

Age of participants at baseline was stratified in 4 categories and baseline demographic, clinical, and fibrinolysis system measures determined for each. Differences between age groups were compared with the use of Pearson chi-square for categorical variables and either Kruskal Wallis or F tests for continuous variables. The Jonckheere-Terpstra Test was used to detect ordering of the differences in the fibrinolysis system measures observed among the incremental age groups. Spearman correlations were used to assess the relationships between the fibrinolytic system measures. Linear regression was used to model the relationship between the fibrinolytic system analytes and age. In models of PAI-1 and D-Dimer, the dependent variable (fibrinolysis measure) was transformed to the natural log to normalize the distribution. The independent variable, age, was divided into 10 year continuous increments. Multivariable linear models were adjusted by baseline variables when differences between the age groups were observed. These variables included gender, race, BMI, history of MI, history of stroke, history of hypertension, previous PCI, previous coronary artery bypass grafting (CABG), triglycerides, hemoglobin A1c (HbA1c), high density lipoprotein (HDL), history of cigarette smoking, duration of DM, baseline use of insulin, sulfonylurea, thiazolidinediones, and biguanide. The effect of gender and race on the age relationship with the fibrinolytic system measures was assessed by adding appropriate interaction terms to the linear models. A p-value of = 0.05 was used to determine statistical significance.

RESULTS

The demographic and clinical data for the 2,321 enrolled patients with DM stratified into four age categories (<50; 50–59; 60–69; and ≥70 years) are shown in Table 1. Nearly one third of the cohort constituted females, and female sex was significantly more prevalent in the oldest age group. Two-thirds of the cohort constituted Caucasians, and this ethnicity was more common in the older patient subsets. Black and Hispanic participants tended to be younger.

The older BARI 2D patients had a more favorable cardiovascular risk profile compared with that in their younger counterparts. They had significantly lower BMIs, lower total and LDL cholesterol and higher HDL cholesterol. Older patients had significantly lower HbA1c values. Despite cultural changes that have occurred over the last several decades, the younger BARI 2D participants had experienced significantly greater exposure to nicotine. Although the older patients tended to have a lower prevalence of MI as judged from history, they tended to have had more frequent exposure to coronary bypass surgery. Nearly equal percentages of older compared with younger patients had undergone revascularization with percutaneous coronary intervention (PCI). In contrast to the trend for MI, the older participants had experienced more frequent cerebrovascular events (TIA/CVA) that may be explained in part by a greater prevalence of hypertension.

Fasting insulin concentrations were similar across the age groups. Similarly, use of insulin, TZDs, and sulfonylurea use did not vary by age. By contrast, use of a biguanide was more common in the younger patients.

The total antigen content and activity of PAI-1 varied considerably across the entire cohort. PAI-1 values ranged from undetectable to as high as 142 AU/ml for the activity measure and 150 ng/ml for the total antigen measure. A distinct rightward skew of the data was notable for both measures (Figure 1A & B). By contrast, the distribution of t-PA antigen was normal (Figure 1C). Both PAI-1 measures correlated inversely with age (Table 2). A step-wise decrement in these measures was apparent from ages less than 50 compared with each

subsequent decade of life (Figure 2). By contrast, the t-PA antigen content did not vary with age. Thus, the ratio of PAI-I to t-PA antigen was significantly lower in patients of advanced age.

Concentrations of fibrinogen varied over a 6 fold range from 128 mg/dL to 784 mg/dL across the cohort (Figure 3). The distribution of fibrinogen, however, like that of t-PA, was Gaussian. Fibrinogen was highest in the oldest age group ($p < 0.01$) compared with that in younger age quartiles. The age related trend of fibrinogen values however did not reach statistical significance ($p = 0.12$, Table 2). The distribution of D-Dimer was rightward skewed with the vast majority of participants having very low values. D-Dimer increased significantly with higher age (Table 2).

In univariate analysis, PAI-1 antigen, PAI-1 activity and PAI-1 antigen/t-PA ratio were all significantly and inversely associated with age (Table 3). After controlling for baseline differences among the age groups, age remained significantly associated with each of the each of these variables. In contrast, t-PA was significantly and directly associated with increasing age. Concentrations of triglycerides correlated directly with PAI-1 activity ($r_s = 0.32$, $p < 0.001$), PAI-1 antigen content ($r_s = 0.31$, $p < 0.001$) and t-PA ($r_s = 0.26$, $p < 0.001$).

Further assessment was performed to determine whether the association of age with these variables differed as a function of gender. For each 10 year increment in age for males, log (PAI-1 antigen) was lower by 0.05 ($p < 0.006$), in females it was lower by 0.01 (p NS). Log (PAI-1 activity) was lower by 0.05 in women ($p = 0.07$) and 0.10 for men ($p < 0.001$) for every 10 year increase in age. The observed gender differences in the PAI-1 antigen and PAI-1 activity relationships with age were not statistically significant ($p < 0.16$). There was no age and gender interaction ($p < 0.49$) for the PAI-1 antigen/t-PA ratio or for t-PA ($p < 0.23$).

The age association with the fibrinolytic system measures was evaluated also with respect to race/ethnicity (Table 4). The differences in the age association with PAI-1 among the racial/ethnic groups was not statistically significant ($p = 0.16$). In non-Hispanic blacks, PAI-1 did not vary with age. For the other non-Hispanic groups, (whites and Asians/others) it did vary significantly with age. The age-PAI-1 relationship was similar in Hispanic and white participants; however, it did not reach statistical significance in Hispanics. Similar relationships with respect to the PAI-1 antigen/t-PA ratio and PAI-1 activity were observed.

To assess whether data were obscured by grouping patients by age only, the analysis was repeated by randomization assignment in addition to age discrimination. The same linear trend of higher age having lower PAI-1 antigen and activity is observed within the randomization groups (Table 5).

DISCUSSION

The principal findings in the present study were the unexpected age associated changes in measures of the fibrinolytic system. With each 10 year increment of age at baseline in diabetic patients with stable CAD, there was significantly lower PAI-1 antigen and activity. Whereas the concentration of t-PA in blood was relatively constant across each decile of age, the ratio of PAI-1 to t-PA was lower with advanced age indicating an unexpected and paradoxical shift (with respect to observations in people without DM) in the balance favoring fibrinolysis (5). This shift was reflected by higher concentrations of D-dimer in plasma in the older patients. These findings suggest that older patients with type 2 DM and stable CAD comprise a subset that may have been protected against life threatening thrombotic events by a favorable shift in the balance between fibrinolysis and thrombosis favoring fibrinolysis. Alternatively, these findings may reflect decreased survival of younger patients with high concentrations of PAI-1.

Regardless of which interpretation is embraced, the results implicate impaired fibrinolysis as a potential determinant of risk.

Concentrations of t-PA and PAI-1 in plasma have been identified as variables contributing to the risk of arterial thrombosis (6–8). Both DM and aging are known to constrain activity of the fibrinolytic system (9–13). Whether the profile observed in this study in older diabetic patients is governed principally by genetic or environmental factors remains unclear. Both play an integral role in determining the overall status of activity of the fibrinolytic system (12,13).

In the present study, the older participants appeared to have more favorable cardiovascular risk profiles. They were leaner, less dyslipidemic, and had been less exposed to nicotine. However, the extent of coronary artery disease was equivalent to or greater than that in younger patients as judged from their history of CAD revascularization with more frequent bypass grafting and a nearly equal incidence of percutaneous revascularization. Fibrinogen concentrations were higher in these patients (14,15). Yet, despite longer exposure to DM, there was a trend toward fewer myocardial infarctions in them. The prevalence of stroke by history was greater in the older patients perhaps reflecting the greater prevalence of hypertension.

In our cohort, older participants had a significantly lower BMI compared with that in younger patients (Table 1) possibly contributing to the lower PAI-1 (16–18).

In our study for each 10 year increment in age for males, both PAI-1 antigen and activity were significantly lower. This relationship was not seen in women. PAI-1 activity was significantly lower in women of advanced age but less so than in men.

Fibrinolytic system measures were assessed in 2,527 non-diabetic participants in the PREVENT study (19,20). Both PAI-1 and t-PA antigen were significantly higher in males compared with females. When stratified by menopausal status, the sex differences in PAI-1 were evident only in comparisons of premenopausal women with men (20). These differences may be explained in part by genetic factors (20). The PAI-1 4G/5G polymorphism was a significant descriptor of PAI-1 concentrations in both males and females. The angiotensin II type I receptor A1166C was a significant predictor of t-PA and PAI-1 increases in females. The bradykinin receptor B2 58CT polymorphism was a significant predictor of t-PA in females.

Gender differences were not seen in the THROMBO study (21). Participation in this study, however, was limited to survivors of MI with no comparisons with normal controls. Because only very high risk patients were enrolled, both male and female patients may have had a high propensity for arterial thrombosis.

Ethnicity may influence the age associated differences in fibrinolytic system variables (18–25). In our study, PAI-1 antigen was significantly lower in those of advanced age in non-Hispanic whites and non-Hispanic Asians/others but not in non-Hispanic Blacks or Hispanics. Multiple regression analysis has shown significant relationships between fibrinolytic systemic measures and waist circumference, BMI, HDL and total cholesterol diastolic blood pressure, fasting glucose, insulin, and insulin resistance as well as race. Race was a significant descriptor of the concentration of the t-PA/PAI-1 complex. The association between measures of the fibrinolytic system and the metabolic syndrome appears to be particularly prominent in Caucasians (23). In a logistic regression model, PAI-1 has appeared to be an independent predictor of the metabolic syndrome in this group. The prospective Multi-Ethnic Study of Atherosclerosis (MESA) assessed hemostatic factors in 6547 men and women aged 45 to 84 years without a history of clinical cardiovascular disease (CVD) living in six U.S. communities (25). PAI-1 was lowest in Black and highest in Chinese subjects.

In conclusion, PAI-1 is inversely related to age in diabetic patients with stable CAD and associated with elevation of D-dimer reflecting augmented fibrinolysis. These results may reflect a protective phenomenon resulting from enhanced survival of some older patients with DM that endowed the older patients with longevity sufficient to enable them to participate in BARI 2D.

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Figure 1. The Distribution of Concentrations of baseline PAI-1 and t-PA

Each measure of the fibrinolytic system varied considerably across the BARI-2D cohort as a whole. The PAI-1 antigen (panel A) and activity (panel B) distributions were rightward shifted whereas the t-PA antigen content was distributed in a more Gaussian fashion (panel C).

Figure 2. Interquartile Range of Fibrinolytic System Variables by Age Quartiles

The PAI-1 antigen (panel A; $p < 0.001$) and antigen content (panel B; $p < 0.001$) were significantly lower in patients within the older quartiles compared with their younger counterparts. t-PA antigen content (panel C) did not vary by age. Data are presented as first quartile, median, and third quartile values.

Figure 3. Baseline distribution of Fibrinogen and Fibrin D-dimer

Fibrinogen was normally distributed. Fibrin D-dimer levels were very low in most of the participants.

Table 1

Baseline Clinical Characteristics in Patients Stratified by Age

Variable	Total (n=2321)	Age Group (Years)			P-value
		< 50 (n=195)	50–59 (n=727)	60–69 (n=897)	
Women	29.6%	31.3%	28.7%	27.0%	34.7%
					0.02
Ethnicity					
Black nH	16.9%	25.1%	18.7%	14.6%	15.3%
Hispanic	12.7%	18.5%	15.3%	11.0%	9.6%
White nH	65.6%	49.2%	60.7%	70.1%	70.9%
Asian/Other nH	4.8%	7.2%	5.4%	4.2%	4.2%
Exercise regularly	25.7	23.1	22.0	26.9	29.9
					0.01
BMI, (kg/m ²) (mean, median)	31.7, 31	33.3, 32	32.4, 32	31.4, 31	30.7, 30
					<0.001
Fasting insulin (μIU/ml) (mean, median)	14.1, 10	14.1, 10	15.0, 10	13.6, 10	13.9, 9
					0.22
Hemoglobin A1c, %	7.66, 7	8.18, 8	7.97, 8	7.60, 7	7.13, 7
					< 0.001
Duration of Diabetes (years) mean, (median)	10.4 (9)	6.9 (5)	8.9 (7)	11.2 (10)	12.7 (10)
					< 0.001
Lipid values (mg/dL ± SD)					
TC	170±41	181±49	175±42	167±41	161.7, 34.3
LDL	96±33	104±37	100±34	94.5, 33.5	91.6, 29.3
HDL	38±10	36±9	38±10	38.6, 10.6	39.0, 10.6
Triglyceride (mean, median)	181, 149	216.4, 179	194.5, 160	173.7, 144	158.4, 139
					< 0.001
Smoker	66.8%	68.7%	70.0%	66.9%	61.2%
					0.01

Variable	Age Group (Years)				P-value
	Total (n=2321)	< 50 (n=195)	50-59 (n=727)	60-69 (n=897)	
Insulin use	27.8%	23.1%	30.0%	28.2%	0.18
TZD use	18.8%	18.5%	19.8%	20.1%	0.09
Sulfonylurea use	53.6%	48.2%	52.1%	55.2%	0.24
Biguanide use	54.1%	57.4%	57.4%	54.4%	0.003
Treated Hypertension, %	82.4%	74.7%	80.2%	85.0%	0.002
History of MI	31.9%	37.8%	34.1%	29.8%	0.07
Prior Stroke, TIA	9.8%	3.6%	7.2%	11.7%	<0.001
Prior CABG	6.4%	2.6%	6.1%	6.8%	0.08
Prior PCI	19.6%	20.5%	19.5%	19.3%	0.98

Table 2

Measures of the Fibrinolytic System in Patients Stratified by Age: mean [median]

Variable	Age Group Years					p-value for ordered differences*
	< 50 (n=195)	50-59 (n=727)	60-69 (n=897)	≥ 70 (n=502)		
PAI-1 antigen (ng/ml)	33.1 [27]	29.5 [25]	25.7 [22]	24.6 [20]		<0.001
PAI-1 activity (AU/ml)	26.1 [21]	23.6 [19]	19.2 [15]	16.9 [13]		<0.001
t-PA (ng/ml)	10.4 [10]	10.1 [10]	10.0 [10]	10.2 [10]		0.46
PAI-1/t-PA ratio	3.5 [3]	3.0 [3]	2.7 [2]	2.5 [2]		<0.001
Fibrinogen (mg/dL)	362.7 [344]	367.1 [360]	359.9 [350]	377.5 [367]		0.12
Fibrin D-Dimer (µg/ml)	0.4 [0]	0.4 [0]	0.5 [0]	0.8 [0]		<0.001

* The Jonckheere-Terpstra Test was used to determine if the differences in the analytes among the age groups were ordered.

Table 3

Regression Models* of Fibrinolytic System Measures and Age

Variable*	Univariate				Multivariable**			
	N	Change/10 year age increment	p-value	R ²	N	Change/10 year age increment	p-value	R ²
Log(PAI-1 antigen)	2179	-0.09	<0.001	0.015	2083	-0.04	0.02	0.21
Log(PAI-1 activity)	2184	-0.15	<0.001	0.034	2088	-0.09	<0.001	0.24
t-PA (ng/ml)	2274	-0.06	0.55	0.00	2179	0.26	0.006	0.21
Log(PAI-1 ag/t-PA ratio)	2171	-0.09	<0.001	0.021	2075	-0.06	<0.001	0.10
Log(D-dimer)	2260	0.31	<0.001	0.086	2169	0.31	<0.001	0.15

* Each line represents a separate model of the fibrinolytic system measure and age.

** Multivariable model included gender, race, BMI, history of MI, history of hypertension, history of stroke, prior PCI, prior CABG, duration of diabetes, HbA1c, triglycerides, HDL, history of cigarette smoking, baseline use of insulin, sulfonyleurea, TZD, and biguanide

Table 4

Multivariable Model* of Log Plasminogen Activator Inhibitor-1 Antigen and Ethnicity

Variable	Change/10 year age increment	p-value
Log(PAI-1 Antigen)		
Among Non-Hispanic Whites	−0.04	<0.02
Among Non-Hispanic Blacks	−0.01	NS
Among Non-Hispanic Other Race	−0.14	0.03
Among Hispanic	−0.04	0.45

* Multivariable model included gender, race, BMI, history of MI, history of hypertension, history of stroke, prior PCI, prior CABG, HbA1c, triglycerides, HDL, history of cigarette smoking, baseline use of insulin, sulfonylurea, TZD, and biguanide

Table 5
Measures of the Fibrinolytic System in Patients Stratified by Age (mean, median) and Randomization Assignment

Baseline Fibrinolysis Measure	Randomization Assignment								p-value * for linear age trend
	Optimal Medical Therapy				Prompt Revascularization				
	<50	50–59	60–69	≥70	<50	50–59	60–69	≥70	
PAI-1 Antigen ng/ml (mean, median)	31.8, 27.0	28.5, 24	26.1, 23	25.3, 21	34.4, 26.5	30.5, 26	25.4, 21	23.9, 20	<0.001
PAI -1 Activity AU/ml (mean, median)	24.2, 21	23.2, 17	19.2, 15	17.5, 14	28.2, 22	23.9, 20	19.3, 15	16.1, 12	<0.001
t-PA ng/ml (mean, median)	10.4, 9.7	10.2, 10	10.3, 9.9	10.4, 10	10.4, 10	10.0, 9.7	9.7, 9.3	10.0, 9.5	0.59
PAI-1/t-PA ratio (mean, median)	3.5, 2.8	2.9, 2.5	2.6, 2.3	2.5, 2.2	3.6, 2.6	3.1, 2.6	2.8, 2.3	2.6, 2.1	<0.001
Fibrinogen mg/dl (mean, median)	361.8, 336	363.4, 350	360.8, 349	382.5, 373	363.6, 356	370.74, 367	358.9, 355	372.2, 361	0.14
Fibrin D-Dimer µg/ml (mean, median)	0.34, 0.22	0.38, 0.23	0.53, 0.32	0.70, 0.50	0.36, 0.19	0.45, 0.28	0.50, 0.32	0.86, 0.51	<0.001
	Insulin Sensitization				Insulin Provision				
PAI-1 Antigen ng/ml (mean, median)	31.3, 28.0	30.0, 26.0	25.6, 22.0	25.4, 20.0	34.9, 26.0	29.0, 24.0	25.8, 22.0	23.8, 20.0	<0.001
PAI -1 Activity AU/ml (mean, median)	26.1, 21	24.0, 19	19.3, 15	17.2, 13	26.2, 22	23.1, 19	19.2, 15	16.5, 13	<0.001
t-PA ng/ml (mean, median)	10.4, 10	10.2, 9.9	10.1, 9.7	10.3, 9.8	10.3, 10	10.1, 9.9	10.0, 9.4	10.2, 10	0.61
PAI-1/t-PA ratio (mean, median)	3.3, 2.7	3.0, 2.5	2.7, 2.3	2.6, 2.2	3.7, 2.8	3.0, 2.5	2.7, 2.3	2.4, 2.2	<0.001
Fibrinogen mg/dl (mean, median)	355.3, 377	367.8, 356.5	355.3, 349	380.3, 372	370.5, 351	366.4, 362	364.1, 355	374.7, 363	0.14
Fibrin D-Dimer µg/ml (mean, median)	0.37, 0.21	0.40, 0.25	0.53, 0.33	0.81, 0.48	0.33, 0.22	0.43, 0.26	0.51, 0.31	0.73, 0.53	<0.001

* p-value represents that of a linear contrast of the age categories from a model with both the randomization assignment and the age categories included