Tissue inhibitor of metalloproteinase-1 (TIMP-1) is an independent predictor of all-cause mortality, cardiac mortality, and myocardial infarction

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Background Matrix metalloproteinases and their inhibitors have been implicated in both vascular and ventricular remodeling, and in atherosclerotic plaque rupture. The prognostic value of plasma tissue inhibitor of metalloproteinase-1 (TIMP-1) levels in patients with established or suspected coronary artery disease is unknown.

Methods Tissue inhibitor of metalloproteinase-1 and matrix metalloproteinase-9 (MMP-9) levels, along with a number of other established biomarkers, were measured in 389 male patients undergoing coronary angiography at a Veterans Administration Medical Center. The patients were then followed prospectively for the occurrence of all-cause mortality, cardiac mortality, and myocardial infarction (MI).

Results Follow-up data at 24 months were available for 97% of the patients. For the entire cohort of patients, TIMP-1 was the only biomarker to independently predict all-cause mortality and MI. In addition, the ratio of TIMP-1 to matrix metalloproteinase-9 was independently predictive of cardiac mortality at 24 months. The 24-month survival rates for patients in the lower quartile (<66.5 ng/mL), interquartile (66.5-100 ng/mL), and upper quartile (>100 ng/mL) of plasma TIMP-1 values were 95.3%, 89.3%, and 72.2%, respectively ($P < .001$). Furthermore, when patients with chest pain were risk stratified into those with and without an acute coronary syndrome, TIMP-1 remained an independent predictor of all-cause mortality in both subgroups.

Conclusions In a cohort of male patients undergoing coronary angiography, a single baseline determination of plasma TIMP-1 is independently predictive of the subsequent risk of death and MI. (Am Heart J 2006;151:1101.e1-1101.e8.)

Abnormalities in the connective tissue component of the vessel wall have been implicated in the genesis of atherosclerosis and its complications.[1] Connective tissue integrity depends on a balance between degradation and repair of extracellular matrix. A family of enzymes known as the matrix metalloproteinases (MMPs) plays a major role in the degradation of collagen and other extracellular matrix macromolecules.[1,2] An important mechanism for the regulation of the activity of the MMPs is via binding to a family of homologous proteins known as the tissue inhibitors of metalloproteinases (TIMPs).[2] Under normal circumstances, the TIMPs are in delicate balance with the MMPs, and matrix is digested in a highly regulated fashion. However, during certain disease states, including atherosclerosis, there is an imbalance between the activities of these 2 families of proteins leading to tissue destruction.[3,4] The MMPs and the TIMPs, through their combined net effect on proteolysis, are now believed to play a critical role in extracellular remodeling during all phases of atherosclerosis, from its genesis and progression to the development of its acute complications.[3,5,6] Furthermore, because these proteins are synthesized in response to cytokines,[7] they may serve to link inflammation and atherosclerosis.

The aim of the present study was to determine if an MMP and its inhibitor could serve as predictive biomarkers for outcomes in patients with coronary artery disease (CAD) and to compare their value in this regard to other established biomarkers. To this end, we examined the levels of a set of biomarkers in a

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Table I. Baseline characteristics

Characteristics	Statistics	Lower quartile (TIMP ≤ 66.5), n = 108	Interquartile (TIMP > 66.5 and ≤100), n = 183	Upper quartile (TIMP >100), n = 98	Total population (N = 389)	P
Age	Mean (SD)	63.7 (9.6)	65.2 (10.0)	67.4 (10.0)	65.3 (10.0)	.02
Race						
Black	n (%)	36 (33.3)	56 (30.6)	30 (30.6)	122 (31.4)	.99
Hispanic		30 (27.8)	52 (28.4)	29 (29.6)	111 (28.5)	
White		42 (38.9)	75 (41.0)	39 (39.8)	156 (40.1)	
Family history of CAD	n (%)	32 (29.6)	49 (26.8)	15 (15.3)	96 (24.7)	.04
Diabetes	n (%)	47 (43.5)	76 (41.5)	46 (46.9)	169 (43.4)	.68
Hypertension	n (%)	85 (78.7)	155 (84.7)	85 (86.7)	325 (83.6)	.25
Active tobacco	n (%)	27 (25.0)	54 (29.5)	39 (39.8)	120 (30.9)	.06
Hyperlipidemia	n (%)	70 (64.8%)	99 (54.1%)	44 (44.9%)	213 (54.8%)	.02
Obesity	n (%)	40 (37.0)	61 (33.3)	35 (25.7)	136 (35.1)	.79
CHF on presentation	n (%)	19 (17.6)	40 (21.9)	43 (43.9)	102 (26.2)	<.001
MI on presentation	n (%)	23 (21.3)	44 (24.0)	40 (40.8)	107 (27.5)	.003
CRI	n (%)	1 (0.9)	4 (2.2)	13 (13.3)	18 (4.6)	<.001
ASA use	n (%)	95 (88.0%)	160 (87.4%)	76 (77.6%)	331 (85.1%)	.05
β-Blocker use	n (%)	76 (70.4%)	121 (66.1%)	70 (71.4%)	267 (68.6%)	.59
ACE-I use	n (%)	59 (54.6%)	112 (61.2%)	65 (66.3%)	236 (60.7%)	.22
Statin use	n (%)	66 (61.1%)	96 (52.5%)	43 (43.9%)	205 (52.7%)	.04
Prior coronary artery bypass graft	n (%)	8 (7.4)	18 (9.8)	9 (9.2)	35 (9.0)	.78
Angiographic score	0-1	43 (39.8)	65 (35.5)	26 (26.5)	134 (34.5)	.12
	≥2	65 (60.2)	118 (64.5)	72 (73.5)	255 (65.5)	
LV systolic function	Normal or mildly reduced	64 (59.3)	114 (62.3)	43 (43.9)	221 (56.8)	.02
	Moderately or severely reduced	43 (39.8)	57 (31.1)	45 (45.9)	145 (37.3)	
Troponin-I	Mean (SD)	6.8 (32.8)	10.3 (54.2)	14.4 (47)	10.4 (47.3)	.09
	Median	0.3	0.3	0.3	0.3	
	25th-75th	0.2-1.5	0.2-1.0	0.2-3.6	0.2-1.7	
Erythrocyte sedimentation rate	Mean (SD)	19.9 (19.9)	21.0 (18.7)	38.5 (32.1)	25.2 (24.4)	<.001
	Median	13	14	29	16	
	25th-75th	5-30	8-30	12-56	8-36	
hs-CRP	Mean (SD)	16.1 (29.9)	18.6 (29.7)	40.9 (58.3)	23.8 (40.5)	<.001
	Median	7.4	8.7	15.0	9.2	
	25th-75th	3.2-14.1	3.8-16	5.6-46.5	3.8-18.8	
MPO	Mean (SD)	19.3 (10.4)	26.0 (21.1)	29.6 (20.0)	25.3 (19.1)	<.001
	Median	16.0	19.3	21.8	19.3	
	25th-75th	12.4-23.6	13.7-30.2	16.0-39.7	13.6-29.1	
PAI-1	Mean (SD)	33.9 (23.1)	42.8 (39.2)	51.9 (37.7)	42.9 (35.9)	.001
	Median	30.3	32.2	42.2	33.4	
	25th-75th	19.0-42.3	56.1-17.7	23.4-70.4	19.0-56.3	
MMP-9	Mean (SD)	20.7 (20.5)	26.6 (25.5)	33.4 (27.3)	26.9 (25.2)	<.001
	Median	14.9	18.2	23.2	18.1	
	25th-75th	11.1-22.3	12.3-32.8	15.4-39.9	12.2-31.4	

ASA, aspirin and ACE-i, angiotensin converting enzyme inhibitor.

well-characterized and prospectively followed population of male patients undergoing coronary angiography for a variety of indications. Of the large class of metalloproteinases and their inhibitors, we chose to study matrix metalloproteinase-9 (MMP-9), which is associated with plaque instability,[4] and tissue inhibitor of metalloproteinase-1 (TIMP-1), which is known to inhibit most active MMPs,[8] to be expressed in atherosclerotic plaques[9,10] and for which there is strong experimental evidence of a direct proatherosclerotic role.[11]

Methods

Study design

This study, which was exploratory and observational in nature, was part of a broader project examining the prognostic significance of a variety of plasma biomarkers in patients undergoing coronary angiography at a Veterans Administration Medical Center. It was approved by the local institutional review board. Written informed consent was obtained from all patients. Between January 1999 and October 2002, 389 male patients undergoing diagnostic coronary angiography were enrolled in the study. The only exclusion

Table II. Univariate analyses of baseline characteristics for all-cause mortality at 24 months in the entire cohort

Variable	P	OR (95% CI)
Age/10 y	.003	1.65 (1.19, 2.28)
Diabetes mellitus	.58	1.18 (0.65-2.13)
Family history of CAD	.11	0.53 (0.24-1.16)
CHF on presentation	<.001	3.64 (1.98-6.68)
Aspirin use	.55	0.79 (0.36-1.72)
β-Blocker use	.34	1.38 (0.71-2.71)
ACE-I use	.37	1.33 (0.71-2.48)
Statin use	.22	0.69 (0.38-1.25)
Hypertension	.92	1.04 (0.46-2.34)
Obesity	.51	0.81 (0.43-1.52)
CRI	.003	4.66 (1.72-12.64)
Hyperlipidemia	.34	0.71 (0.42-1.35)
MI on presentation	.17	1.54 (0.83-2.88)
Active tobacco use	.67	1.15 (0.61-2.15)
Angiographic score	<.001	1.47 (1.20-1.81)
LV function	.004	1.53 (1.15-2.04)
TIMP-1	<.0001	2.13 (1.61-2.81)
hs-CRP	.012	1.71 (1.24-2.37)
MMP-9	.0887	0.78 (0.58-1.04)
MPO	.3422	1.15 (0.86-1.54)
PAI-1	.5511	0.92 (0.68-1.23)
TIMP-1/MMP-9 ratio	<.0001	1.87 (1.37-2.56)
Erythrocyte sedimentation rate	<.0001	2.14 (1.50-3.06)

criteria for participation in the study were active gastrointestinal bleeding or a hemoglobin concentration of <8 g/dL. Clinical information was obtained by interview and review of the medical records. Fasting blood was obtained from patients at the time of angiography. The patients were then followed prospectively for the development of clinical events.

Laboratory methods

Aliquoted plasma samples stored at −70°C were thawed and, using commercially available enzyme-linked immunosorbent assay kits, the levels of the following biomarkers were measured: TIMP-1 (EMD Biosciences, San Diego, CA), MMP-9 (EMD Biosciences), high-sensitivity C-reactive protein (hs-CRP; Life Diagnostics, West Chester, PA), myeloperoxidase (MPO; Assay Designs, Ann Arbor, MI), and plasminogen activator inhibitor 1 (PAI-1; Diapharma, West Chester, OH). The sensitivities of the TIMP-1, MMP-9, hs-CRP, MPO, and PAI-1 assays were 0.0096, 0.1, 0.1, 0.13, and 0.5 ng/mL, respectively. The intra-assay coefficients of variation for TIMP-1, MMP-9, hs-CRP, MPO, and PAI-1 were <5.2%, <10%, <7.6%, <5.5%, and <3.0%, respectively.

Indications for coronary angiography

The indications for coronary angiography were classified into 5 categories. (1) *ST-elevation myocardial infarction (MI)*. This group (5.9%) included patients who, up to within a week of their angiogram, had presented with ≥2 mm ST-segment elevation in ≥2 consecutive electrocardiogram leads. All such patients had enzymatically confirmed myocardial infarction. (2) *Non–ST-elevation MI*. This group (21.6%) consisted of patients with chest pain and enzymatic evidence of MI but without ST-segment elevation on presenting electrocardiogram. (3) *Chest pain with negative results of enzymes*. This group (61.9%) consisted of patients who had chest pain but lacked enzymatic evidence of MI. Patients in this category were further subdivided into unstable angina (3A) or stable angina (3B). (4) *Evaluation of congestive heart failure (CHF) and/or severe left ventricular (LV) dysfunction*. This group (6.2%) included patients with severe LV dysfunction and/or CHF for whom the principal indication for angiography was evaluation of coronary anatomy as part of their workup for heart failure or LV dysfunction. (5) *Valvular heart disease*. This group (4.4%) included patients with echocardiographically identified valvular heart disease who were undergoing cardiac catheterization either for confirmation of diagnosis and/or preoperative assessment of coronary arteries.

Table III. Multivariate analysis for all-cause mortality at 24 months in the entire cohort

Variable	P	OR (95% CI)
Age/10 y	.13	1.03 (0.99-1.07)
CHF on presentation	.008	2.55 (1.28-5.11)
Angiographic score	.004	1.41 (1.12-1.77)
TIMP-1	.0001	1.82 (1.34-2.48)

Patients presenting with chest pain (indications 1-3) were further classified as either acute coronary syndrome (ACS) if they had presented with ST-elevation MI, non–ST-elevation MI, or unstable angina, or as non-ACS if their chest pain did not meet criteria for ACS.

Definition of risk factors and clinical syndromes

Diabetes was defined as known and treated diabetes mellitus. Patients were diagnosed as hypertensive if they were documented to have a blood pressure of ≥140/90 mm Hg on ≥2 occasions or were on antihypertensive therapy. Hyperlipidemia was diagnosed in patients who had been given lipid-lowering medication or had a history of total cholesterol levels of >240 mg/dL.[12] Smoking was defined as the inhaled use of cigarettes, cigars, or pipes in any quantity. Obesity was defined as a body mass index of ≥30 kg/m^2. Chronic renal insufficiency (CRI) was defined as a serum creatinine of ≥2.0 mg/dL. Congestive heart failure on presentation was defined as the presence of either radiographic or clinical evidence of pulmonary venous congestion within the preceding 24 hours of angiography. Myocardial infarction on presentation was diagnosed by a history of chest discomfort and troponin I of >1.0 ng/mL.

Angiographic scoring system

An angiographic scoring system was devised based upon (*a*) the traditional definition of an angiographically significant stenosis as one with a ≥50% obstruction and (*b*) the anatomic territory subtended by the diseased artery or graft. Using visual estimation of stenosis severity, angiograms were scored as follows: any obstructive lesion of ≥50% in 1 of the 3 coronary arteries or their major (≥2.5 mm) branches received a score of 1. Multiple obstructive lesions of ≥50% in a single artery or one of its major branches still only received a score of 1, except in the case of a left dominant system. In the case of a left dominant system, an obstruction of ≥50% in the proximal

Table IV. Multivariate analysis for cardiac mortality at 24 months in the entire cohort

Variable	*P*	OR (95% CI)
Angiographic score	.001	1.62 (1.23-2.15)
CHF on presentation	.006	3.11 (1.38-7.03)
TIMP-1/MMP-9 ratio	.0097	1.60 (1.12-2.29)

Table V. Multivariate analysis for MI at 24 months in the entire cohort

Variable	*P*	OR (95% CI)
TIMP-1	.0031	1.55 (1.16-2.08)
LV function	.03	1.40 (1.03-1.89)
Age/10 y	.02	1.52 (1.06-2.18)
Angiographic score	.09	1.23 (0.97-1.55)

portion of the left circumflex artery received a score of 2. Similarly, in a left dominant system, an obstruction ≥50% in both a large obtuse marginal branch and a left posterior descending artery also received a score of 2. On the other hand, an obstruction of ≥50% in a left dominant system, which was isolated to either a left posterior descending artery or an obtuse marginal (but not both), received a score of 1. An obstruction of ≥50% in the left main coronary artery received a score of 2 in a right dominant system and 3 in a left dominant system. A bypass graft with an obstructive lesion of ≥50% received a score of 1. Patent grafts or those with an obstructive lesion of ≤50% received a score of 0.

Left ventricular systolic function was assessed by contrast ventriculography as normal (ejection fraction [EF] ≥55%), mildly (EF 45-54%), moderately (EF 31-44%), or severely reduced (EF ≤30%).

Clinical end points

Patients were followed for the occurrence of death and MI. Myocardial infarction during follow-up was defined by a history of chest pain with an associated elevation of either troponin I of >1.0 ng/mL or troponin T of >0.1 ng/mL. A death was classified as cardiac if the predominant and immediate cause was related to MI or ischemia, arrhythmia, refractory congestive heart failure, or if the death was sudden and unexpected in nature. The information regarding the etiology and date of death was obtained using the following modalities: death certificate, social security death index, conversation with next of kin and/or primary physician, and review of medical records.

Statistical analysis

This study was part of a broader project examining the prognostic significance of a variety of plasma biomarkers in patients undergoing coronary angiography. As such, there were no a priori calculations with respect to sample size or statistical power as it relates specifically to TIMP-1. The study population was divided into 3 groups based on the 25th and 75th percentiles of TIMP-1 values. Summary statistics for continuous variables were presented as means (with SDs) and medians (with interquartile ranges), and comparisons between groups were performed using the nonparametric Kruskal-Wallis test. All biomarkers were log transformed and normalized. Categorical data were summarized as frequencies and percentages, and comparisons between groups were performed with Pearson χ^2 test or Fisher exact test.

Time-to-event at 24 months was presented with Kaplan-Meier curves for the individual end points of all-cause mortality, cardiac mortality, and MI. Comparisons between groups were performed using the log rank test. The predictors of all-cause mortality, cardiac mortality, and MI at 24 months were identified with univariate logistic regression and the results presented as odds ratios with 95% CIs. Multiple logistic regressions with backward selection of variables were used to identify the independent predictors.

All analyses used 2-sided tests with overall significance level of $\alpha = .05$. Adjustments for multiple testing were performed using the Hochberg-Bonferroni multiple-testing procedure.[13] Adjustments for multiplicity for each of the 3 end points indicated that they all retained statistical significance using this procedure.

Results

Baseline characteristics and association of TIMP-1 with clinical variables

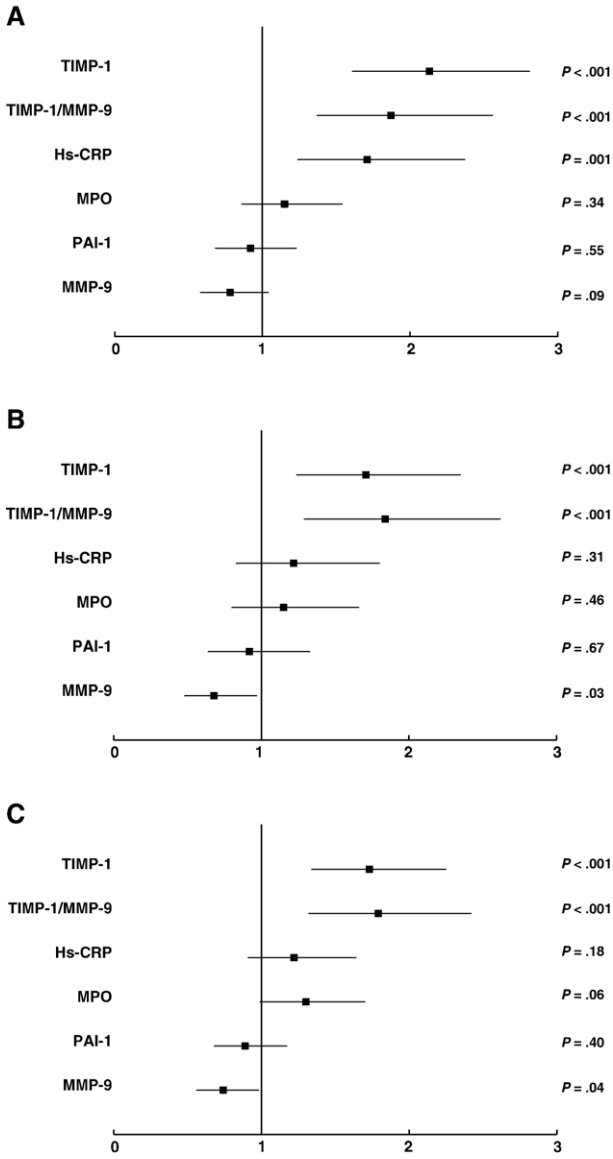
A total of 389 male patients were enrolled in the study. Two-year follow-up data were available for 97% of the patients. The baseline characteristics of the study population stratified by the lower-, inter-, and upper-quartile TIMP-1 values are shown in Table I. Elevated TIMP-1 levels were seen association with older age, CHF on presentation, LV dysfunction, MI on presentation, and CRI. In addition, TIMP-1 levels were also positively correlated with the erythrocyte sedimentation rate, as well as with the levels of MMP-9, hs-CRP, PAI-1, and MPO. In contrast, family history and hyperlipidemia were inversely correlated with TIMP-1 values.

With respect to LV function, TIMP-1 (OR 1.49, 95% CI 1.18-1.89, $P = .0.001$), hs-CRP (OR 1.35, 95% CI 1.06-1.71, $P = .01$), and MMP-9 (OR 0.70, 95% CI 0.55-0.89, $P = .004$) were each independently associated with LV dysfunction by multivariate analysis. With regard to MI on presentation, CAD score (OR 1.22, 95% CI 1.02-1.46, $P = .03$), active tobacco use (OR 2.74, 95% CI 1.62-4.62, $P < .001$), hs-CRP (OR 2.25, 95% CI 1.68-3.00, $P < .0001$), and TIMP-1 (OR 1.34, 95% CI 1.04-1.71, $P = .02$) were each independently associated with this baseline characteristic by multivariate analysis.

Association of TIMP-1 with clinical outcomes at 24 months

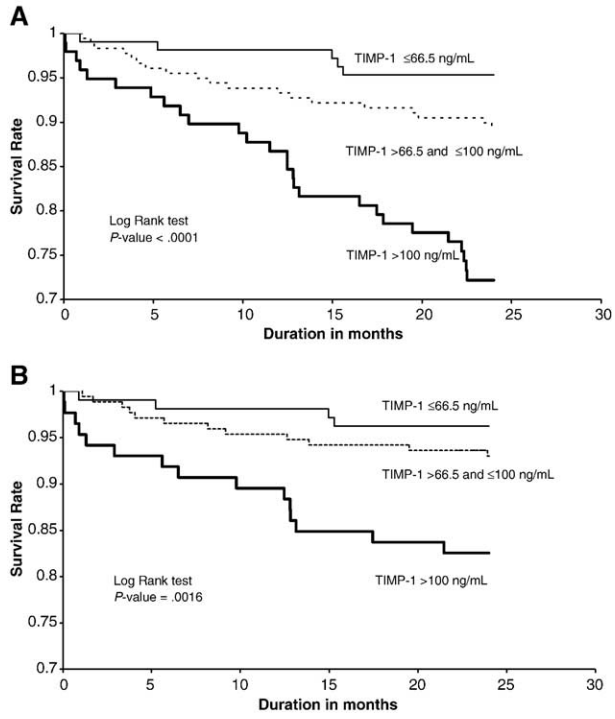
For the 97% of patients in whom 24-month follow-up data were available, there were a total of 51 deaths (13%), of which 31 (61%) were classified as cardiac in etiology. Similarly, 61 (16%) had developed an MI (fatal or nonfatal) by 24 months. The results of univariate and multivariate analyses for the prediction of all-cause

Figure 1



A, Odds ratio for all-cause mortality at 24 months. **B**, Odds ratio for cardiac mortality at 24 months. **C**, Odds ratio for MI at 24 months.

Figure 2



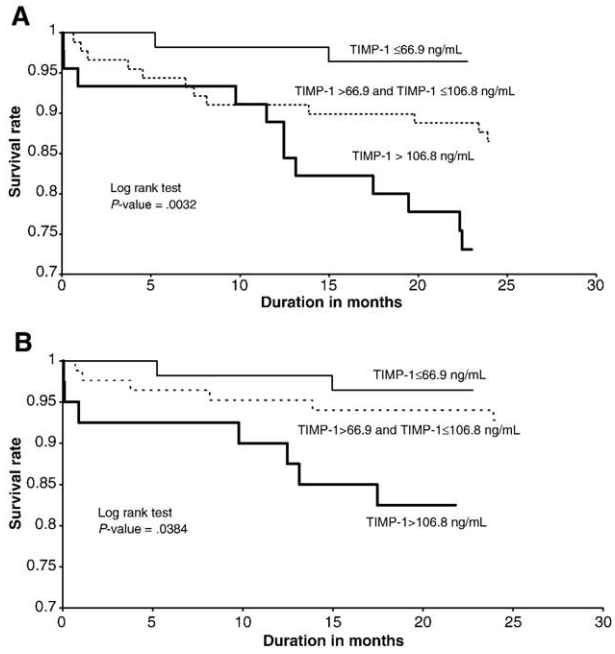
A, Survival rate (all-cause mortality) at 24 months by TIMP-1 intervals in entire cohort. **B**, Survival rate (cardiac mortality) at 24 months by TIMP-1 intervals in entire cohort.

mortality are presented in Tables II and III, respectively. Using the same variables listed in Table II, univariate predictors for the outcomes of cardiac mortality and MI at 24 months were identified and entered into separate multivariate models, the results of which are shown in Tables IV and V, respectively. Based on univariate analyses, the unadjusted odds ratio for the development of each of the 3 major end points was greater for TIMP-1 than for any other biomarker (Figure 1). Furthermore, TIMP-1 or its ratio with MMP-9 was the only biomarker found to be an independent predictor of each of these individual end points on multivariate analysis. When the analysis for MI was restricted to nonfatal events (n = 51), TIMP-1 was still the only independently predictive biomarker (OR 1.69, 95% CI 1.25-2.29, $P < .001$).

Using the 25th and 75th percentiles as prespecified cut-off points for TIMP-1 levels, Kaplan-Meier curves were derived for the entire cohort of patients with TIMP-1 values of <66.5 ng/mL, between 66.5 and 100 ng/mL, and >100 ng/mL (Figure 2). Kaplan-Meier plots demonstrated a significant increase in mortality with increasing TIMP-1 values. In particular, TIMP-1 values exceeding 100 ng/mL were strongly predictive of all-cause and cardiac mortality. For all-cause mortality, the survival rates at 24 months in the 3 groups were 95.3%, 89.3%, and 72.2%, respectively ($P < .001$). For cardiac death, the rates were 96.2%, 93.0%, and 82.6%, respectively ($P = .002$), whereas for noncardiac death they were 99.0%, 96.4%, and 87.4%, respectively ($P < .001$).

Patients with chest pain associated with an acute coronary syndrome had higher baseline TIMP-1 values

Figure 3



A, Survival rate (all-cause mortality) at 24 months by TIMP-1 intervals in the ACS sub-population. **B**, Survival rate (cardiac mortality) at 24 months by TIMP-1 intervals in the ACS sub-population.

compared to patients with chest pain and no ACS (median of 81.1 vs 78.3, respectively, $P < .05$). Similarly, the ACS group had higher baseline hs-CRP values compared with the non-ACS chest pain group (median of 13.2 vs 6.8, respectively, $P < .0001$). In comparison to the non-ACS chest pain patients, the ACS group had worse outcomes at 24 months, as manifested by a higher incidence of all-cause mortality (13.6% vs 6.5%, $P < .05$), any MI (19.8% vs 9.3%, $P < .05$), and nonfatal MI (18.2% vs 7.3%, $P < .05$). To determine whether TIMP-1 retained its predictive value in both the ACS and non-ACS groups, we performed separate analyses in each of these subpopulations with the same univariate and multivariate models used to predict outcomes for the entire cohort. For the patients presenting with ACS, TIMP-1 was still an independent predictor of all-cause mortality at 24 months by multivariate analysis (OR 1.49, 95% CI 1.01-2.21, $P = .0442$). Furthermore, the ratio of TIMP-1 to MMP-9 was an independent predictor of each of the individual end points of cardiac mortality (OR 1.82, 95% CI 1.12-2.97, $P = .0164$) and MI (OR 1.57, 95% CI 1.07-2.30, $P = .0204$) by multivariate analysis. For the non-ACS chest pain patients, TIMP-1 was again an independent predictor of the individual end point of all-cause mortality at 24 months by multivariate analysis (OR 2.70, 95% CI 1.02-7.15, $P = .0449$).

Kaplan-Meier curves were generated for the ACS subpopulation using the 25th and 75th percentiles as prespecified cut-off points for TIMP-1 levels corresponding to values of <66.9 ng/mL, between 66.9 and 106.8 ng/mL, and >106.8 ng/mL (Figure 3). Once again, Kaplan-Meier plots demonstrated a significant increase in mortality with increasing TIMP-1 values. In particular, TIMP-1 values exceeding 106.8 ng/mL were strongly predictive of all-cause and cardiac mortality. For all-cause mortality, the survival rates at 24 months in the 3 groups were 96.4%, 86.7%, and 73.3%, respectively ($P = .003$). For cardiac death, the rates were 96.4%, 93.3%, and 84.1%, respectively ($P = .04$).

Discussion

The most significant finding of our study was that TIMP-1 levels were powerful predictors of the clinical outcomes of death and MI in this cohort of patients referred for coronary angiography. Of the biomarkers assayed in our study, only TIMP-1 was predictive of the development of MI at 24 months on multivariate analysis. Similarly, TIMP-1 (or its ratio with MMP-9) was the only biomarker predictive of all-cause and cardiac mortality on multivariate analysis.

To our knowledge, this is the first report of the predictive value of TIMP-1 for MI, as well as for cardiac and all-cause mortality. The ability to predict mortality using a single baseline determination of TIMP-1 in a population of patients referred for cardiac catheterization is notable and may relate to the elevated risk of the study population. The elevated baseline cardiovascular risk profile of this population is manifested in the clinical, angiographic, and laboratory data. For example, the median hs-CRP value for this cohort (9.2 mg/L) approximates that of a previously reported level (10 mg/L) used to define a population at high risk.[14] In an attempt to determine if the predictive power of TIMP-1 was in fact related to baseline risk, patients with chest pain were further stratified into those with and without an acute coronary syndrome. When the patients were categorized in this manner, the predictive power of TIMP-1 was still preserved in each of the 2 subgroups. Specifically, in the higher-risk ACS group, TIMP-1 remained an independent predictor of all-cause mortality, whereas its ratio with MMP-9 was independently predictive of each of the individual end points of cardiac mortality and MI. Furthermore, even in the lower-risk non-ACS population of chest pain patients, TIMP-1 was still an independent predictor of all-cause mortality at 24 months. These findings attest to the powerful prognostic power of TIMP-1 in patients with chest pain associated with varying risk profiles.

The finding that TIMP-1 is a powerful and independent predictor of death and MI raises the possibility that TIMP-1 is proximately, or perhaps even causally, related to the underlying atherosclerotic pathophysiology. For example, TIMP-1 is known to induce proliferation in a variety of cell types by mechanisms independent of MMP inhibition.[15] Recently, TIMP-1 has also been demonstrated to have a mitogenic effect on human aortic smooth muscle cells, suggesting that it may directly contribute to the excessive smooth muscle cell proliferation seen in association with atherosclerosis.[16] Tissue inhibitor of metalloproteinase-1 is known to promote angiogenesis,[17,18] to regulate apoptosis,[19] and to amplify inflammation.[20] Thus, in addition to being a potential marker of inflammation, TIMP-1 may also be directly involved in the pathogenesis of atherosclerosis and its complications. Further supporting this involvement is our finding that plasma TIMP-1 levels were elevated in patients presenting with acute MI. This observation is in accord with the literature[21] and is consistent with the growing body of evidence implicating macrophages and matrix degradation in the etiology of plaque rupture.[3,4]

Finally, our findings of a significant and independent correlation between TIMP-1 levels and LV systolic dysfunction are consistent with those of a recent study from the Framingham population, which also found a similar inverse relationship between plasma TIMP-1 levels and echocardiographically defined LV systolic function.[22] Collectively, these observations support a role for TIMP-1 in remodeling of the left ventricle in various disease states. Left ventricular remodeling has been shown to be associated with derangements in the balance between the accumulation and degradation of cardiac extracellular matrix.[23,24] In an experimental model of hemodynamic pressure overload, TIMP-1 messenger RNA and protein expression was increased in parallel with increasing LV mass.[25] In addition, inhibition of MMPs has been shown to reduce LV dilation in animal models of heart failure.[26] Thus, similar to its apparent role in atherosclerosis, elevated TIMP-1 levels in the context of LV systolic dysfunction may constitute both a marker of disease as well as an important mechanism contributing to its pathogenesis.

Study limitations

This study has a number of limitations. First, it was conducted in an exclusively male population. Second, the population was a high-risk cohort as evidenced by both clinical and laboratory parameters as well as by the high event rate for death and MI. Therefore, it is unknown whether TIMP-1 levels would be similarly predictive of events in a low-risk population. Along the same lines, larger studies in healthy populations are needed to determine the reference range of TIMP-1 and the factors that influence its levels in the absence of atherosclerotic disease. Third, the size of our population was small and the study was not designed with a priori calculations with respect to sample size or statistical power. As such, the findings need to be confirmed in larger and prospectively designed studies.

In conclusion, the observations derived from this study are consistent with the growing body of evidence demonstrating the presence of inflammation at all phases of atherothrombosis. Tissue inhibitor of metalloproteinase-1 appears to be an important inflammatory marker/mediator by virtue of its association with the complications of atherosclerosis and its predictive power for the end points of death and MI.

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