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Baseline serum matrix metalloproteinase-9 level predicts long-term prognosis after coronary revascularizations in stable coronary artery disease

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Abstract

Objectives: This study aimed to investigate whether baseline serum levels of matrix metalloproteinases (MMPs) could predict long-term prognosis of coronary revascularizations.

Designs and methods: Ninety-one consecutive patients receiving coronary revascularizations (58 percutaneous coronary interventions and 33 coronary artery bypass graft surgeries) for stable coronary artery disease (CAD) were studied. Baseline serum levels of high-sensitive C-reactive protein (hsCRP), MMP-2, -3 and -9 drawn before revascularization were correlated to the clinical adverse events within >12 months after revascularizations.

Results: Baseline characteristics were similar between the two groups. There were total 22 major adverse cardiovascular events during a mean period of 27 months. Only baseline serum MMP-9 level independently predicted future cardiovascular events after coronary revascularization either by multivariate analysis (relative risk 3.18, $p=0.028$) or by Kaplan–Meier analysis ($p=0.021$).

Conclusions: Baseline serum MMP-9 level predicted the prognosis after coronary revascularizations, suggesting its potential role in risk stratification before revascularization strategies for stable CAD.

Keywords: Coronary artery bypass graft surgery; Coronary artery disease; High-sensitive C-reactive protein; Matrix metalloproteinases; Percutaneous coronary intervention; Prognosis

Introduction

Chronic inflammation process may play the important pathologic role in the development and progression of atherosclerosis plaque. Several inflammation mediators have been proven to correlate with the severity or the prognosis of coronary artery disease (CAD). Matrix metalloproteinases (MMPs) which are mainly secreted by monocyte-derived macrophage and vascular smooth muscle cells are a family of zinc-containing endoproteinases [1]. The members of this family have been identified in human atherosclerotic plaque shoulders and regions of foam cell accumulation and may thus contribute to the lesion progression, plaque vulnerability and de novo atherosclerotic remodeling [2–4]. The expression of serum MMP-2 and MMP-9 has been found increased in patients with acute coronary syndrome [5]. It was further indicated that the serum level of MMP-9 might be a sensitive inflammation marker [6] and a predictor of cardiovascular mortality in patient with CAD [7]. Recently, we also demonstrated that baseline serum MMP-3 and high-sensitive C-reactive protein (hsCRP) levels could be associated with future cardiovascular events in stable CAD patients under medical treatment [8 9]. However, the particular impact of different basal serum MMPs levels to long-term prognosis after

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coronary artery revascularization procedures such as percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG) has not been well addressed. This study was conducted to investigate the role of baseline serum levels of MMP-2, -3 and -9 and other inflammation markers such as hsCRP in predicting future adverse cardiovascular events after different strategies of coronary revascularization in a cohort of stable CAD patients.

Methods

Study population

Between March 1999 and June 2002, a series of 500 consecutive patients with stable anginal chest pain for coronary artery angiography (CAG) were initially evaluated. CAD was diagnosed if there was at least one lesion with >50% stenosis in luminal diameter on CAG according to the American College of Cardiology/American Heart Association lesion classification. The subsequent treatment strategy including medical treatment and coronary revascularization (PCI or CABG) was discussed in detail with the patients if their CAD was confirmed by CAG. The exclusion criteria included the episode of congestive heart failure within 1 year before the diagnostic coronary angiogram or acute coronary syndrome including acute myocardial infarction or unstable angina during hospitalization, uncontrolled congestive heart failure (NYHA functional class III to IV or with clinical evidence of decompensate heart failure), uncontrolled hypertension (blood pressure >180/110 mm Hg), severe valvular heart disease, chronic liver disease, renal insufficiency and chronic systemic inflammatory disease. Besides, diabetes mellitus itself has been known as an important confounding factor for cardiovascular events. The inflammatory status could be varied with fluctuated plasma sugar levels in diabetic patients especially those without adequate control. Thus, patients with inadequately controlled fasting plasma sugar (>140 mg/dL) and/or glycated hemoglobin level (>7.0%), either with or without medication, were also excluded.

Among the 226 patients fulfilling the inclusion criteria, 135 decided to take medication for their stable CAD. Thus, a total of 91 patients who decided to receive coronary revascularization were prospectively enrolled. There were 58 patients with PCI and 33 with CABG within 2 weeks after CAG. The revascularization strategy was decided according to the disease severity and the patients' willingness and was preceded under standard procedure. The indication of stent implantation during the PCI was operator dependent. The risk factors including blood pressure, fasting plasma sugar, smoking and lipid status were assessed at the time of enrollment. The study protocol was approved by hospital review board and the informed consent was obtained from each patient.

Blood sampling

After overnight fasting, 20 mL of blood was drawn from peripheral vessels just before CAG in each patient. The blood samples were either analyzed immediately for lipid profiles or stored at −80 °C until analysis for other biomarkers. Patients were excluded if they had received any drugs with antioxidant activity, vitamin or food additives within 4 weeks before blood sampling.

Measurement of lipid profiles and serum biomarker

The lipid profiles including total cholesterol, total triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and other serum biochemical parameters were analyzed by Hitachi 7600-310 auto analyzer (Hitachi; Tokyo, Japan). Serum hsCRP levels were measured by enzyme-linked immonosorbent assay (ELISA) method using a commercially available kit (Dade Behring, Marburg, Germany) with the manufacturer's reagents. The detection limit for hsCRP was 0.02 mg/L; intra- and inter-assay coefficient of variations were 6.4%. Serum levels of total form of MMPs (MMP-2, MMP-3 and MMP-9) were determined using commercially available enzyme-linked immunoassays (Biotrak-Amersham Pharmacia Biotech, Uppsala, Sweden) with the manufacturer's reagents and instruction. Intra-assay coefficient of variations determined in our laboratory were 6.3%; between assay coefficient of variations were 7.8%. Sensitivities were 0.37, 1.25 and 0.6 ng/mL for MMP-2, MMP-3 and MMP-9 respectively. All of the methodology in our study had been published before [8,9].

Clinical follow-up for adverse cardiovascular events

The patients with initially stable condition after coronary revascularization were prospectively followed up regularly in 1 month interval for at least 12 months in the same cardiology clinic of a medical center. If the patients' condition was stable throughout 1 year, they would then be followed up every 3 months until the end of the study. At follow-up, information was obtained for any main adverse cardiovascular events including death of cardiac causes, fatal or non-fatal myocardial infarction. The unscheduled ischemic-driven coronary revascularizations were also recorded if they were performed for the onset of drug-refractory angina and clinical evidence of myocardial ischemia. Information about the clinical events was mainly obtained according to the records of hospital charts, which were then re-confirmed by interview or telephone inquiry with the patients and/or their families.

Statistical analysis

Data were expressed as mean ± SD if normally distributed or as median (range) otherwise. Mean levels of variables were compared by ANOVA test for continuous variables and by a χ^2 test for categorical variables. The numerical variables and frequency between groups were compared by Student's t test, χ^{2}-test and/or Mann–Whitney U test as appropriate. Correlations were performed with Pearson's correlation method. Univariate and multivariate Cox proportional hazards regression analyses were used to determine the independent predictors of the end point in each group. The Kaplan–Meier method with log-rank test was applied for survival analysis. To find out the optimal

cutoff value of serum markers for future cardiovascular events, we analyzed our coronary revascularization patients by receiver operating characteristic curve analysis. $p<0.05$ was considered statistically significant. All computations were carried out with SPSS, version 10.7 (SPSS Inc. Chicago, Illinois).

Results

Patient characteristics

Table 1 demonstrates the baseline characteristics of the 91 patients receiving coronary revascularization including 58 patients with PCI and another 33 patients with CABG. Though multi-vessels disease tended to be more frequently seen in patients receiving CABG than in those with PCI, there were no significant differences in age, gender, previous PCI or CABG history, baseline lipid profile, serum hsCRP, MMPs levels, and medications between the two patient groups. In all patients with revascularization, there was no correlation between serum hsCRP and MMP-9 levels ($R=0.022$, $p=0.866$, by Pearson's correlation method).

Clinical follow-up of cardiovascular events

All of the patients with revascularization were followed up to 68 months (median, 27 months) after the procedures. During the whole follow-up period, a total of 22 adverse cardiovascular events including 6 cardiac deaths (6.9% of all patients), 3 non-fatal myocardial infarctions (3.4% of all patients), 13 ischemic-driven revascularization including 9 repeated PCI (10.3% of all patients) and 4 unscheduled CABG (4.6% of all patients) were identified. The indications of repeated revascularization procedures were target vessel restenosis in 12 (92.3%) and the progression of atherosclerotic disease in 5 (38%) of the 13 patients. There were 4 patients with both target vessel restenosis and the progression of atherosclerotic disease. All of the patients developed drug-refractory angina and clinical evidences of myocardial ischemia before repeated revascularization procedures.

Baseline characteristics in patients with and without cardiovascular events after coronary revascularization

Table 2 shows the comparisons between patients with and without adverse cardiovascular events after coronary revascularization. Compared to those without events, patients with adverse cardiovascular events were older ($p=0.031$) at baseline. The lipid profiles and convention risk factors were similar in these 2 groups. As shown in Fig. 1, the serum hsCRP and MMP-9 levels were higher in patients with future cardiovascular events. However, there was no statistically significant difference.

Predictors of future cardiovascular events after all coronary revascularization including PCI and CABG

Receiver operating characteristics curve analysis was used to determine the cutoff value of age, hsCRP and MMP-9 for the risk of future cardiovascular events after coronary revascularization including both PCI and CABG. The optimal cutoff points of age, hsCRP and MMP-9 were 70 years, 0.1 mg/dL and 34.88 ng/mL, respectively.

Table 3 shows the predictors of future cardiac events after coronary revascularization in all the study patients. The results of univariate Cox analysis indicated that baseline serum MMP-9 value >34.88 ng/mL was significantly associated with

Table 1
Basic characteristics of patients receiving different revascularization strategies

Characteristics	PCI ($n=58$)	CABG ($n=33$)	Total revascularization (PCI+CABG, $n=91$)
Age, year	68.6±10.8	67.6±8.9	68.2±10.1
Male gender (%)	56 (96.6)	31 (93.9)	87 (95.6)
Hypertension (%)	44 (75.9)	21 (63.6)	65 (71.4)
Smoking (%)	24 (41.4)	6 (18.2)	30 (33)
Diabetes mellitus (%)	1 (1.7)	2 (6.1)	3 (3.3)
Previous myocardial infarction (%)	10 (17.2)	4 (12.1)	14 (15.4)
Previous PCI (%)	10 (17.2)	5 (15.2)	15 (16.5)
Previous CABG (%)	5 (8.6)	2 (6.1)	7 (7.7)
No. of affect coronary artery			
1 vessel	24	5	29
2 vessels	20	7	27
3 vessels	13	21	34
Left ventricular ejection fraction (%)	63.0±16.6	54.8 ±19.4	60.0±18.0
Aspartate aminotransferase (U/L)	21.6 ±8.8	22.3±9.7	21.7±9.0
Alanine aminotransferase (U/L)	22.4±15.8	24.6±19.5	23.1±17.0
Creatinine (mmol/L)	82.4±15.0	82.5±16.5	82.5±15.7
Creatinine kinase (U/L)	55.0±24.6	49.5±24.7	52.9±24.5
Triglyceride (mmol/L)	1.5±0.9	1.4±0.7	1.5±0.8
Total cholesterol (mmol/L)	4.6±0.97	4.8±0.86	4.6±0.93
Total cholesterol/High-density lipoprotein ratio	4.9±1.29	5.1±1.52	5.0±1.37
Low-density lipoprotein cholesterol (mmol/L)	2.9±0.72	3.1±0.70	3.0±0.72
High-density lipoprotein cholesterol (mmol/L)	0.97±0.24	0.98±0.24	0.97±0.24
High-sensitive C-reactive protein (mg/dL)	0.299 (0.016–2.520)	0.305 (0.016–3.220)	0.301 (0.016–3.220)
MMP2 (ng/mL)	953.5± 193.06	922.0± 187.81	942.7±190.20
MMP3 (ng/mL)	125.5± 49.26	118.0± 48.49	122.8±48.82
MMP9 (ng/mL)	49.0±45.36	48.8±34.98	49.0±41.50
Drug at enrollment			
Aspirin (%)	55 (94.8)	27 (81.8)	82 (90.1)
Nitrate (%)	19 (32.7)	8 (24.2)	27 (29.7)
Calcium channel blocker (%)	29 (50)	20 (60.6)	49 (53.8)
Beta-blocker (%)	25 (43.1)	7 (21.2)	32 (35.2)
ACEI/ARB (%)	35 (60.3)	14 (42.5)	49 (53.9)
Diuretics (%)	5 (8.6)	9 (27.3)	14 (15.4)
Statins (%)	20 (34.5)	10 (30.3)	30 (33.0)

Data are presented as No. (%) or mean±SD unless otherwise indicated. Median (range). ACEI: angiotensin II converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CABG: coronary artery bypass graft surgery; MMP: matrix metalloproteinase; PCI: percutaneous coronary intervention.

Table 2
Comparison of patients with or without clinical events after coronary revascularization

Variables	Revascularization (PCI+CABG)		
	Without events (n=65)	With events (n=22)	p value
Age, years	66.9±10.8	71.3±7.5	0.031
Male gender (%)	62 (95.3)	20 (90.9)	0.579
Hypertension (%)	47 (64.0)	15 (68.1)	0.690
Diabetes mellitus (%)	2 (3.1)	1 (4.5)	1.000
Smoker (%)	24 (36.9)	6 (27.2)	0.241
Aspartate aminotransferase (U/L)	21.5±8.3	22.3±10.7	0.737
Alanine aminotransferase (U/L)	23.9±16.0	21.2±19.3	0.526
Creatinine (mmol/L)	83.5±16.8	80.4±12.9	0.425
Creatinine kinase (U/L)	49.8±24.3	59.7±24.1	0.102
Triglyceride (mmol/L)	1.5±0.8	1.4±0.7	0.412
Total cholesterol (mmol/L)	4.7±0.9	4.6±0.9	0.921
Low-density lipoprotein cholesterol (mmol/L)	3.0±0.3	3.0±0.7	0.671
High-density lipoprotein cholesterol (mmol/L)	1.0±0.3	0.9±0.2	0.609
Total cholesterol/High-density lipoprotein ratio	5.0 (2.4–8.8)	5.0 (2.8–7.1)	0.981
High-sensitive C-reactive protein (mg/dL)	0.263 (0.027–0.962)	0.319 (0.016–3.220)	0.649
MMP-2 (ng/mL)	944.2±197.9	940.2±181.5	0.938
MMP-3 (ng/mL)	121.9±52.4	122.0±40.1	0.795
MMP-9 (ng/mL)	48.0±44.6	51.2±33.8	0.745
Left ventricular ejection fraction (%)	60±15.6	59±23.2	0.652

Data are presented as No. (%) or mean±SD unless otherwise indicated. Median (range). CABG: coronary artery bypass graft surgery; MMP: matrix metalloproteinase; PCI: percutaneous coronary intervention.

future cardiovascular events (p=0.026) whereas baseline serum hsCRP level >0.1 mg/dL (p=0.065) and age >70 years (p=0.052) were borderline significant. In multivariate Cox proportional hazards analysis, after adjusting with age, hsCRP and other conventional risk factors, serum MMP-9 level >34.88 ng/mL was still the only independent predictor of future cardiovascular events after coronary revascularization (relative risk [RR], 3.178; 95% confidence interval [CI], 1.14–8.89; p=0.028). Besides, Kaplan–Meier analysis was also done to examine the predictive value of baseline serum MMPs levels for future adverse cardiovascular events. Consistent with that by

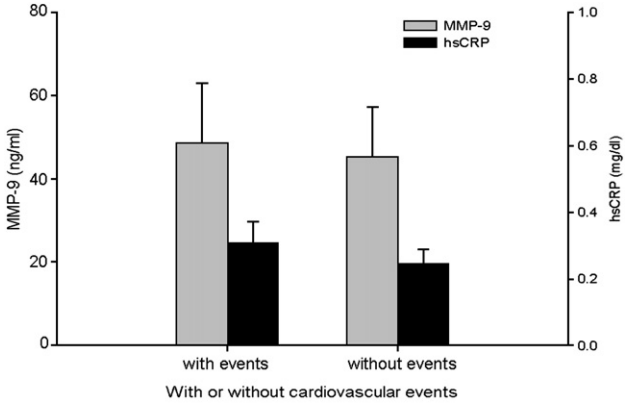

Fig. 1. Comparison of baseline MMP-9 and hsCRP level between patients with or without future cardiovascular events. The baseline MMP-9 and hsCRP level was higher in patients with future cardiovascular events. However, it is not significant.

Table 3
Predictors of future clinical cardiovascular events in all patients receiving revascularization

Parameters	RR (95% CI)	p value
Univariate COX proportional hazards regression		
Age >70 years	2.187 (0.992–4.821)	0.052
hsCRP >0.1 mg/dL	2.460 (0.947–6.391)	0.065
MMP-9 >34.88 ng/mL	2.706 (1.124–6.511)	0.026
Multivariate Cox proportional hazards regression		
Age >70 years	2.620 (0.983–6.983)	0.054
MMP-9 >34.88 ng/mL	3.178 (1.137–8.885)	0.028

multivariate Cox proportional hazards analysis, patients with a baseline serum MMP-9 level >34.88 ng/mL had more future cardiovascular events than those with an MMP level ≤34.88 ng/mL (p=0.021 by log-rank test) (Fig. 2). The difference in future cardiovascular events could be significantly shown even within the first year of follow-up. There were no correlations between baseline MMP-2, MMP-3 or hsCRP level and the rate of patients' event-free survival.

Further subgroup analysis was then conducted to determine if MMP-9 level could be related to the long-term prognosis in patients with PCI and in those with CABG individually. By Kaplan–Meier analysis with log-rank test, baseline serum MMP-9 levels were shown to predict future cardiovascular events in either PCI group (p=0.0374) or CABG group (p<0.001). The results indicated the predictive value of baseline serum MMP-9 level in patients with different revascularization strategies.

Comparison of basic characteristics between patients with different serum MMP-9 levels

Table 4 showed the comparisons between the two groups of patients with different baseline serum MMP-9 levels (MMP-9 >34.88 ng/mL and ≤34.88 ng/mL). There was no significant difference in other basic characteristics between the two groups.

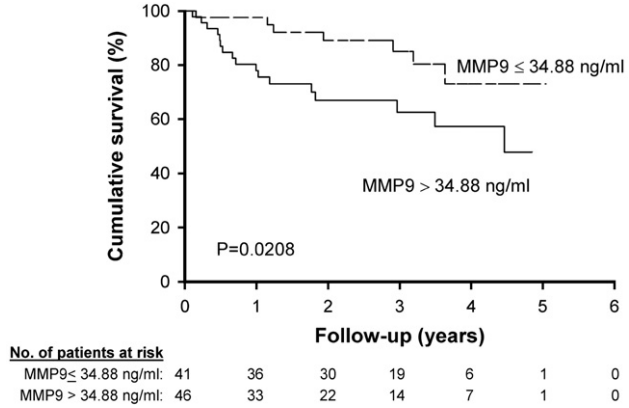

Fig. 2. Kaplan–Meier curves of event-free survival for major cardiovascular events after all coronary revascularization (including both percutaneous coronary intervention and coronary artery bypass grafts) according to baseline serum matrix metalloproteinase-9 levels (ng/mL). The event-free survival rate was significantly reduced in patients with baseline serum MMP-9 level >34.88 ng/mL (p=0.0208 by log-rank test).

Table 4
Basic characteristics of patients with coronary revascularization according to different serum matrix metalloproteinase-9 values

Variables	PCI			CABG			Revascularization (PCI+CABG)		
	≤34.88 ng/mL (*n*=27)	>34.88 ng/mL (*n*=27)	*p* value	≤34.88 ng/mL (*n*=14)	>34.88 ng/mL (*n*=19)	*p* value	≤34.88 ng/mL (*n*=41)	>34.88 ng/mL (*n*=46)	*p* value
Age (years)	68.8±9.4	67.5±12.0	0.86	67.9±8.0	67.4±9.8	0.92	68.5±8.9	67.5 ±11.0	0.99
Male gender (%)	26 (96.3)	26 (96.3)	1.00	13 (92.9)	18 (94.7)	1.00	39 (95.1)	44 (95.7)	1.00
Hypertension (%)	21 (77.8)	20 (74.1)	1.00	10 (71.4)	11 (57.9)	0.66	31 (75.6)	31 (67.4)	0.54
Diabetes mellitus (%)	1 (3.7)	0 (0%)	1.00	0 (0)	2 (10.5)	0.49	1 (2.4)	2 (4.3)	1.00
Smoker (%)	13 (48.1)	10 (37.0)	0.58	1 (7.1)	5 (26.3)	0.20	14 (34.1)	15 (32.6)	1.00
Previous myocardial infarction (%)	4 (14.8)	6 (22.2)	0.72	3 (21.4)	1 (5.3)	0.28	7 (17.1)	7 (15.2)	1.00
Number of affected coronary arteries			0.63			0.78			0.54
1 vessel	12 (44.4%)	13 (48.1%)		3 (21.4%)	2 (10.5%)		15 (36.5%)	15 (32.6%)	
2 vessels	10 (37.0%)	7 (25.9%)		3 (21.4%)	4 (21.1%)		13 (31.7%)	11 (24.0%)	
3 vessels	5 (18.5%)	7 (25.9%)		8 (57.1%)	13 (68.4%)		13 (31.7%)	20 (43.4%)	
Triglyceride (mmol/L)	1.5±0.9	1.6±0.9	0.58	1.5±0.6	1.5±0.7	0.95	1.7±0.7	1.5±0.4	0.70
Total cholesterol (mmol/L)	4.8±0.9	4.5 ±1.0	0.21	4.8±0.7	4.8±1.0	0.71	4.8±0.8	4.6±1.0	0.27
Low-density lipoprotein cholesterol (mmol/L)	3.0 ±0.7	2.8±0.8	0.41	1.0±0.6	3.2±0.8	0.82	3.1±0.7	2.9±0.8	0.47
High-density lipoprotein cholesterol (mmol/L)	0.98±0.2	0.97±0.2	0.74	1.0±0.2	0.96±0.2	0.59	0.99±0.3	0.97±0.2	0.58
Total cholesterol/High-density lipoprotein ratio	5.1 (2.9–8.3)	4.8 (2.4.–7.2)	0.65	5.0 (2.8–8.1)	5.2 (2.9–8.8)	0.79	5.1 (2.8–8.3)	5.0 (2.4–8.8)	0.70
High-sensitive C-reactive protein (mg/dL)	0.276 (0.027–0.962)	0.316 (0.016–0.2.52)	0.44	0.385 (0.016–3.220)	0.232 (0.037–0.770)	0.41	0.316 (0.016–3.220)	0.286 (0.016–2.520)	0.88
MMP-2 (ng/mL)	956.9±197.9	941.6±191.9	0.79	966.2±208.8	898.3±179.7	0.53	960.2±196.3	926.4±186.4	0.47
MMP-3 (ng/mL)	271.7±26.7	212.9 ± 99.0	0.44	124.7±40.3	111.8±55.8	0.30	212.3±63.9	202.4±93.8	0.98
MMP-9 (ng/mL)	23.9±6.6	74.1±53.3	<0.01	24.7±5.6	66.6±37.0	<0.01	24.2±6.2	71.0±47.0	<0.01
Left ventricular ejection fraction (%)	64 (41–85)	64 (20–87)	0.99	51 (15–78)	58 (25–77)	0.59	59 (15–85)	61 (20–87)	0.68

Data are presented as No. (%), median (range), or mean±SD. CABG: coronary artery bypass graft surgery; MMP: matrix metalloproteinase; PCI: percutaneous coronary intervention.

The medications used at enrollment were also comparable between the two groups except for more frequent use of long-acting nitrates in patients with serum MMP-9 levels >34.88 ng/mL than in those with lower levels (43.5% versus 14.6%, $p=0.007$). Besides, there was only a trend of more usage of statins in patients with baseline serum MMP-9 ≤34.88 ng/mL than in those with MMP-9 >34.88 ng/mL (43.9% versus 19.6%, $p=0.093$).

Comparison of major cardiovascular events during follow-up between patients with different serum MMP-9 levels

The major cardiovascular events in patients with high and low serum MMP-9 levels (cutoff value was 34.88 ng/mL) were listed according to different revascularization strategies. As that shown in Table 5, there were more major cardiovascular events including cardiac death, non-fatal MI and ischemic-driven revascularization during the follow-up period in patients with baseline MMP-9 level >34.88 ng/mL than in those with MMP-9 level ≤34.88 ng/mL (37.0% vs. 12.2%, $p=0.011$). The incidence of cardiac death (8.7% vs. 4.9%) and that of non-fatal MI (4.3% vs. 2.4%) tended higher, though not statistically significantly, in patients with MMP-9 >34.88 ng/mL. The subgroup analysis indicated that in PCI group, patients with MMP-9 >34.88 ng/mL had significantly more repeated ischemic-driven revascularization at follow-up than those with MMP-9 ≤34.88 ng/mL (23.9% vs. 4.9% $p=0.029$).

Table 5
Major cardiovascular events during follow-up in patients with coronary revascularization according to different serum MMP-9 values

Variables	PCI			CABG			Revascularizations (PCI+CABG)		
	≤34.88 ng/mL (*n*=27)	>34.88 ng/mL (*n*=27)	*p* value	≤34.88 ng/mL (*n*=14)	>34.88 ng/mL (*n*=19)	*p* value	≤34.88 ng/mL (*n*=41)	>34.88 ng/mL (*n*=46)	*p* value
Total major events during follow-up (%)	4 (14.8)	13 (48.1)	0.01	1 (7.1)	4 (21.1)	0.36	5 (12.2)	17 (37.0)	0.01
Cardiac death (%)	1 (3.7)	1 (3.7)	1.00	1 (7.1)	3 (15.8)	0.62	2 (4.9)	4 (8.7)	0.68
Acute myocardial infarction (%)	1 (3.7)	1 (3.7)	1.00	0 (0)	1 (5.3)	1.00	1 (2.4)	2 (4.3)	1.00
Repeated revascularization	2 (7.4)	11 (40.7)	0.01	0 (0)	0 (0)	–	2 (4.9)	11 (23.9)	0.02
PCI (%)	2 (7.4)	7 (25.9)		0 (0)	0 (0)	–	2 (4.9)	7 (15.2)	
CABG (%)	0 (0)	4 (14.8)		0 (0)	0 (0)	–	0 (0)	4 (8.7)	

Data are presented as No. (%). CABG: coronary artery bypass graft surgery; PCI: percutaneous coronary intervention.

Discussion

Atherosclerosis is suggested as a vascular inflammatory process and circulating inflammatory biomarkers such as hsCRP [9,10] had been reported to be correlated with the development of future adverse cardiovascular events in patients with CAD. However, rare information has been provided to evaluate the role of different serum biomarkers for long-term prognosis after coronary revascularizations such as PCI and CABG. In the present study, it was well demonstrated that baseline serum MMP-9 level, rather than hsCRP and other clinical parameters, was associated with an increased risk of future adverse cardiovascular events after coronary revascularizations with either PCI or CABG. To our best knowledge, this is the first study indicating the universal role of baseline serum MMP-9 level for long-term prognosis after different coronary revascularization strategies in stable CAD patients. Furthermore, the baseline serum MMP-9 levels were measured before revascularization procedures in this study. It is then possible to stratify the potential risk and evaluate the long-term outcome even before different coronary revascularization is performed. The above issue may have important impact to clinical decision making and future large-scale cohort study may warrant confirming our findings.

Baseline serum MMP-9 level and future cardiovascular events after coronary revascularization

MMPs had been identified in vascular remodeling process and play an important role in the pathogenesis and progression of atherosclerosis especially plaque formation and rupture [11] Serum MMP-9 level could also be correlated to the severity of CAD [12,13] and to the rapid luminal narrowing of coronary artery in patients with stable angina [14]. In the present study, though the baseline characteristics were comparable, the use of nitrates was more frequently in patients with baseline MMP-9 value >34.88 ng/mL. In these patients, there might be more clinical angina symptoms and more diffuse atherosclerosis involved in the distal and small vessels that could be independent from the number of stenotic vessels on coronary angiography and baseline hsCRP value. This is compatible with previous report by Tayebjee et al. that neither coronary stenosis score nor coronary atheroma score was correlated with MMP-9 levels in stable CAD patients [15]. Similar to our findings, there were no correlations between hsCRP and MMP-9 value. Taken altogether, one may speculate that in a portion of the CAD patients, though stable clinically, vascular MMP-9 might have been activated for the progression of atherosclerosis as well as plaque destabilization even before the development of flank vascular inflammation that could be indicated by serum hsCRP level. Besides, it also suggests that baseline MMP-9, rather than hsCRP, could play the complex pathogenetic roles for the development of future events, though the underlying mechanisms may be different, after PCI and CABG.

It has been demonstrated that MMP-9 activity could be increased concomitantly with the formation of neointima in saphenous vein organ culture [16]. Kalela et al. also indicated that MMP-9 level could be correlated to early vein graft occlusion in patients without previous myocardial infarction, suggesting the critical and direct role of MMP-9 in the development of graft restenosis after CABG [17]. In the present study, though no ischemic-driven repeated revascularization was recorded, there were 4 cardiac deaths and 1 acute myocardial infarction giving an adverse event rate of 15.1% (3–7 per year) in the average follow-up period of 2.3 years after CABG. Interestingly, most (80%, 3 deaths and 1 acute myocardial infarction) of the events developed in patients with baseline MMP-9 level >34.88 ng/mL, compatible with previous suggestion that serum and/or tissue MMP-9 level may contribute to the development of adverse events after CABG. The predominance of death and acute myocardial infarction and lack of ischemic-driven repeated coronary revascularizations also suggest the severe and malignant consequence of graft restenosis and/or atherosclerosis progression as the causes of adverse events in our study.

On the other hand, previous in vitro and in vivo studies suggested that increased levels of MMPs in coronary arteries undergoing percutaneous intervention may contribute to vascular remodeling and restenosis by promoting migration of vascular smooth muscle cells [18,19]. Furthermore, the revascularization procedures themselves might directly injure the vessels and induce the expression of MMP-9 that could contribute to future cardiovascular events either by destabilizing the plaques or by enhancing the formation of neointimal hyperplasia or both [20,21]. The above may provide the rationales to the current findings that baseline serum MMP-9 level could significantly be related to the long-term outcome, especially the ischemic-driven repeated revascularization after PCI in stable CAD patients.

Clinical implication of serum MMP-9 level to coronary revascularization

The findings of independent prognosis predictive value of MMP-9 may be useful for early risk stratification before coronary revascularization in stable CAD patients. However, it should be noted that the production of MMP-9 might be attenuated by some medications such as hydroxymethylglutaryl coenzyme A reductase inhibitors statins in specific patient groups [22]. Our recent studies also suggest that statins could suppress MMPs levels and the suppression might last even after statin withdrawal [23,24]. In the present study, there was a tendency of more usage of statins in patients with baseline MMP-9 level ≤34.88 ng/mL. Though the potential impacts of statin usage to our patients cannot be completely excluded, baseline MMP-9 level is still an independent predictor for future cardiovascular events. However, it is not known whether these events could be prevented by reducing serum MMP-9 level in stable CAD patients. Further clinical clarification is required before the pathogenesis role of MMP-9 could be confirmed.

Study limitations

There were some limitations of this study. First, though the study sample size was relatively small and the study patients were relatively stable and less diabetic, baseline MMP-9 level

could still predict the cardiovascular events after different coronary revascularizations. A large-scale prospective study should be launched for further evaluation of the prognostic role of MMP-9 in different patient populations such as those with DM or with unstable CAD. Second, serum biomarkers were measured only once before coronary revascularization and it was then unable to determine how they were changed dynamically after revascularization procedure and during follow-up. Third, the rate of bare metal stent implantation was similar between patients with and those without future cardiovascular events. Since this study was commenced mainly before the drug eluting stent era, whether these findings could be applied to patients with drug eluting stent should be further evaluated.

Conclusions

In stable CAD patients, baseline serum MMP-9 level, rather than hsCRP, is an independent predictor for future cardiovascular events after PCI or CABG, suggesting its universal role in risk stratification before different revascularization strategies. Future large-scale studies are required to verify its prognostic impacts to different coronary revascularization strategies, particularly PCI with drug eluting stents, in different groups of patients including those with acute coronary syndrome.

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