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Serial Measurement of Monocyte Chemoattractant Protein-1 After Acute Coronary Syndromes

Results From the A to Z Trial

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Objectives This study sought to determine whether the novel biomarker monocyte chemoattractant protein (MCP)-1 adds prognostic value to standard risk assessment tools and biomarkers after acute coronary syndromes (ACS).

Background Monocyte chemoattractant protein-1 is a chemokine recruiting signal for monocytes that may function as both a mediator and biomarker of ACS.

Methods Monocyte chemoattractant protein-1 was measured at baseline (n = 4,244), 4 months (n = 3,603), and 12 months (n = 2,950), and correlated with clinical events in the Z phase of the A to Z (Aggrastat to Zocor) trial, which compared early intensive versus delayed and less intensive statin therapy after ACS.

Results Rates of death and the composite end points of death or myocardial infarction (MI); death, MI, or heart failure; and cardiovascular death, MI, readmission for ACS, or stroke increased across baseline quartiles of MCP-1 and among patients with MCP-1 greater than versus less than or equal to the pre-specified threshold of 238 pg/ml ($p < 0.01$ for each). After adjustment for standard risk predictors and levels of C-reactive protein and B-type natriuretic peptide, MCP-1 >238 pg/ml remained independently associated with mortality (hazard ratio 2.16; 95% confidence interval 1.54 to 3.02) and with each composite end point, and increased the C-statistic of the fully adjusted mortality model from 0.76 to 0.78 ($p < 0.0001$). A value of MCP-1 >238 pg/ml at the 4-month follow-up visit was also independently associated with mortality after 4 months (hazard ratio 1.76; 95% confidence interval 1.12 to 2.76). Elevated MCP-1 levels did not identify patients who derived incremental benefit from intensive statin therapy.

Conclusions Monocyte chemoattractant protein-1 provides independent prognostic value in the acute and chronic phases after ACS and merits further evaluation as a prognostic marker and potential therapeutic target. (J Am Coll Cardiol 2007;50:2117–24) © 2007 by the American College of Cardiology Foundation

As specific inflammatory pathways contributing to the development, progression, and complications of atherosclerosis have been elucidated, a number of novel biomarkers

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Abbreviations and Acronyms

ACS = acute coronary syndrome
BNP = B-type natriuretic peptide
CRP = C-reactive protein
LDL-C = low-density lipoprotein cholesterol
MCP = monocyte chemoattractant protein
MI = myocardial infarction
ULN = upper limit of normal

and potential drug targets have been identified. Monocyte chemoattractant protein (MCP)-1 is a member of the C-C chemokine family that is produced by monocytes/macrophages, smooth muscle cells, and endothelial cells within atherosclerotic plaques (1). It is recognized by CCR-2 receptors on monocytes and serves as a chemotactic agent to recruit monocytes into the vascular wall (2). In animal models, atherosclerosis is promoted when MCP-1 expression is increased (3), and is inhibited when the gene for either MCP-1 (4) or CCR-2 (5) is deleted. Monocyte chemoattractant protein-1 stimulates tissue factor (6) and superoxide (7) production by monocytes, which may contribute to the transition from stable atherosclerosis to the acute coronary syndrome (ACS) phenotype.

The role of MCP-1 in human atherosclerosis is supported by reports of higher MCP-1 levels and increased rates of myocardial infarction (MI) associated with certain polymorphisms in the MCP-1 gene (8). Moreover, in population studies, plasma levels of MCP-1 are positively correlated with most cardiovascular risk factors, with measures of coronary atherosclerosis burden, and with incident coronary and peripheral artery disease (9–11). In preliminary studies performed in patients with ACS, higher levels of MCP-1 have been associated with an increased risk for death and recurrent ischemic events, independent of standard risk predictors (12,13). These studies, however, have not evaluated the prognostic value of MCP-1 after accounting for more established biomarkers, including C-reactive protein (CRP) (14) and B-type natriuretic peptide (BNP) (15,16). Moreover, studies to date have focused on measurements of MCP-1 during the initial ACS hospitalization, and few data are available in the chronic phase after ACS.

Both MCP-1 and CCR-2 have emerged as attractive targets for existing and novel therapies, based on the animal studies described above, as well as on human studies showing that effective preventive therapies such as statins (17–19) and thiazolinediones (20) reduce cellular expression and circulating levels of MCP-1. We evaluated measurement of MCP-1 in a large population of patients stabilized after ACS and enrolled in the A to Z (Aggrastat to Zocor) trial, to determine whether: 1) measurement of MCP-1 in the hospital setting and/or during outpatient follow-up adds to the prognostic value of standard measurements such as creatinine clearance and low-density lipoprotein cholesterol (LDL-C), as well as emerging biomarkers such as CRP and BNP; 2) plasma levels of MCP-1 were modified by intensive statin therapy; and 3) elevated MCP-1 levels could identify patients who derived incremental benefit from intensive statin therapy.

Methods

Study population. The design and primary results of the A to Z trial have been previously reported (21,22). Phase A was an open-label noninferiority trial comparing enoxaparin with unfractionated heparin among patients with non–ST-segment elevation ACS also receiving tirofiban and aspirin (23). Phase Z was a randomized, double-blind trial performed in 4,497 patients ages 21 to 80 years with non–ST-segment elevation ACS or ST-segment elevation MI, in which an early intensive statin strategy (simvastatin 40 mg/day for 1 month, followed by 80 mg/day through the end of the study) was compared with a delayed and less intensive strategy (placebo for 4 months followed by simvastatin 20 mg/day through the end of the study). Patients were excluded from participation in the A to Z trial if they were taking a statin at the time of enrollment, if they had a serum creatinine level >2 mg/dl, or if revascularization was planned. Follow-up was for at least 6 months and up to 2 years. The current study population included all patients enrolled in Phase Z with a blood sample available for measurement of MCP-1 at either baseline or 4 months.

Measurement of MCP-1 and other biomarkers. Plasma was collected in tubes containing ethylenediamine tetracetic acid at the time of enrollment into Phase Z (median 3.5 days after symptom onset), and at the 4- and 12-month visits, and shipped refrigerated overnight to a central storage facility, where aliquots were frozen at −80°C. Aliquots were shipped on dry ice to the TIMI (Thrombolysis In Myocardial Ischemia) Core Laboratory at the Brigham and Women's Hospital Clinical Laboratories, where they were analyzed in batch. Monocyte chemoattractant protein-1 was measured on the automated enzyme immunoassay analyzer Triturus (Grifols USA, Miami, Florida) using the human MCP-1 enzyme-linked immunosorbent assay (Bender MedSystems, Burlingame, California). The limit of detection was 2.31 pg/ml. The coefficient of interassay variation was 8.7%.

High-sensitivity testing for CRP was performed as previously described using the CRP-Latex (II) immunoturbidimetric assay (Denka Seiken, Tokyo, Japan) on a Hitachi 911 immunoanalyzer (Roche Diagnostics, Indianapolis, Indiana) (14). The pre-specified level for defining CRP elevation at baseline (during the acute phase of ACS) was 15 mg/l (24), and during the chronic phase was 3 mg/l (25). Brain natriuretic peptide was measured using the ADVIA Centaur BNP assay (Bayer Healthcare LLC, Tarrytown, New York) as previously described (16). Brain natriuretic peptide elevation was pre-specified as >80 pg/ml based on previous work with this analyte (15). All biomarkers were measured by personnel blinded to clinical outcomes and treatment allocation.

Study end points. The primary outcome for this substudy was all-cause mortality. As secondary end points, we also evaluated MI; and the composites of death and MI; and death, MI, and new or worsening heart failure; as well as the Phase Z trial primary end point of cardiovascular death, MI, readmission for ACS, and stroke. Cardiovascular death included sudden death and death caused by pump failure, MI, stroke, or after a cardiovascular procedure. An MI was defined as ischemic symptoms or electrocardiographic changes plus elevation in cardiac biomarkers ≥2× upper limit of normal (ULN). Procedural MI required either pathologic Q waves or biomarker elevation ≥3× ULN (percutaneous coronary intervention) or ≥5× ULN (coronary artery bypass graft). An ACS was defined as ischemic symptoms plus either ≥0.5 mm ST-segment deviation, ≥2 mm T-wave change, or biomarker elevation greater than or equal to the ULN but below the MI threshold. Stroke was defined as a sudden focal neurological deficit not reversible within 24 h. New or worsening heart failure required initiation or titration of heart failure medications. All end points except for heart failure were adjudicated by a Clinical Events Committee.

Statistical methods. Patients were divided into quartiles based on the distribution of MCP-1 at baseline and at 4 months. Based on our previous substudy of the OPUS-(Orbofiban in Patients with Unstable coronary Syndromes)-TIMI 16 trial showing that MCP-1 levels >238 pg/ml were independently associated with death and MI after ACS (12), we also pre-specified a threshold of 238 pg/ml as a dichotomous threshold for the present analyses.

Baseline characteristics were compared across MCP-1 quartiles using the chi-square trend test for categorical variables and the "nptrend" test for continuous variables (an extension of the Wilcoxon rank-sum test). The Wilcoxon rank-sum test was used to compare MCP-1 levels between treatment groups. Event rates were estimated using the Kaplan-Meier method and compared between groups using the log-rank test. Stratified analyses were performed using the pre-specified levels of CRP and BNP described above. Cox proportional hazards models were used to adjust for baseline variables known to be associated with adverse outcomes in ACS, including age, gender, weight, prior MI, history of diabetes, current smoking, index diagnosis, creatinine clearance, use of ACE inhibitors, randomized treatment assignment, and levels of LDL-C, CRP, and BNP (all as continuous variables). The C-statistic (analogous to the area under the receiver-operator characteristic curve) was calculated, and the likelihood ratio test was used to compare the discrimination of the models before and after the addition of MCP-1.

Analyses of the association of the 4-month MCP-1 levels and the changes in MCP-1 from baseline to 4 months with subsequent outcomes were performed using a landmark analysis beginning at 4 months. These analyses do not preserve randomization, which was performed at baseline; therefore comparisons between treatment groups based on 4-month MCP-1 values should be considered exploratory only. Cox proportional hazards models were performed with adjustment for age, gender, history of diabetes, current smoking, index diagnosis, treatment assignment, and levels of LDL-C, CRP, and BNP measured at 4 months.

All analyses were performed by the TIMI Study Group using STATA 9.2 (STATA Corporation, College Station, Texas).

Results

No differences in baseline characteristics were detected between the overall Phase Z study population (n = 4,497) and the subgroups with MCP-1 measured at baseline (n = 4,244), at 4 months (n = 3,603), or at 12 months (n = 2,950) (data not shown). Clinical characteristics according to levels of MCP-1 at baseline are shown in Table 1. Higher MCP-1 levels were associated with older age, female gender, diabetes, hypertension, prior MI or heart failure, prior aspirin use, lower creatinine clearance, higher triglycerides, and lower HDL cholesterol ($p < 0.01$ for each). Baseline MCP-1 levels were not associated with baseline CRP or BNP levels, but were associated with 1-month CRP levels in the placebo group (Table 1). Although MCP-1 levels were lower among smokers in univariable analyses, this difference disappeared after adjustment for age ($p = 0.24$).

Influence of statin therapy on MCP-1 levels. Monocyte chemoattractant protein-1 levels were similar at baseline in the 2 treatment groups ($p = 0.46$). Over the first 4 months, the median increase in MCP-1 was greater in the placebo arm than in the simvastatin 40 mg/80 mg arm (24 vs. 13 pg/ml; $p = 0.002$), resulting in modestly lower MCP-1 levels in the simvastatin 40 mg/80 mg arm at 4 months ($p = 0.005$) (Fig. 1). At 12 months, reflecting the comparison of simvastatin 80 mg versus simvastatin 20 mg, no differences in MCP-1 levels were seen ($p = 0.22$) (Fig. 1).

Association between baseline MCP-1 levels and outcomes. Rates of each of the end points, including death; MI; the composite end point of death or MI; the composite end point of death, MI, or heart failure; and the primary Phase Z composite increased across baseline quartiles of MCP-1 ($p < 0.01$ for each) (Table 2). Please note that risk in the 4th quartile did not exceed that in the 3rd quartile. Patients above the pre-specified MCP-1 cutoff point of 238 pg/ml were also at increased risk for mortality ($p < 0.0001$) (Fig. 2), as well as each of the secondary end points ($p < 0.01$ for each) (Table 2). In stratified analyses, patients with MCP-1 levels >238 pg/ml were at increased risk for mortality whether CRP was >15 or ≤15 mg/l or whether BNP was >80 or ≤80 pg/ml (Fig. 3). In multivariable analyses adjusting for baseline variables, index diagnosis, creatinine clearance, LDL-C, CRP, and BNP, a baseline MCP-1 level >238 pg/ml remained associated with mortality (adjusted hazard ratio 2.16; 95% confidence interval 1.54 to 3.02), and with each of the other end points

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Table 1 Association Between Enrollment Clinical Variables and Baseline Levels of MCP-1

Variable	Quartile 1 (<190 pg/ml) n = 1,070	Quartile 2 (190–255 pg/ml) n = 1,052	Quartile 3 (256–350 pg/ml) n = 1,074	Quartile 4 (>350 pg/ml) n = 1,048	p Trend
Age, yrs	58 (50, 67)	60 (52, 69)	62 (53, 70)	64 (55, 71)	<0.001
Weight, kg	79 (69, 89)	80 (70, 90)	80 (70, 90)	79 (69, 90)	0.63
Female gender, %	20	19	27	31	<0.001
White race, %	86	86	85	85	0.72
Current smoker, %	46	41	39	35	<0.001
Diabetes, %	19	19	23	23	0.008
Hypertension, %	47	49	51	53	0.001
Family history of premature coronary artery disease, %	20	21	22	21	0.51
Prior MI, %	14	17	17	20	<0.001
Prior CHF, %	4	5	4	7	0.001
Prior chronic aspirin use, %	28	30	36	38	<0.001
ACE inhibitor use, %	54	56	57	58	0.10
Index ST-segment elevation MI, %	42	40	38	39	0.11
Creatinine clearance, ml/min	79 (64, 97)	77 (62, 94)	76 (60, 93)	71 (55, 89)	<0.001
Total cholesterol, mg/dl*	183 (162, 203)	184 (163, 204)	187 (168, 208)	186 (163, 206)	0.008
LDL cholesterol, mg/dl*	112 (93, 130)	111 (94, 130)	113 (97, 132)	111 (93, 131)	0.43
HDL cholesterol, mg/dl*	39 (34, 46)	39 (34, 46)	39 (33, 45)	38 (32, 45)	0.009
Triglycerides, mg/dl*	140 (109, 186)	145 (114, 194)	153 (118, 206)	158 (123, 209)	<0.001
CRP, mg/l	22 (8, 48)	19 (8, 43)	20 (8, 43)	19 (8, 47)	0.29
CRP at 1 month, mg/l†	2.1 (1.1, 4.7)	2.3 (1.2, 5.1)	3.2 (1.4, 6.5)	2.6 (1.3, 5.7)	0.001
BNP, pg/ml	11 (0, 42)	11 (0, 45)	12 (0, 42)	13 (0, 50)	0.24

Categoric data are reported as percentages and continuous data as median (25th, 75th percentile). *The analysis of the association between lipids and monocyte chemoattractant protein (MCP-1) used 1-month values from the placebo group only. †Placebo group only.

ACE = angiotensin-converting enzyme; BNP = brain natriuretic peptide; CHF = congestive heart failure; CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction.

(Table 2). The addition of MCP-1 increased the C-statistic of the fully adjusted mortality model from 0.76 to 0.78 ($p < 0.0001$).

Follow-up measurements of MCP-1 and subsequent outcomes. Increasing quartiles of MCP-1 measured at 4 months were also associated with the end point of death; the composite end point of death or MI; the composite end point of death, MI, or heart failure; and the primary Phase Z composite end point ($p < 0.01$ for each) (Table 3). No association was observed between 4-month MCP-1 quartiles and subsequent MI. When the threshold of 238 pg/ml for MCP-1 was used, a significant association was observed between MCP-1 and mortality (Fig. 4) and each of the composite end points (Table 3). Although modestly attenuated, the association between 4-month levels of MCP-1 and subsequent outcomes remained significant after multivariable adjustment that included age, gender, history of diabetes, current smoking, index diagnosis, treatment assignment, and levels of LDL-C, CRP, and BNP at 4 months (Table 3). The addition of 4-month MCP-1 levels to the 4-month mortality models increased the C-statistic from 0.72 to 0.73 ($p = 0.01$).

The 3,467 subjects who had MCP-1 measurements performed at both baseline and 4 months were categorized into 4 groups based on whether MCP-1 was >238 pg/ml at both baseline and 4-month follow-up (n = 1,580 [45.6%]), >238 pg/ml at baseline but ≤238 pg/ml at follow-up (n = 323 [9.3%]), ≤238 pg/ml at baseline but >238 pg/ml at follow-up (n = 601 [17.3%]), or ≤238 pg/ml at both time points (n = 963 [27.8%]). Mortality after 4 months was higher among patients with MCP-1 levels >238 pg/ml at both the baseline evaluation and the 4-month visit, compared with those in the other 3 groups ($p = 0.004$) (Fig. 5).

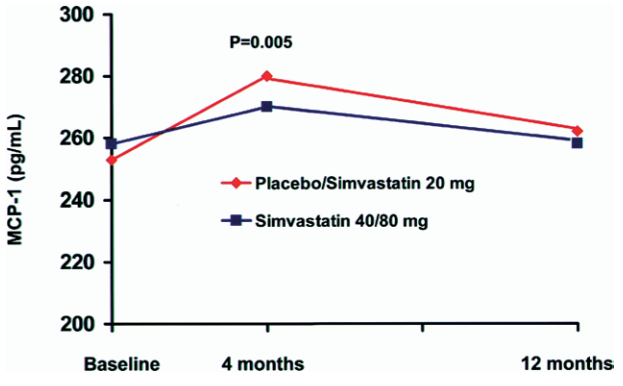

Figure 1 Influence of Early and Intensive Statin Therapy on Median Plasma Levels of MCP-1

Although levels of monocyte chemoattractant protein (MCP)-1 were significantly lower in the simvastatin 40 mg/80 mg arm at 4 months, the difference between the groups was quantitatively modest.

Table 2 Association Between MCP-1 Levels at Baseline and Events Through End of Study

End Point	Quartile 1 (<190 pg/ml) n = 1,070	Quartile 2 (190–255 pg/ml) n = 1,052	Quartile 3 (256–350 pg/ml) n = 1,074	Quartile 4 (>350 pg/ml) n = 1,048	p Trend	MCP-1 (≤238 pg/ml) n = 1,860	MCP-1 (>238 pg/ml) n = 2,384	p Value
Death, %	2.6	5.0	8.4	6.7	<0.0001	3.4	7.4	<0.0001
Adjusted HR (95% CI)	1 (referent)	1.81 (1.07–3.08)	3.13 (1.92–5.10)	2.26 (1.37–3.73)		1 (referent)	2.16 (1.54–3.02)	
MI, %	5.3	6.5	8.6	8.0	0.009	5.7	8.2	0.003
Adjusted HR (95% CI)	1	1.25 (0.85–1.86)	1.63 (1.13–2.36)	1.25 (0.85–1.86)		1	1.33 (1.02–1.74)	
Death or MI, %	7.5	11.0	14.3	13.5	<0.0001	8.7	13.8	<0.0001
Adjusted HR (95% CI)	1	1.41 (1.02–1.95)	1.82 (1.34–2.46)	1.51 (1.10–2.07)		1	1.46 (1.18–1.82)	
Death/MI/CHF, %	10.1	13.8	17.1	15.8	<0.0001	11.3	16.4	<0.0001
Adjusted HR (95% CI)	1	1.35 (1.01–1.79)	1.64 (1.25–2.15)	1.34 (1.01–1.77)		1	1.36 (1.12–1.65)	
A to Z primary composite, %	11.7	14.8	16.6	18.1	<0.0001	12.8	17.2	0.0001
Adjusted HR (95% CI)	1	1.19 (0.91–1.54)	1.31 (1.02–1.69)	1.26 (0.98–1.63)		1	1.20 (1.00–1.44)	

All models adjusted for age, gender, weight, prior MI, use of ACE inhibitors, history of diabetes, current smoking, index diagnosis, treatment assignment, creatinine clearance, LDL cholesterol, CRP, and BNP. CI = confidence interval; HR = heart rhythm; other abbreviations as in Table 1.

Effect of intensive statin therapy in subgroups defined by MCP-1 levels. Randomization to the early intensive statin arm was associated with similar effects in patients with baseline (Table 4) or 4-month (Table 5) MCP-1 levels >238 versus ≤238 pg/ml. Findings were unchanged when patients were divided at the median MCP-1 level (data not shown).

Combined measurement of MCP-1, CRP, and BNP. A strong, stepwise association was observed between the number of biomarkers that were above the pre-specified thresholds and subsequent mortality, both for baseline measurements as well as for 4-month measurements. After multivariable adjustment, a >7-fold gradient was observed between those subjects with 0 versus all 3 markers elevated at either time point (Fig. 6).

Discussion

In a large and well-characterized population of patients stabilized early after ACS, we found that higher MCP-1 levels were associated with an increased risk for long-term death and major adverse cardiac outcomes, independent of standard measurements such as creatinine clearance and LDL-C, as well as established biomarkers such as CRP and BNP. In addition, MCP-1 levels measured 4 months after ACS also provided independent prognostic value. Monocyte chemoattractant protein-1 appeared to be more strongly associated with mortality than with composite outcomes that included nonfatal end points. At both base-

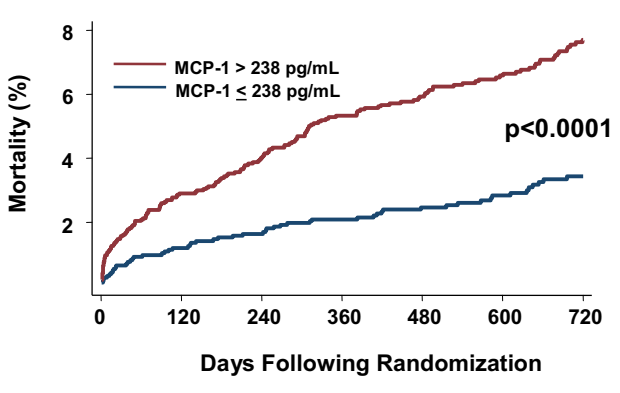

Figure 2 Baseline MCP-1 Levels and Mortality After ACS

Nelson-Aalen cumulative hazard estimates comparing patients with baseline monocyte chemoattractant protein (MCP)-1 levels >238 versus ≤238 pg/ml. ACS = acute coronary syndrome.

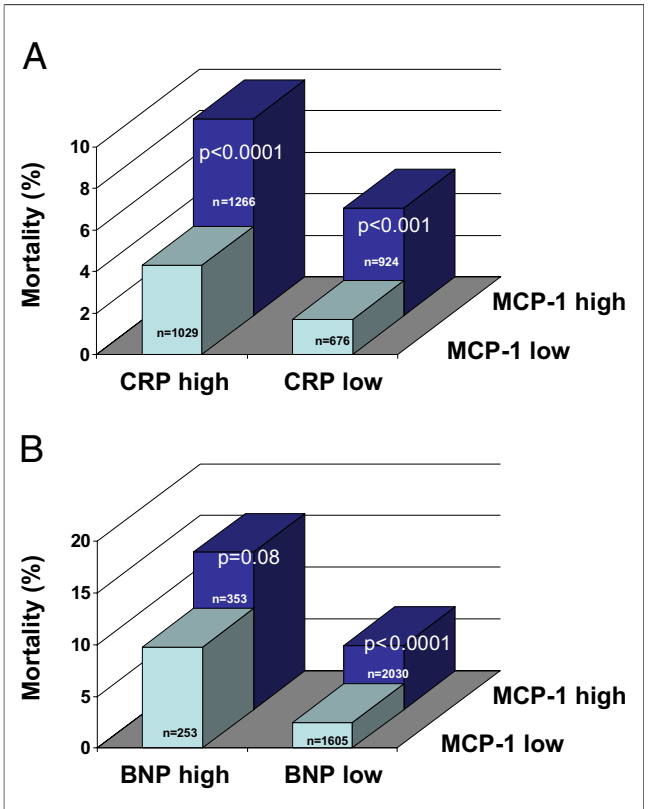

Figure 3 Association Between Baseline Levels of MCP-1 and Mortality

Levels are stratified by C-reactive protein (CRP) **(A)** and brain natriuretic peptide (BNP) **(B)**. High monocyte chemoattractant protein (MCP)-1 levels are defined as >238 pg/ml, high CPR as >15 mg/l, and high BNP as >80 pg/ml.

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Table 3 Association Between MCP-1 Levels at 4 Months and Events From 4 Months Through End of Study

End Point	Quartile 1 (<210 pg/ml) n = 907	Quartile 2 (210–273 pg/ml) n = 895	Quartile 3 (274–364 pg/ml) n = 899	Quartile 4 (>364 pg/ml) n = 902	p Trend	MCP-1 (≤238 pg/ml) n = 1,333	MCP-1 (>238 pg/ml) n = 2,270	p Value
Death, %	2.0	3.3	3.8	4.5	0.009	2.3	4.0	0.009
Adjusted HR (95% CI)	1 (referent)	2.06 (1.08–3.96)	2.01 (1.06–3.79)	2.23 (1.19–4.18)		1	1.76 (1.12–2.76)	
MI, %	2.4	3.0	3.9	3.5	0.11	2.8	3.4	0.48
Adjusted HR (95% CI)	1	1.40 (0.75–2.62)	1.55 (0.84–2.86)	1.52 (0.82–2.81)		1	1.09 (0.71–1.68)	
Death or MI, %	4.0	5.7	7.1	7.2	0.005	4.8	6.7	0.01
Adjusted HR (95% CI)	1	1.61 (1.01–2.57)	1.74 (1.11–2.74)	1.74 (1.11–2.74)		1	1.40 (1.02–1.94)	
Death/MI/CHF, %	4.5	6.9	8.3	8.1	0.003	5.4	7.9	0.004
Adjusted HR (95% CI)	1	1.71 (1.19–2.62)	1.76 (1.16–2.66)	1.65 (1.08–2.51)		1	1.40 (1.04–1.88)	
A to Z primary composite, %	5.7	7.2	8.4	9.3	0.007	6.3	8.4	0.04
Adjusted HR (95% CI)	1	1.35 (0.92–2.00)	1.30 (0.89–1.92)	1.51 (1.04–2.20)		1	1.23 (0.93–1.61)	

All models adjusted for age, gender, history of diabetes, current smoking, index diagnosis, treatment assignment, LDL cholesterol, CRP, and BNP.
Abbreviations as in Tables 1 and 2.

line and 4 months, the addition of MCP-1 to the fully adjusted multivariable models modestly but significantly improved discrimination for mortality, as assessed by the C-statistic and the likelihood ratio tests, which have been advocated as rigorous statistical tools for the evaluation of new biomarkers (26). Finally, when included in a simple multiple-biomarker panel with CRP and BNP, a strong, graded, and independent association was shown between the number of elevated markers and subsequent mortality. These findings suggest that MCP-1 may have value as a biomarker for risk stratification in both the initial and the chronic phases after an ACS event, and support additional investigation of MCP-1 (and CCR-2) as therapeutic targets.

We also prospectively confirmed that an MCP-1 threshold of 238 pg/ml, derived from a previous large study of patients with ACS (12), identifies patients at increased risk for adverse events in both the acute and the chronic setting after ACS. Patients with levels persistently above this threshold seemed to be at particularly high risk for death compared with those with persistently lower levels, or levels that were only transiently above this threshold.

Because MCP-1 plays a direct pathogenic role in atherosclerosis development and progression and also stimulates tissue factor and oxidant production, the predictive value of MCP-1 may reflect increased atherosclerotic burden, enhanced plaque vulnerability, or both. Of particular importance is the finding that MCP-1 provides prognostic information that is not redundant with that provided by CRP. In contrast to CRP, which increases markedly in response to the ACS event, MCP-1 levels changed little between baseline and 4 months, suggesting that plasma MCP-1 levels may reflect chronic rather than acute pathophysiologic processes. Although relatively little is known about the kinetics of MCP-1 release into the plasma, we and others have reported that MCP-1 levels are only slightly higher in patients with ACS than in normal control subjects

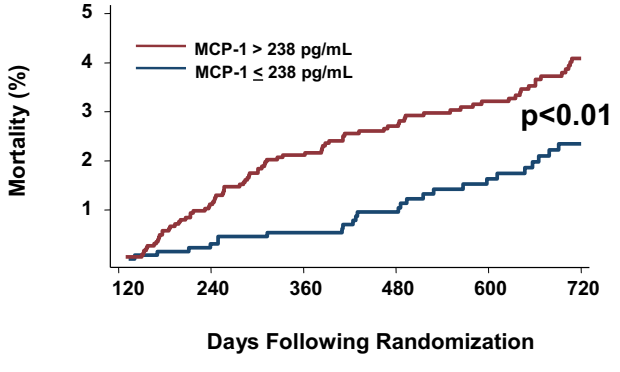

Figure 4 MCP-1 Levels at 4 Months After ACS and Subsequent Mortality

Nelson-Aalen cumulative hazard estimates showing the association between monocyte chemoattractant protein (MCP)-1 levels >238 versus ≤238 pg/ml at 4 months and mortality from 4 months through the end of the study period. Events before 4 months were censored. ACS = acute coronary syndrome.

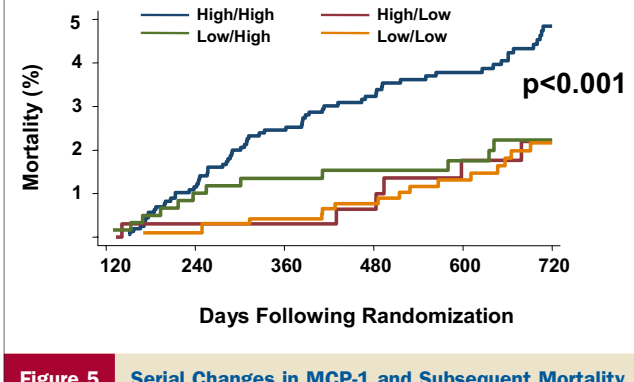

Figure 5 Serial Changes in MCP-1 and Subsequent Mortality

Nelson-Aalen cumulative hazard estimates in subgroups defined by monocyte chemoattractant protein (MCP)-1 levels at baseline and at 4 months. High MCP-1 levels are defined as >238 pg/ml and low as ≤238 pg/ml. Each curve represents a subgroup defined by baseline/4 month MCP-1 levels. Events before 4 months were censored. Patients with MCP-1 levels >238 pg/ml at both baseline and 4 months had significantly higher mortality rates compared with the other groups.

Table 4 Hazard Ratios Comparing Early Intensive Versus Delayed Conservative Simvastatin Stratified by Baseline MCP-1 Levels

End Point	MCP-1 ≤238 pg/ml	MCP-1 >238 pg/ml
Death	0.67 (0.41–1.12)	0.83 (0.61–1.12)
Death or MI	0.81 (0.59–1.11)	0.90 (0.72–1.12)
Death/MI/CHF	0.74 (0.56–0.99)	0.89 (0.73–1.10)
A to Z primary	0.84 (0.64–1.08)	0.87 (0.71–1.06)

All interaction p values >0.3.
Abbreviations as in Table 1.

(12,13), a finding that indicates that MCP-1 will not be useful as a diagnostic marker in ACS but rather may be a stable indicator of long-term cardiovascular risk. This hypothesis is supported by data from population studies, in which plasma levels of MCP-1 reflect the burden of coronary artery disease risk factors and the presence of subclinical atherosclerosis and correlate poorly with acute-phase reactants such as CRP (9,11). Even when measured at 4 months, a time when CRP levels would be expected to reflect the chronic state rather than the acute influences of the ACS event, MCP-1 levels clearly provided prognostic information that was independent of that provided by CRP.

Previous studies in animals and humans have reported that statins significantly reduce cellular expression of MCP-1 and the CCR-2 receptor as well as circulating levels of MCP-1 in plasma (17–19). Here, in a study more than 30-fold larger than these previous studies, although we did find that early and intensive treatment with simvastatin after ACS resulted in significantly lower MCP-1 levels versus placebo, this effect was quantitatively very modest. At 12 months, reflecting a comparison of 20- and 80-mg doses of simvastatin, MCP-1 levels were similar between the 2 arms. Moreover, we found no evidence showing that higher MCP-1 levels identified patients more likely to benefit from aggressive statin therapy. We have also recently reported the absence of an interaction between CRP levels, treatment assignment, and clinical outcomes in the A to Z study (14). These findings suggest that MCP-1 measurement will not be useful as a tool for monitoring statin therapy or for identifying patients for more aggressive statin treatment. However, given the clear pathogenic role for MCP-1 in atherosclerosis and its complications, and the association of plasma levels of MCP-1 with coronary risk factors, atherosclerosis burden, and clinical events, MCP-1 should be further studied as a biomarker "target" for novel atherosclerosis therapies.

Table 5 Hazard Ratios Comparing 80 mg Versus 20 mg Simvastatin Stratified by 4-Month MCP-1 Levels

End Point	MCP-1 ≤238 pg/ml	MCP-1 >238 pg/ml
Death	0.48 (0.22–1.04)	0.77 (0.50–1.18)
Death or MI	0.54 (0.32–0.93)	0.89 (0.64–1.24)
Death/MI/CHF	0.62 (0.38–1.00)	0.87 (0.65–1.18)
A to Z primary	0.79 (0.51–1.22)	0.76 (0.56–1.02)

All interaction p values >0.1.
Abbreviations as in Table 1.

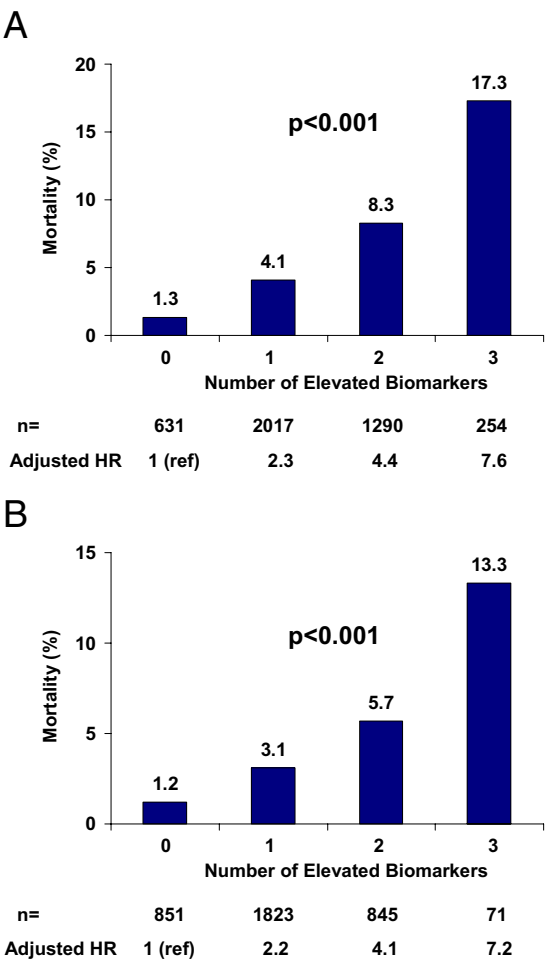

Figure 6 Incorporation of MCP-1 Into a Multiple Biomarker Panel

Unadjusted association between the number of elevated biomarkers (monocyte chemoattractant protein [MCP]-1, brain natriuretic peptide [BNP], and C-reactive protein [CRP]) at baseline **(A)** and at 4 months **(B)** and subsequent mortality. An MCP-1 elevation was defined as >238 pg/ml, and BNP elevation as >80 pg/ml; CRP elevation at baseline was defined as >15 mg/l and at 4 months as >3 mg/l. Multivariable adjustment is shown at the bottom of each panel using variables described in the text. HR = hazard ratio.

Monocyte chemoattractant protein-1 has also shown some promise as a biomarker for disease monitoring in other inflammatory diseases, such as juvenile rheumatoid arthritis, where plasma levels decrease concordant with clinical signs of improvement and persistent reductions seem to predict longer remission (27). Future studies testing more specific anti-inflammatory therapies will be needed to determine whether MCP-1 has a sufficient dynamic range to be useful as a measurable target for atherosclerosis therapies. Specific cytokine antagonists, including monoclonal antibodies against MCP-1 and CCR-2, are currently under investigation in rheumatoid arthritis (28). If these therapies are proven safe, investigation in atherosclerosis may be warranted as well.

Conclusions

Plasma levels of MCP-1 provide prognostic value in both the acute and the chronic period after ACS that is complementary to that of standard clinical variables and emerging biomarkers such as CRP and BNP. The influence of statins on MCP-1 is modest, and MCP-1 is not useful for identifying patients who benefit from aggressive statin regimens after ACS. Future studies are needed to evaluate whether MCP-1 should be included in multiple-biomarker panels for risk stratification and whether this biomarker can be used as a measurable target for antiatherosclerosis therapies.

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