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Plasma Myeloperoxidase Predicts Incident Cardiovascular Risks in Stable Patients Undergoing Medical Management for Coronary Artery Disease

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BACKGROUND: Myeloperoxidase (MPO) concentrations predict adverse clinical outcomes in the setting of acute coronary syndromes and heart failure, but the prognostic role of MPO in stable patients with known atherosclerotic burden is unclear.

METHODS: We examined plasma MPO concentrations and their relationship with prevalent significant coronary artery disease (defined as >50% stenosis in any coronary vessel) and incident major adverse cardiovascular events (MACEs), including death, myocardial infarction, and stroke, in a 3-year prospective follow-up study of 1895 patients undergoing elective coronary angiography.

RESULTS: The median plasma MPO concentration was 101 pmol/L (interquartile range 68–187 pmol/L). Patients with plasma MPO concentrations >322 pmol/L (14.6% of population) had increased risk of developing future MACEs [hazard ratio (HR) 1.78, 95% CI 1.33–2.37, $P < 0.001$], and MPO as a single variable predictor of MACE showed an area under the ROC curve of 0.67. After adjusting for traditional cardiac risk factors, creatinine clearance, B-type natriuretic peptide, and high-sensitivity C-reactive protein (hsCRP), increased MPO concentrations remained significantly associated with incident MACEs over the ensuing 3-year period (HR 1.71; 95% CI 1.27–2.30, $P < 0.001$). In patients with increased hsCRP, MPO ≤322 pmol/L was associated with lower event rates than observed with MPO >322 pmol/L.

CONCLUSIONS: Plasma MPO concentrations provide independent prognostic value for the prediction of long-term incident MACEs in a stable, medically managed patient population with coronary artery disease. In individuals with increased hsCRP concentrations, we observed lower risk of incident MACEs when concomitant MPO concentrations were low vs when MPO concentrations were high.

Although surgical or percutaneous revascularization remains one of the useful tools in the management of atherosclerotic coronary artery disease (CAD),[3] the majority of patients with recognized atherosclerotic burden do not fulfill indications for imminent revascularization. It is in this context that aggressive risk factor modification, particularly when targeting high-risk individuals, continues to serve a primary role in preventing adverse consequences. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial recently showed comparable cardiovascular outcomes among stable subjects with significant coronary atherosclerosis randomized to treatment with either aggressive preventive medical intervention or percutaneous coronary intervention plus aggressive preventive medical intervention *(1)*. The ability to identify individuals at increased risk for major adverse cardiac events among subjects with existing atherosclerotic heart disease is of considerable interest, so that new interventions and approaches might be developed for treatment of this high-risk group. Indeed, early administration of statin therapy in patients with evidence of systemic inflammation [as indicated by increased high-sensitivity C-reactive protein (hsCRP)] may have contributed to improved cardiovascular outcomes *(2)*.

Myeloperoxidase (MPO) is a leukocyte-derived enzyme that has been shown to have multiple mechanistic links with vulnerable plaque development *(3)*. Enriched within culprit lesions of subjects who experience sudden cardiac death *(4)*, MPO has been linked to activation of protease cascades and both proapoptotic

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[3] Nonstandard abbreviations: CAD, coronary artery disease; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; hsCRP, high-sensitivity C-reactive protein; MPO, myeloperoxidase; CrCl, creatinine clearance; MACE, major adverse cardiovascular event; BNP, B-type natriuretic peptide; AUC, area under the curve; HR, hazard ratio; NRI, net reclassification improvement; IDI, integrated discrimination improvement.

and prothrombotic pathways that are believed to be involved in plaque fissuring *(5, 6)*, development of superficial erosions *(4)*, and intracoronary thrombus generation during sudden cardiac death *(3)*. MPO has also been shown to directly promote catalytic consumption of nitric oxide, leading to development of endothelial dysfunction *(7, 8)*. Systemic MPO concentrations have been shown to provide prognostic value in the setting of chest pain and acute coronary syndromes *(9, 10)*. On the other side of the spectrum, systemic MPO concentrations independently predict risk for development of incident cardiovascular disease and death in apparently healthy middle-aged subjects in epidemiological studies *(11)*. Recently, it was reported that in the setting of a high coronary artery calcium score assessed by electron-beam computed tomography in asymptomatic patients, concomitant increases in MPO were associated with a substantial increase in cardiovascular risk *(12)*. Herein, we examine the potential for plasma MPO concentrations to identify who may be at heightened long-term risk among a large stable (nonacute) cohort of patients with angiographically documented coronary artery stenosis in the setting of aggressive medical therapy for their coronary artery disease.

Methods

STUDY POPULATION

The Cleveland Clinic GenBank study was a large, single-center, contemporary, prospective cohort study from 2001 to 2006 that established a well-characterized clinical repository with clinical and longitudinal outcomes data from consenting individuals undergoing elective diagnostic coronary angiography (either cardiac catheterization or coronary computed tomography angiography). All GenBank participants gave written informed consent, and the Institutional Review Board of the Cleveland Clinic approved the study protocol. For this analysis, we examined 2460 consecutive individuals without evidence of myocardial infarction (cardiac troponin I <0.03 μg/L) but with evidence of significant atherosclerotic burden ($\geq$50% stenosis at any coronary artery), with blood samples collected for biomarker analysis. Blood was collected before any heparin administration. We excluded 565 subjects who received percutaneous or surgical revascularization within 30 days before or after cardiac catheterization to ensure a patient cohort destined to receive medical management of their coronary artery disease. Data were recorded for standard cardiac risk factors including age, sex, history of diabetes mellitus, cigarette smoking, systolic blood pressure, and fasting lipids. Because the majority of participants had relatively preserved renal function, an estimate of creatinine clearance (CrCl) was calculated using the Cockcroft–Gault equation.

ENDPOINTS

Major adverse cardiovascular event (MACE) was defined as death, nonfatal myocardial infarction, or nonfatal cerebrovascular accident after enrollment. Endpoints were collected by in-person prospective follow-up including letter solicitation and reply cards, chart review, and direct contact by study staff. We ascertained adjudicated outcomes over the ensuing 3 years for all participants after enrollment.

PLASMA MPO ASSAY

Venous blood samples were collected in EDTA tubes and immediately processed and frozen at −80 °F until analysis. Plasma myeloperoxidase concentrations were measured by use of the Abbott Architect platform (Abbott Laboratories), a chemiluminescent automated immunoassay using MPO-specific monoclonal antibodies in a 2-step sandwich format. The assay has a dynamic range of 0–10 000 pmol/L, with a limit of detection $<$20.0 pmol/L and a functional sensitivity of $<$50.0 pmol/L (total CV 20%) *(13)*. B-type natriuretic peptide (BNP), hsCRP, serum creatinine, fasting blood glucose, and fasting lipid profiles were also measured simultaneously on the same platform.

STATISTICAL ANALYSIS

We used Student *t*-test or Wilcoxon rank-sum test for continuous variables and χ^2 test for categorical variables to examine the difference between the groups; Cochran–Armitage test for trend analyses across quartiles; and ROC curve analyses and 5-fold cross-validation to determine the optimal plasma MPO cutoff. For a given cutoff, we used a logistic regression model to estimate the risk of MACE. The 5-fold cross-validation divides the data into 5 approximately equally sized portions. A logistic regression model is trained on 4 parts of the data and then estimates the risk of MACE in the fifth part. This is repeated for each of the 5 parts. We calculated the area under the curve (AUC) with the estimated risk. This process was carried out for a grid of MPO cutoff values, ranging from 250 to 650 with an increment of 1. The optimal cutoff was chosen to maximize AUC values. Kaplan–Meier analysis with Cox proportional hazards regression was used for time-to-event analysis to determine hazard ratios (HRs) and 95% confidence intervals (95% CIs) for MACEs. Adjustments were made for individual traditional cardiac risk factors including age, sex, cholesterol concentrations, systolic blood pressure, smoking history, and family history of premature coronary artery disease, and CrCl, as well as standard cardiac biomarkers such as BNP and hsCRP to predict incident

Table 1. Baseline characteristics.[a]

	MPO ≤322 pmol/L	MPO >322 pmol/L	*P* value
n	1618	277	
Demographics and cardiovascular risk factors			
Age, years	64 (11)	63 (11)	0.329
Male, %	73	68	0.098
Diabetes mellitus, %	33	29	0.220
Hypertension, %	76	71	0.127
History of myocardial infarction, %	47	56	0.016
Systolic blood pressure, mmHg	133 (120–149)	130 (115–144)	0.012
Smoker (former or current), %	0.70	0.66	0.177
Laboratory data			
BNP, ng/L	89 (39–205)	112 (42–245)	0.092
hsCRP, mg/L	2.0 (0.9–4.4)	2.2 (1.0–5.4)	0.052
LDL cholesterol, mmol/L	2.4 (1.9–2.9)	2.4 (1.8–2.8)	0.135
HDL cholesterol, mmol/L	0.8 (0.7–1.0)	0.8 (0.7–1.0)	0.088
Triglycerides, mmol/L	1.4 (1.0–1.9)	1.3 (0.9–1.9)	0.021
CrCl, $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$	76 (101–127)	74 (94–122)	0.027

[a] Data are mean (SD) or median (interquartile range).

3-year MACE risks. We evaluated the improvement in model performance introduced by the inclusion of MPO using net reclassification improvement (NRI) and integrated discrimination improvement (IDI) as described by Pencina et al. *(14)*. *P* values compare models with and without MPO. Both models were adjusted for traditional risk factors including age, sex, smoking, HDL cholesterol, LDL cholesterol, systolic blood pressure, and diabetes mellitus. Cutoff values for NRI estimation used a ratio of 6:3:1 for low-, medium-, and high-risk categories owing to the nonparametric distribution. We estimated 3-year predicted probabilities of a MACE event from random survival forests methodology. All analyses were performed using R 2.8.0. A *P* value <0.05 was considered statistically significant.

Results

SUBJECT CHARACTERISTICS

In our study cohort of 1895 subjects, the mean (SD) and median plasma MPO concentrations were 199 (277) pmol/L and 101 pmol/L (interquartile range 68–187 pmol/L), respectively. The baseline characteristics of the study population are given in Table 1. The optimal MPO cutoff value >322 pmol/L was determined by ROC as described. Interestingly, patients with increased plasma MPO concentrations (>322 pmol/L, or 14.6% of study cohort) were more likely to have a history of myocardial infarction, a lower systolic blood pressure, and lower concentrations of fasting triglyceride and estimated CrCl than those with lower MPO concentrations.

PLASMA MPO AND MACE

At 3 years of follow-up, a total of 279 first-time events (including 184 deaths, 87 myocardial infarctions, 22 strokes, with some having more than 1 event) were observed. The AUC for plasma MPO was 67%, and increasing quartiles of MPO concentrations were associated with higher rates of 3-year MACEs ($P < 0.01$) (Fig. 1). At optimal cutoff of 322 pmol/L, MPO was predictive of higher 3-year MACEs (HR 1.78; 95% CI 1.33–2.37, $P < 0.001$) (Fig. 2). After adjusting for traditional risk factors (including Framingham risk factors), CrCl, BNP, and hsCRP, plasma MPO >322 pmol/L remained independently predictive of 3-year MACEs (HR 1.71; 95% CI 1.27–2.30, $P < 0.001$). Plasma MPO still provided incremental value in predicting 3-year MACEs when analyzed as continuous variable with log-transformation (HR 1.26, 95% CI 1.11–1.43, $P < 0.001$). Further, after adjustments for traditional risk factors including Framingham risk factors and CrCl, BNP, and hsCRP, MPO remained an independent predictor of 3-year all-cause mortality (HR 1.71, 95% CI 1.26–2.31) and 3-year incident risk of nonfatal MI (HR 1.85, 95% CI 1.13–3.05) (Table 2). Moreover, addition of MPO to traditional risk factors

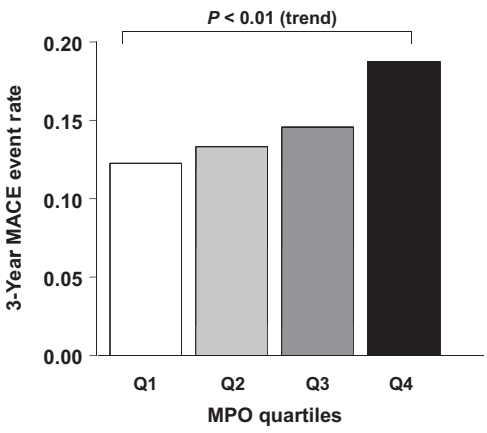

Fig. 1. Event rates at 3 years according to quartiles of MPO.

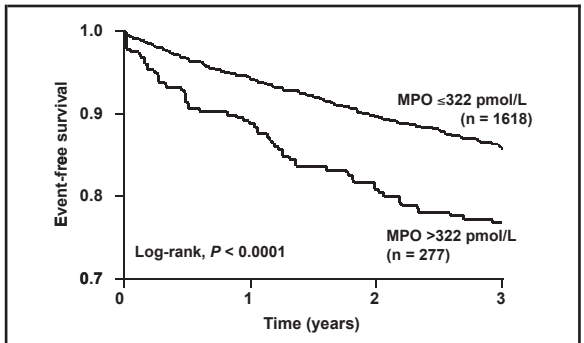

Fig. 2. Kaplan–Meier analysis for 3-year MACEs stratified according to MPO cutoff of 322 pmol/L.

resulted in significant integrated discrimination improvement (IDI 10%, $P < 0.001$) and significant event-specific net reclassification (NRI 6%, $P = 0.022$).

RELATIONSHIP BETWEEN MPO, hsCRP, AND CARDIOVASCULAR RISK

There was weak correlation between plasma MPO and hsCRP concentrations (Spearman $r = 0.186$, $P < 0.0001$). Within the cohort of subjects with hsCRP ≤2 mg/L, 14% of subjects had MPO concentrations >322 pmol/L, and these patients demonstrated a higher risk of adverse cardiac events in the ensuing 3 years than those without increased plasma MPO concentrations (Fig. 2). Equivalent risk for MACEs was observed among those with high hsCRP >2 mg/L but low plasma MPO (≤322 pmol/L), vs those with high MPO but low hsCRP—both representing the intermediate-risk category with a single positive biomarker (Fig. 3).

Discussion

Previous studies have identified the prognostic role of MPO following acute myocardial infarction *(10)*, acute heart failure *(15)*, and chronic stable heart failure *(16)* and in apparently healthy middle aged *(11)* or elderly *(17)* subjects. Our study extends the ability of MPO concentrations in risk prediction for vulnerable plaque to the setting of stable patients undergoing elective coronary angiography for signs and symptoms suggestive of coronary artery disease. The key finding from this large, well-characterized cohort of stable patients under medically managed coronary evaluation is that higher plasma MPO concentrations portend poorer long-term prognoses after adjusting for standard risk factors, cardiac-specific biomarkers, and alternative markers of inflammation in the presence of atherosclerotic burden. The results confirmed prior reports of independent predictive value for long-term cardiovascular mortality risk in coronary angiography patients *(18)* and extend the results to observed increased risks for 3-year incident nonfatal myocardial infarction, stroke, or death. These results thus indicate that MPO concentrations seem to provide prognostic value in medically managed stable patients with CAD. Further, when including those with revascularization within 30 days (total n = 2460), the prognostic value of MPO remained statistically significant (unadjusted HR 1.71, 95% CI 1.32–2.22, $P < 0.001$; adjusted HR 1.65, 95% CI 1.26–2.17, $P < 0.001$). Further support of the concept that MPO may play a pathophysiologic role in promoting vulnerable plaque across the spectrum of atherosclerotic coronary artery disease may be seen by the findings that in the setting of increased hsCRP, a low MPO concentration may provide reassurance of lower cardiovascular risk profile.

Participation of systemic inflammatory processes in the development of adverse cardiovascular events has been popularized with extensive literature on leukocyte counts and hsCRP concentrations, although a wide range of different inflammatory participants may be involved *(19)*. Although the majority of clinical studies related to the prognostic role of MPO have focused on the acute ischemic setting *(7, 9, 10, 20)*, recent data suggest that higher concentrations of MPO in apparently healthy individuals may predict future development of coronary events, particularly in those with evidence of subclinical atherosclerotic plaque *(11, 12)*. The MPO concentrations measured in this patient cohort appeared lower than those previously reported, in part because of the different assays being used *(13)* and also because of the relatively stable, medically managed patient population being studied (some of which may not even have raised MPO concentra-

Table 2. Prognostic value of plasma MPO above a cutoff of 322 pmol/L in the prediction of MACEs.

	3-Year MACE		3-Year death		3-Year nonfatal myocardial infarction		3-Year nonfatal stroke	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Unadjusted	1.78 (1.33–2.37)	<0.001	1.78 (1.25–2.53)	0.001	1.88 (1.14–3.09)	0.013	1.38 (0.47–4.07)	0.557
Adjusted[a]	1.71 (1.27–2.30)	<0.001	1.71 (1.26–2.31)	<0.001	1.85 (1.13–3.05)	0.015	1.58 (0.51–4.89)	0.426

[a] Adjusted for age, sex, LDL and HDL cholesterol, systolic blood pressure, former or current cigarette smoking, diabetes mellitus, history of myocardial infarction, CrCl, BNP, and hsCRP.

tions, as previously described *(21)*). A strength of this analysis is the direct evidence of atherosclerotic burden as demonstrated by presence of significantly obstructed coronary arteries determined by coronary angiography, which is the clinical gold standard, rather than relying on clinical history or events as determination of underlying plaque vulnerability. This may also explain why a previous smaller study did not demonstrate significant differences in prognosis between high and low MPO concentrations in patients with stable angina where atherosclerotic burden was not known *(22)*. We also included only those with significant CAD and followed a standard MACE outcome at 3 years in a patient population treated with contemporary medical therapy, which differs from a smaller published study including both CAD and non-CAD subjects with cardiac mortality at 13-year follow-up as endpoint *(18)*.

Our findings provide further insight into the use of biomarkers to better predict the natural history of coronary atherosclerosis, particularly in the context of an ongoing debate regarding the pros and cons of invasive vs conservative medical approach to the treatment of coronary artery disease. In the COURAGE trial, there was no significant reduction in the risk of death, myocardial infarction, or other major cardiovascular events when percutaneous coronary intervention was added to optimal medical therapy *(1)*. Our patient cohort has comparable event rates (14.7% at 3 years) although with a slightly lower degree of coronary stenosis (at least 70% stenosis in any coronary artery in COURAGE). Our findings further demonstrated that by assessing both MPO and hsCRP at their respective cutoff values, about 57% of subjects with higher risk of developing future MACEs can be identified. In contrast, we observed that among those with increased hsCRP (>2 mg/L), a low concentration of MPO is associated with reduced risk for MACEs. Whether this population can benefit from more aggressive risk factor modification or pharmacologic therapy (such as high-dose statins above and beyond current guideline recommendation targets, as implicated in a recent trial targeting increased hsCRP to initiate statin therapy *(2)*) will require further investigations.

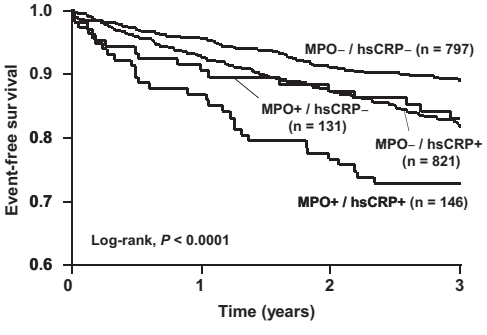

Fig. 3. Kaplan–Meier analysis for 3-year MACEs stratified according to MPO (cutoff of 322 pmol/L) and hsCRP (cutoff of 2 mg/L).

Another interesting finding of the present study is the lack of a strong association between MPO and hsCRP, an observation that has also been reported in several previous studies with alternative populations *(9, 21, 23, 24)*. These findings suggest that MPO concentrations help to differentiate a leukocyte-based pathophysiologic contribution to cardiovascular disease, from a generalized systemic inflammatory process as monitored only with positive acute-phase proteins such as C-reactive protein. Indeed, being enriched in vulnerable plaques *(25)*, MPO serves as an enzymatic source of eicosanoids and bioactive oxidized lipids that can generate atherogenic forms of lipoproteins *(26)*. Mechanistic studies have also indicated that MPO catalyzes the formation of several reactive oxidant species and impacts regional nitric oxide concentrations *(7, 8)*. Interestingly, MPO concentrations demonstrate strong correlations with the degree of endothelial dysfunction, independent of hsCRP values and coronary artery disease status *(23)*, and this process may also have contributed to increased vulnerability of atherosclerotic plaque by increasing atherothrombotic risk, as well as ischemic burden. MPO has been shown to enhanced tissue factor pathway activity

levels in coronary endothelium *(27)*, and MPO-generated oxidized lipids have been shown to modulate platelet hyperresponsiveness in the setting of dyslipidemia *(28)*. These observations may help to further explain why MPO concentrations provide independent prognostic value in predicting future MACE in a cardiac troponin–negative cohort even when adjusted for traditional cardiac risk factors and novel cardiac biomarkers such as hsCRP and BNP concentrations.

There are several limitations of the study. The lack of direct visualization of plaque composition or a universal definition of vulnerable plaque precludes recognition of any association between systemic MPO concentrations and plaque characteristics. Whereas the decision not to proceed with revascularization in the presence of significantly obstructive atherosclerotic coronary artery disease was determined by the treating physicians who were blinded to MPO plasma concentrations, this factor may still have allowed the introduction of a selection bias in the subject cohort from the presence of potential confounding factors that may have affected such clinical decisions. The small event rates of cerebrovascular accidents in our cohort limited our ability to determine the prognostic value of MPO in predicting future occurrences of such events. Furthermore, our results were based on a cut point optimized in this dataset, and hence may overestimate the strength of the risk relationship. With different studies using different assays with different cutoff values for different populations, there is a need to identify clinically useful cut points through a consensus of results based on FDA-cleared assay results. Although the data on interventions that can directly influence outcomes in patients with high MPO concentrations remain sparse, there have been mechanistic studies identifying the potential role of therapy with high-dose statins such as rosuvastatin that can reduce MPO concentrations in humans *(29)*. Hence, in parallel with results from trials targeting high hsCRP *(2)*, increased MPO concentrations may warrant more intensive treatment goals for modifiable risk reduction. Of interest, several inhibitors of MPO are currently commencing early-phase clinical investigations, and therefore a targeted reduction of MPO activity may become feasible in the future.

In conclusion, plasma MPO concentrations provide independent prognostic value for the prediction of long-term incident MACEs in a stable, medically managed patient population with coronary artery disease. In individuals with increased hsCRP concentrations and concomitantly low MPO concentrations, we observed lower risk of incident MACEs than that for individuals in whom both marker values were high.

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