

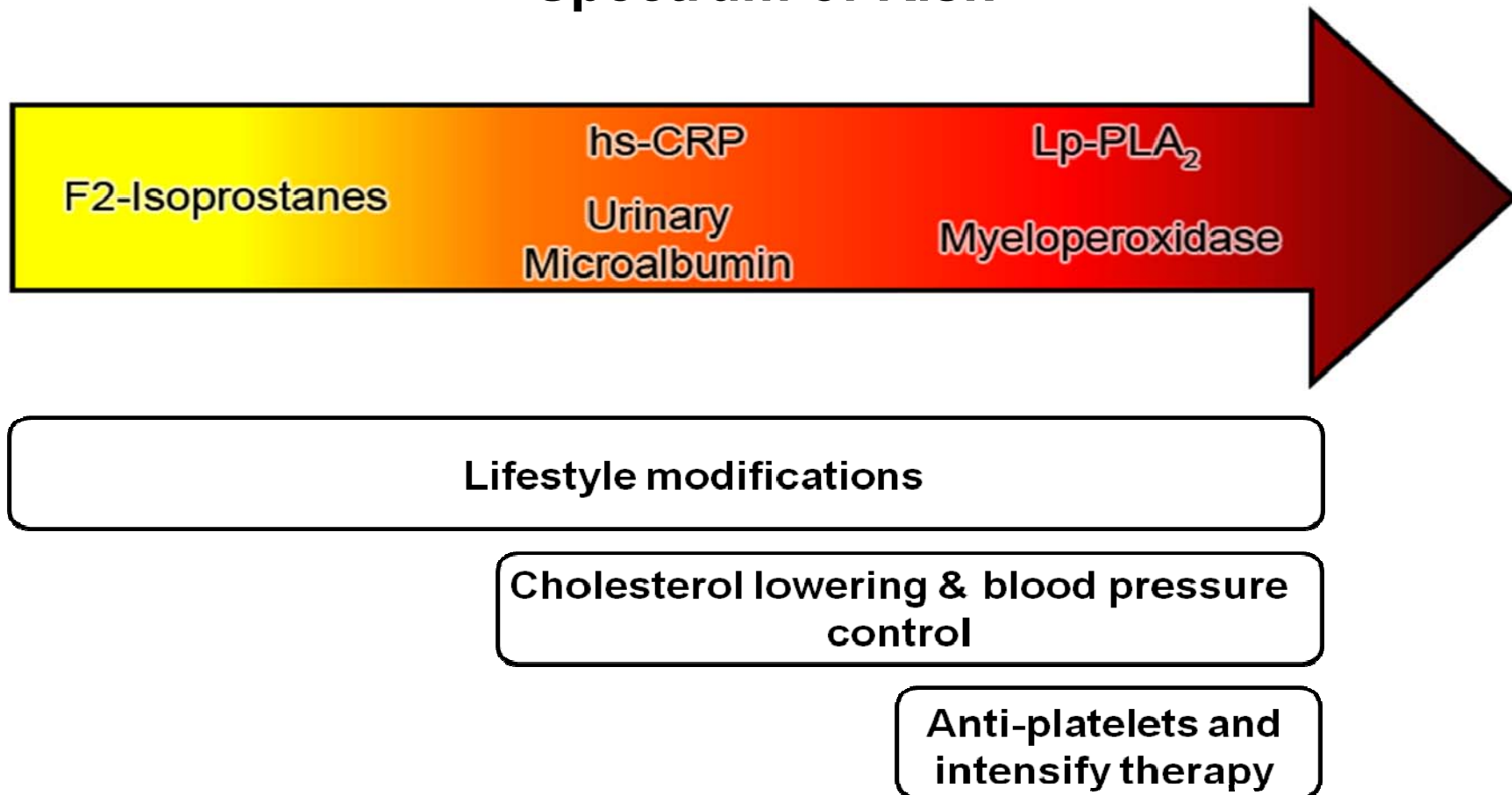
Cleveland HeartLab has established a **reliable** and **affordable** group of inflammatory biomarkers that offer additive and complimentary insight into a patient's risk for heart disease



**Do you know your patient's  
inflammatory state and cardiovascular risk?**

# Cleveland HeartLab Inflammatory Panel Overview

## Spectrum of Risk



**Did you know?**  
**50% of patients having heart attacks had *normal* lipids?<sup>1</sup>**

# F<sub>2</sub>-Isoprostanes (F<sub>2</sub>-IsoPs)

Measurement of F<sub>2</sub>-isoprostanes is the “gold standard”  
to assess oxidative stress *in vivo*<sup>2</sup>

## What are F<sub>2</sub>-IsoPs?

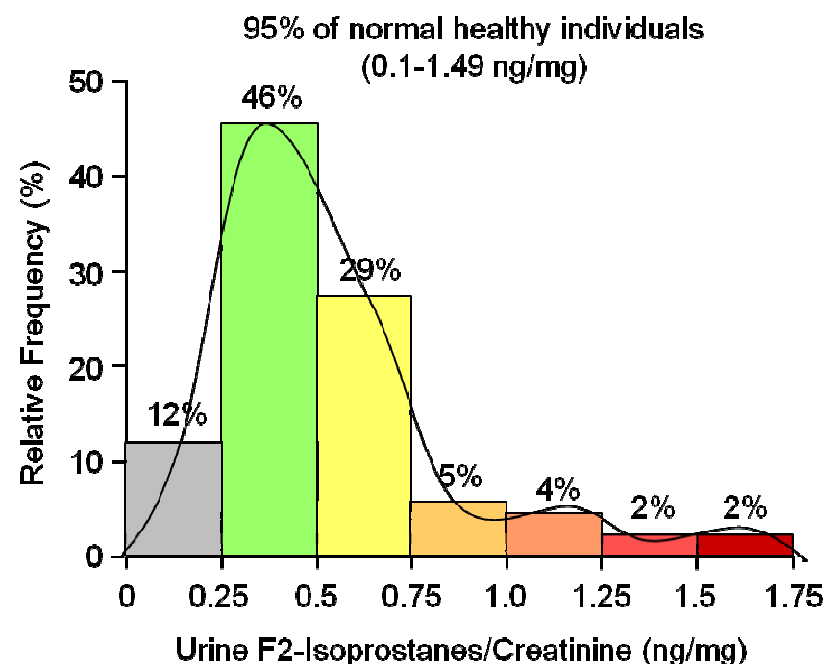
- F<sub>2</sub>-IsoPs are prostaglandin-like compounds produced by free radical mediated oxidation of arachidonic acid.<sup>3</sup>

## What is the function of F<sub>2</sub>-IsoPs?

- F<sub>2</sub>-IsoPs are potent vasoconstrictors.<sup>4</sup>
- F<sub>2</sub>-IsoPs promote platelet activation resulting in thrombosis, or blood clotting.<sup>5</sup>

## Why measure F<sub>2</sub>-IsoPs?

- Elevated levels of urinary F<sub>2</sub>-IsoPs are seen in conditions associated with increased risk for atherosclerosis<sup>6</sup> and certain forms of cancer.<sup>7,8</sup>
- Lower steady state levels are associated with improved cardiovascular fitness and reduced risk.
- F<sub>2</sub>-IsoPs are elevated with increased red meat intake<sup>9</sup> and decreased with exercise.<sup>10</sup>



# High Sensitivity-CRP (hs-CRP)

hs-CRP testing is useful in predicting a *healthy* person's risk for cardiovascular disease.<sup>11</sup>

## What is CRP?

- C-reactive protein, CRP, is an acute-phase protein released into the blood by the liver during inflammation.

## Why measure CRP?

- CRP is a well-documented clinical marker of general and cardiac-related inflammation.
- Elevated CRP is associated with the risk of future adverse cardiovascular events (heart attack, stroke and death) in apparently healthy individuals<sup>12,13</sup> and in individuals with stable coronary artery disease.<sup>14</sup>
- Reductions in both CRP and LDL cholesterol are associated with reduction in the rate of atherosclerosis progression<sup>15</sup> and improved clinical outcomes.<sup>16</sup>
- Introduction of statin therapy in patients with elevated hs-CRP, even with normal lipid status, markedly reduces risks for heart attack, stroke and death.<sup>1</sup>

hs- CRP Levels (mg/L)	Risk Assessment
<1.0	<b>Low Risk</b>
1.0-3.0	<b>Moderate Risk</b>
>3.0	<b>High Risk</b>

# Urinary Microalbumin/Creatinine Ratio

Microalbuminuria screening is beneficial for detection and prevention of cardiovascular and renal disease in patients with diabetes as well as the general population.<sup>17</sup>

## What is microalbuminuria?

- Microalbuminuria assesses glomerular endothelial functioning by measuring the amount of albumin, a serum protein, in urine.

## Why measure microalbuminuria?

- Microalbuminuria assesses microvascular integrity or endothelial function.
- Increases in urinary albumin excretion in the 'normal' range is associated with increased risk for development of cardiovascular morbidity and mortality, as well as all-cause mortality.<sup>17-22</sup>
- The higher the microalbuminuria, the higher the risk for heart attack, stroke and death.<sup>18</sup>
- The higher the microalbuminuria, the higher the risk for development of kidney disease, particularly in the setting of diabetes and hypertension.<sup>23</sup>

Urinary microalbumin/ creatinine ratio (mg/g)		Risk Assessment
Females	Males	
<7.5	<4.0	<b>Low Risk</b>
7.5-30.0	4.0-30.0	<b>Medium Risk</b>
>30.0	>30.0	<b>High Risk</b>

# Myeloperoxidase (MPO)

**MPO is involved in all stages of the atherosclerotic process from initial development of endothelial dysfunction and cholesterol deposition in the artery wall, to development of plaque rupture<sup>24</sup>**

## What is MPO and its function?

- MPO plays a role in host defense, helping to kill invading pathogens by generating anti-microbial reactive oxidants.<sup>25</sup>
- MPO oxidizes LDL making it atherogenic<sup>26</sup> and HDL rendering it dysfunctional contributing to cholesterol accumulation in the artery wall.<sup>27</sup>
- MPO diminishes nitric oxide bioavailability leading to endothelial dysfunction.<sup>28</sup>
- MPO activates protease cascades that are linked to plaque vulnerability.<sup>29</sup>

## Why measure MPO?

- MPO accumulates in the artery wall and is enriched in culprit lesions in subjects who experience sudden cardiac death.<sup>30</sup>
- MPO mediates vascular inflammation that propagates plaque formation.<sup>31</sup>
- Elevated MPO levels predict the risk of coronary artery disease in subgroups otherwise associated with low risk.<sup>32</sup>
- Elevated MPO levels independently predict the early risk of future cardiovascular events in patients with acute coronary syndromes up to 24 months *preceding* an event.<sup>33,34</sup>

Serum MPO Levels (pmol/L)	Risk Assessment
<894	<b>Low Risk</b>
895-1657	<b>Moderate Risk</b>
>1657	<b>High Risk</b>

# Lp-PLA<sub>2</sub> (PLAC)

Lp-PLA<sub>2</sub> levels aid in assessing the risk for coronary artery disease and ischemic stroke associated with atherosclerosis<sup>35</sup>

## What is Lp-PLA<sub>2</sub>?

- Lipoprotein-associated phospholipase A<sub>2</sub> (Lp-PLA<sub>2</sub>) is an enzyme associated with vascular inflammation and increased stroke risk.<sup>35</sup>

## What is the function of Lp-PLA<sub>2</sub>?

- Lp-PLA<sub>2</sub> hydrolyzes oxidized phospholipids<sup>36</sup> linked to pro-inflammatory biological activities.

## Why measure Lp-PLA<sub>2</sub>?

- Lp-PLA<sub>2</sub> accumulates within human atherosclerotic plaques and vulnerable lesions.<sup>37</sup>
- Elevated Lp-PLA<sub>2</sub> levels can predict the development of coronary artery disease in apparently healthy individuals<sup>38,39</sup> and the risk of future adverse cardiac and cerebrovascular events.<sup>40</sup>
- Measurement of Lp-PLA<sub>2</sub> can help identify patients at increased risk for heart attack, stroke or death.

Lp-PLA <sub>2</sub> Levels (ng/L)	Risk Assessment
<200	<b>Low Risk</b>
200-235	<b>Moderate Risk</b>
>235	<b>High Risk</b>

# Cleveland HeartLab Clinical Reference Laboratory

## Inflammatory Markers - Test Menu

Test	CPT Code	Description	Sample Type	Reference Range
Myeloperoxidase	83876	Vulnerable Plaque, CVD, Vascular Inflammation	EDTA Plasma	<894 pmol/L Low Risk 895 - 1657 pmol/L Moderate Risk >1657 pmol/L High Risk
hs-CRP	86141	General/Vascular Inflammation, CVD	EDTA Plasma	<1.0 mg/L Low Risk 1.0 - 3.0 mg/L Moderate Risk >3.0 mg/L High Risk
Lp-PLA <sub>2</sub> (PLAC)	83698	Stroke, CVD	EDTA Plasma	<200 ng/L Low Risk 200-235 ng/L Moderate Risk >235 ng/L High Risk
F2-Isoprostanes/ Creatinine Ratio	83789/82570	Sedentary Lifestyle, Oxidative Stress, CVD	Random Urine	<1.49 ng/mg Low Risk >1.49 ng/mg High Risk
Microalbumin/ Creatinine Ratio	82043/82570	Renal Microvascular Disease, Hypertension, CVD	Random Urine	<30 mg/g Low Risk ≥30 mg/g High Risk

Cleveland HeartLab offers many other important and additive cardiovascular tests. Please contact us for more information.

## REFERENCES

1. Ridker PM et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *New Engl J Med.* 2008; 359: 2195-2207.
2. Morrow JD. Quantification of isoprostanes as indices of oxidant stress and the risk of atherosclerosis in humans. *Arterioscler Thromb Vasc Biol.* 2005; 25: 279-286.
3. Morrow JD et al. A series of prostaglandin F<sub>2</sub>-like compounds are produced in vivo in humans by a non-cyclooxygenase, free radical-catalyzed mechanism. *Proc Natl Acad Sci USA.* 1990; 87: 9383-9387.
4. Morrow JD et al. The F<sub>2</sub>-isoprostane, 8-epi-prostaglandin F<sub>2a</sub>, a potent agonist of the vascular thromboxane/endoperoxide receptor, is a platelet thromboxane/endoperoxide receptor antagonist. *Prostaglandins.* 1992; 44: 155-163.
5. Minuz et al. The F<sub>2</sub>-isoprostane 8-epiprostaglandin F<sub>2a</sub> increases platelet adhesion and reduces the antiadhesive and antiaggregatory effects of NO. *Arterioscler Thromb Vasc Biol.* 1998; 18: 1248-1256.
6. Schwedhelm E et al. Urinary 8-iso-prostaglandin F<sub>2a</sub> as a risk marker in patients with coronary heart disease: A matched case-control study. *Circulation.* 2004; 109: 843-848.
7. Rossner P Jr et al. Relationship between urinary 15-F<sub>2t</sub>-isoprostane and 8-oxodeoxyguanosine levels and breast cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2006; 15: 639-644.
8. Epplein M et al. Association of plasma micronutrient levels and urinary isoprostane with risk of lung cancer: the multiethnic cohort study. *Cancer Epidemiol Biomarkers Prev.* 2009; 18: 1962-1970.
9. Tappel A. Heme of consumed red meat can act as a catalyst of oxidative damage and could initiate colon, breast and prostate cancers, heart disease and other diseases. *Med Hypotheses.* 2007; 68: 562-564.
10. Shi M et al. Effects of anaerobic exercise and aerobic exercise on biomarkers of oxidative stress. *Environmental Health and Preventative Medicine.* 2007; 12: 202-208.
11. Retrieved January 6, 2010, from <http://www.labtestsonline.org/understanding/analytes/hscrp/test.html>.
12. Ridker PM et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med.* 1997; 336: 973-979.
13. Rost NS et al. Plasma concentration of C-reactive protein and risk of ischemic stroke and transient ischemic attack: the Framingham study. *Stroke.* 2001; 32: 2575-2579.
14. Ndrepepa G et al. N-terminal probrain natriuretic peptide and C-reactive protein in stable coronary heart disease. *Am J Med.* 2006; 119: 355.e1-355.e8.
15. Nissen SE et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med.* 2005; 352: 29-38.
16. Ridker PM et al. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med.* 2005; 352: 20-28.
17. Lambers Heerspink HJ et al. Update on microalbuminuria as a biomarker in renal and cardiovascular disease. *Curr Opin Nephrol Hypertens.* 2006; 15: 631-636.
18. Gerstein HC et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA.* 2001; 286: 421-426.
19. Hillege HL et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation.* 2002; 104: 1777-1782.
20. Klausen K et al. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. *Circulation.* 2004; 111: 32-35.
21. Kistorp C et al. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. *JAMA.* 2005; 293: 1609-1616.
22. Arnlöv J et al. Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: the Framingham heart study. *Circulation.* 2005; 112: 969-975.
23. Sarafidis PA et al. Insulin resistance, microalbuminuria, and chronic kidney disease. *Current Hypertension Reports.* 2008; 10: 249-251.
24. Nicholls SJ and Hazen SL. Myeloperoxidase and cardiovascular disease. *Arterioscler Thromb Vasc Biol.* 2005; 25: 1102-1111.
25. Klebanoff SJ et al. Antimicrobial activity of myeloperoxidase. *Methods Enzymol.* 1984; 105: 399-403.
26. Podrez EA et al. Myeloperoxidase-generated reactive nitrogen species convert LDL into an atherogenic form *in vitro*. *J Clin Invest.* 1999; 103: 1547-1560.
27. Zheng L. et al. Apolipoprotein A-I is a selective target for myeloperoxidase-catalyzed oxidation and functional impairment in subjects with cardiovascular disease. *J Clin Invest.* 2004; 114: 529-541.
28. Eiserich JP et al. Myeloperoxidase: A leukocyte-derived vascular NO oxidase. *Science.* 2002; 296: 2391-2394.
29. Fu X et al. Hypochlorous acid oxygenates the cysteine switch domain of pro-matrix metalloproteinase (MMP-7): A mechanism for matrix metalloproteinase activation and atherosclerotic plaque rupture by myeloperoxidase. *J Biol Chem.* 2001; 276: 41279-41287.
30. Tavora F et al. Monocytes and neutrophils expressing myeloperoxidase occur in fibrous caps and thrombi in unstable coronary plaques. *BMC Cardiovascular Disorders.* 2009; 9: 27-33.
31. Hazen SL and Heinecke JW. 3-chlorotyrosine, a specific marker of myeloperoxidase-catalyzed oxidation, is markedly elevated in low density lipoprotein isolated from human atherosclerotic intima. *J Clin Invest.* 1997; 99: 2075-2081.
32. Meuwese MC et al. Serum myeloperoxidase levels are associated with the future risk of coronary artery disease in apparently healthy individuals: the EPIC-Norfolk prospective population study. *J Am Coll Cardiol.* 2007; 50: 159-165.
33. Baldus S. et al. Myeloperoxidase serum levels predict risk in patients with acute coronary syndromes. *Circulation.* 2003; 108: 1440-145.
34. Cavadoglu E et al. Usefulness of baseline plasma myeloperoxidase levels as an independent predictor of myocardial infarction at two years in patients presenting with acute coronary syndrome. *Am J Cardiol.* 2007; 99: 1364-1368.
35. Retrieved December 20, 2009, from <http://www.plactest.com/>.
36. MacPhee C et al. Lipoprotein-associated phospholipase A<sub>2</sub>, platelet-activating factor acetylhydrolase, generates two bioactive products during the oxidation of low-density lipoprotein: use of a novel inhibitor. *Biochem J.* 1999; 338: 479-487.
37. Kolodgie FD et al. Lipoprotein-associated phospholipase A<sub>2</sub> protein expression in the natural progression of human coronary atherosclerosis. *Arterioscler Thromb Vasc Biol.* 2006; 26: 2523-2529.
38. Ballantyne CM et al. Lipoprotein-associated phospholipase A<sub>2</sub>, high-sensitivity C-reactive protein, and risk for incident coronary artery disease in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. *Circulation.* 2004; 109: 837-842.
39. Daniels LB et al. Lipoprotein-associated phospholipase A<sub>2</sub> is an independent predictor of incident coronary heart disease in an apparently healthy older population. *J Am Coll Cardiol.* 2008; 51: 913-919.
40. Ballantyne CM et al. Lipoprotein-associated phospholipase A<sub>2</sub>, high sensitivity C-reactive protein, and risk for incident ischemic stroke in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. *Arch Intern Med.* 2005; 165: 2479-2484.

Did you know?

50% of patients having heart attacks had *normal* lipids?<sup>1</sup>

