Physician's Pocket Treatment Guide

Cardio IQ®
Advanced Cardiovascular Testing

Quest Diagnostics™

Table of Contents

Interpretation of Abnormal Results

Elevated LDL Cholesterol Level

Lipid Disorder

LDL is one of the classes of lipoproteins that transports cholesterol to tissues and organs. Lowering LDL-C levels is a primary focus of the NCEP-ATP III and 2013 ACC/AHA ASCVD Risk and Treatment Guidelines. Elevated LDL-C levels are an independent risk factor for CVD and associated with a 1.6-fold increased risk of CVD events.

Contributing Factors

Genetics/demographics

- Genetic predisposition[1]

Lifestyle

- High consumption of saturated fats[1]
- Overweight or obese[1]
- Sedentary lifestyle[2]

Illness

- Nephrotic syndrome,[1] hypothyroidism[1]

Drugs

- Androgens,[3] progestins,[4] thiazide diuretics,[1] cyclosporines,[1] tacrolimus[1]
- Selective serotonin reuptake inhibitors[5] (SSRIs)
- Atypical antipsychotics[6]

Treatment Considerations

Dietary/lifestyle intervention

- Cardioprotective diet[2]
- Restricted saturated fat[2]
- Fat weight loss[1]

Pharmacological intervention

- Statins[1]
- Nicotinic acid[1]
- Bile acid sequestrants[1]

For informational purposes only, every physician and healthcare practitioner needs to make treatment decisions for their patients based on their clinical evaluation of the patient and the physician's own education and experience.

Low HDL Cholesterol Level

Lipid Disorder

HDL is the major class of lipoproteins that facilitates cholesterol transport from cells, plasma cholesterol esterification, cholesterol transfer to other lipoproteins, and cholesterol transfer to the liver for excretion (reverse cholesterol transport). Low HDL-C levels are a secondary focus of NCEP-ATP III guidelines. Low HDL-C levels are independently associated with a 1.7-fold to 2.4-fold increased risk for CVD.

Contributing Factors

Genetics/demographics

- Genetic predisposition[1]

Lifestyle

- High triglyceride levels[1]
- High consumption of simple carbohydrates[7]
- Overweight or obese[1]
- Sedentary lifestyle[8]
- Smoking[1]

Illness

- Insulin resistance/diabetes mellitus[1]
- Liver,[9] kidney,[10] and thyroid disease[11]

Drugs

- Nonselective beta blockers,[1] androgens,[1] progestins,[3] isotretinoins[3]

Treatment Considerations

Dietary/lifestyle intervention

- Cardioprotective diet[12]
- Fat weight loss[1]
- Regular aerobic exercise[1]
- Smoking cessation[13]
- Omega-3 fish oil[1]

Pharmacological intervention

- Nicotinic acid[1]
- Fibrates[3]
- Thiazolidinediones[3]
- Some statins[1]

Disease intervention

- Correct insulin resistance[1]
- Control diabetes mellitus[1]

Elevated Triglyceride Level

Lipid Disorder

A triglyceride is an ester derived from glycerol and 3 fatty acids. The major lipid in chylomicrons, VLDLs, and IDLs. Hypertriglyceridemia may increase risk for CVD. Elevated triglyceride levels are a secondary focus of NCEP-ATP III guidelines. Elevated triglyceride levels are a component of the metabolic syndrome and are associated with a 1.7-fold to 4.0-fold increased risk for CVD.

Contributing Factors

Genetics/demographics

- Genetic predisposition[1]
- Pregnancy and lactation[2]

Lifestyle

- High consumption of simple carbohydrates and saturated fats[2]
- Overweight or obese[1]
- Sedentary lifestyle[2]
- Smoking[2]

Illness

- Insulin resistance/diabetes mellitus/ metabolic syndrome[1]
- Hypothyroidism,[1] renal failure,[14] excess alcohol intake[1]

Drugs

- Androgens,[3] estrogens,[1] beta blockers,*[15] thiazide diuretics,[3] glucocorticosteroids,[3] cyclosporines,[2] protease inhibitors,[3] tacrolimus,[2] sertraline,[16] isotretinoin,[17] valproate[18]

Treatment Considerations

Dietary/lifestyle intervention

- Regular aerobic exercise[1]
- Fat weight loss[1]
- Avoid high glycemic foods[1]
- Low simple carbohydrate and saturated fat diet[1]
- Avoid alcohol consumption[1]

Pharmacological intervention

- Fibrates[1]
- Nicotinic acid[1]
- Omega-3 fish oil[1]
- Thiazolidinediones (pioglitazone but NOT rosiglitazone)[3]
- Some statins[1]

Disease intervention

- Treat triglyceride levels >500 mg/dL to help prevent acute pancreatitis[1]

*Effect on elevating triglyceride levels is limited to newer beta blockers (eg, pindolol, acebutolol, nebivolol, atenolol) and not older beta blockers (eg, propranolol, metoprolol).

Elevated LDL Particle Number

Lipid Disorder

Ion mobility measures the number of particles in each of the 8 LDL subclasses. These 8 subclasses comprise the LDL particle number. An elevated total LDL particle number is associated with a 1.4-fold increased risk for CVD.

Contributing Factors

Genetics/demographics

- Genetic predisposition[1]

Lifestyle

- High consumption of saturated fats[1]
- Overweight or obese[1]
- Sedentary lifestyle[1]

Illness

- Nephrotic syndrome,[10]
- Hypothyroidism[1]

Drugs

- Androgens,[3] thiazide diuretics,[19] cyclosporines,[20] tacrolimus[21]
- SSRIs[22]
- Atypical antipsychotics[23]

Treatment Considerations

Dietary/lifestyle intervention

- Cardioprotective diet[24]
- Restricted saturated fat[1]
- Fat weight loss[1]

Pharmacological intervention

- Statins[1]
- Nicotinic acid[1]
- Bile acid sequestrants[1]

Elevated Small and/or Medium LDL Particle Number

Lipoprotein Subfraction Disorders

Ion mobility measures the number of particles in each of the 8 LDL subclasses. Six of these 8 subclasses are small LDL subclass particles. These smaller particles are associated with rapid uptake into the endothelium contributing to accelerated atherosclerosis. There is a 1.3-fold increased risk for CVD associated with the small LDL trait and a 1.4-fold increased risk with the medium LDL trait.

Contributing Factors

Genetics/demographics

- Genetic predisposition[25]
- High triglyceride and low HDL-C levels[2]

Lifestyle

- High consumption of simple carbohydrates[26]
- Overweight or obese[27]
- Sedentary lifestyle[28]

Illness

- Insulin resistance/diabetes mellitus/ metabolic syndrome[2]

Drugs

- Nonselective beta blockers[29]

Treatment Considerations

Dietary/lifestyle intervention

- Avoid simple carbohydrate diet[26]
- Fat weight loss[2]
- Regular exercise[28]
- Omega-3 fish oil[30]

Pharmacological intervention

- Thiazolidinediones[31]
- Nicotinic acid[32]
- Fibrates[33]
- Statins (minor effect)*[34]

Disease intervention

- Consider evaluation of cardiometabolic function[35]
- Noninvasive imaging[36]
- Additional blood tests[2]
- Identify and correct insulin resistance[2]
- Control diabetes mellitus[2]

*Effect is specific to atorvastatin.

Pattern B Phenotype/Decreased LDL Peak Size

Lipoprotein Subfraction Disorders

Pattern B is described as a predominance of small LDL subclass particles as represented on the Ion Mobility patient result figure. Pattern B represents an atherogenic lipid profile that is associated with a 1.3-fold increased risk for CVD.

Decreased LDL Peak Size

Further assessment of pattern includes measurement of peak size. An average size of LDL peak subclass particles measuring less than 218 angstroms, as measured with Ion Mobility, is associated with a 1.35-fold increased risk for CVD.

Contributing Factors

Genetics/demographics

- Genetic predisposition[37]
- High triglyceride and low HDL-C levels[2]

Lifestyle

- High consumption of simple carbohydrates[38]
- Overweight or obese[39]
- Sedentary lifestyle[2]

Illness

- Insulin resistance/diabetes mellitus/ metabolic syndrome[40]

Drugs

- Nonselective beta blockers[29]

Treatment Considerations

Dietary/lifestyle intervention

- Avoid simple carbohydrate diet[26]
- Fat weight loss[26]
- Regular exercise[41]
- Omega-3 fish oil[30]

Pharmacological intervention

- Thiazolidinediones[42]
- Nicotinic acid[43]
- Fibrates[44]
- Statins (minor effect)

Disease intervention

- Consider evaluation of cardiometabolic function[45]
- Noninvasive imaging[46]
- Additional blood tests[47]
- Identify and correct insulin resistance[26]
- Control diabetes mellitus[26]

Decreased Large HDL Level

Lipoprotein Subfraction Disorders

Ion Mobility identifies 5 subclasses of HDL, 1 is identified as the large HDL subclass. Decreased levels of the large HDL subclass are associated with a 1.8-fold increased risk for CVD. Large HDL particles are functionally associated with an antioxidant, paraoxanase, which may help protect the arterial wall.

Contributing Factors

Genetics/demographics

- Genetic predisposition[1]
- High triglyceride levels[2]

Lifestyle

- High consumption of simple carbohydrates[48]
- Overweight or obese[1]
- Sedentary lifestyle[2]
- Smoking[1]

Illness

- Insulin resistance/diabetes mellitus[1]
- Liver,[2] kidney,[2] and thyroid disease[2]

Drugs

- Nonselective beta blockers,[1] androgens,[1] progestins[49]

Treatment Considerations

Dietary/lifestyle intervention

- Avoid simple dietary carbohydrates[2]
- Fat weight loss[2]
- Regular exercise[2]
- Smoking cessation[2]
- Omega-3 fish oil[50]

Pharmacological intervention

- Nicotinic acid[1]
- Nicotinic acid plus statin[1]
- Statins (minor effect)[1]
- Fibrates when triglyceride levels are elevated[1]

Disease intervention

- Correct insulin resistance[1]
- Control diabetes mellitus[1]

Elevated ApoB Level

Apolipoprotein Disorders

Apolipoprotein B (ApoB) is a chief structural protein of all non-HDL lipoproteins. The amount of ApoB is considered to correspond to the number of atherogenic particles. Elevated ApoB levels are associated with a 2.0-fold to 2.5-fold increased risk for CVD.

Contributing Factors

Genetics/demographics

- Genetic predisposition[2]

Lifestyle

- High consumption of saturated fats[51]
- Overweight or obese[52]
- Sedentary lifestyle[53]

Illness

- Nephrotic syndrome[54]
- Hypothyroidism[55]

Drugs

- Androgens,[56] progestins,[57] thiazide diuretics,[58] cyclosporines,[59] tacrolimus,[60] atypical antipsychotics[61]

Treatment Considerations

Dietary/lifestyle intervention

- Cardioprotective diet[62]
- Restricted saturated fat[51]
- Fat weight loss[2]

Pharmacological intervention

- Statins[59]
- Nicotinic acid[63]
- Bile acid sequestrants[1]

Elevated Lp(a) Level

Apolipoprotein Disorders

Lipoprotein(a) (Lp(a)) is a heterogeneous lipoprotein that shares many properties with LDL, but Lp(a) is metabolically distinct from LDL. It contains a structurally unique protein, apolipoprotein(a), the size of which is genetically determined and highly variable. High plasma Lp(a) concentrations are associated with a 1.5-fold to 5.3-fold increased risk for CVD.

Contributing Factors

Genetics/demographics

- Genetic predisposition[2]
- Menopausal loss of estrogen may increase Lp(a) levels by 20% to 30%[64]

Illness

- Chronic renal failure[65]
- Nephrotic syndrome[66]
- Hypothyroidism[67]
- Diabetic nephropathy[68]

Treatment Considerations

Pharmacological intervention

- Nicotinic acid[69]
- Niaspan 2000 mg per day decreases Lp(a) levels by ~24%[2]
- IR Niacin 3000 mg per day decreases Lp(a) levels by ~36%[2]
- Fibrates (limited effect)[70]
- Mipomersen[2]
- PCSK9 inhibition[2]
- Anacetrapib[2]

Disease intervention

- Consider evaluation of cardiometabolic function[2]
- Noninvasive imaging[71]
- Additional blood tests[2]
- Consider that some statins may elevate Lp(a) levels in some patients[71]
- Aggressively treat all associated atherogenic conditions[2]
- LDL or Lp(a) apheresis in some extreme cases of resistance to Lp(a)-lowering drugs[70]

Elevated Fibrinogen Level

Inflammatory Disorders

Fibrinogen is a plasma glycoprotein that can be transformed into a fibrin clot in response to vascular or tissue injury. The combination of elevated fibrinogen level with other CVD risk factors produces an additive risk and can substantially increase disease potential. There are 2 fibrinogen assays available: one measures clotting, the other antigen level. Elevated fibrinogen is associated with inflammation and a 1.4-fold to 2.5-fold increased risk for CVD.

Contributing Factors

Genetics/demographics

- Genetic predisposition[2]
- Sex (women often have higher levels)[72]

Lifestyle

- Tobacco use[2]
- Overweight[2]
- Increasing age[2]
- Sedentary lifestyle[2]

Illness

- Insulin resistance/diabetes mellitus[73]
- Hypertension[74]
- Postmenopausal state[75]
- Acute/chronic inflammation[72]

Drugs

- Oral contraceptives,[75] gemfibrozil[76]

Treatment Considerations

Dietary/lifestyle intervention

- Fat weight loss[77]
- Increase physical activity[77]
- Smoking cessation[2]

Pharmacological intervention

- Nicotinic acid[78]
- Fibrates: fenofibrate may reduce whereas gemfibrozil may elevate[70]

Disease intervention

- Consider evaluation of cardiometabolic function[2]
- Noninvasive imaging[2]
- Additional blood tests[2]
- Control hypertension[74]
- Control diabetes mellitus[73]

Elevated hs-CRP Level

Inflammatory Disorders

CRP is a plasma protein produced by the liver in response to systemic inflammation. The high sensitivity CRP (hs-CRP) test accurately determines CRP levels in the low range of 1-10 mg/L. Elevated hs-CRP levels correlate with the presence of the metabolic syndrome, insulin resistance, endothelial dysfunction, and impaired fibrinolysis. hs-CRP can discern the low levels of inflammation associated with a 1.5-fold to 2.0-fold increased risk for CVD.

Contributing Factors

Lifestyle

- Obese[2]
- Stress[79]
- Smoking[2]
- Adiposity in women[2]

Illness

- Systemic inflammation[2]
- Insulin resistance/diabetes mellitus/ metabolic syndrome[2]

Drugs

- Hormone-replacement therapy,[80] contraceptives[80]

Treatment Considerations

Dietary/lifestyle intervention

- Cardioprotective diet[2]
- Fat weight loss[2]

Pharmacological intervention

- Statins[2]
- Statins plus ezetimibe[81]
- Fibrates[82]
- Nicotinic acid[83]

Disease intervention

- Consider evaluation of cardiometabolic function[2]
- Noninvasive imaging[84]
- Additional blood tests[2]

Elevated Lp-PLA$_2$ Level

Inflammatory Disorders

The Lp-PLA$_2$ test [94218(X)] measures the activity of an enzyme that plays a causal role in the vascular inflammatory process. This test measures the disease activity within the arterial wall under the calcified cap of an atherosclerotic plaque; such activity indicates a potential thinning of the cap and thus a potential for plaque rupture. Elevated Lp-PLA$_2$ activity levels have been associated with a 2-fold increased risk for developing coronary heart disease (CHD) at 7 years independent of non-HDL cholesterol levels. Also, elevated Lp-PLA$_2$ activity levels indicate a 2-fold increased risk of having a CHD event (MI, coronary revascularization or CHD-related death) at 5 years. In some studies, tests that measured Lp-PLA$_2$ activity (such as the one offered by Quest Diagnostics), as compared with Lp-PLA$_2$ mass levels, had a higher predictive value for cardiovascular events.

Contributing Factors

Genetics/demographics

- Increasing age in both sexes[85]
- Increased carotid intima-media thickness[86]

Lifestyle

- Tobacco use[87]
- Sedentary lifestyle[88]

Illness

- Metabolic syndrome[89]
- Elevated blood glucose level[70]
- Hypertension[87]

Treatment Considerations

Dietary/lifestyle intervention

- Omega-3 fish oil supplements[90]
- Diet high in Omega-3 fatty acids[90]

Pharmacological intervention

- Statins[70]
- Fenofibrate*[70]
- Nicotinic acid plus statins*[91]
- Ezetimibe[92]
- Combination of statin with other suggested drugs results in further Lp-PLA$_2$ reduction[93]
- Antihypertensive therapy for optimal BP control[94]

Disease intervention

- Consider evaluation of cardiometabolic function[2]
- Noninvasive imaging[95]
- Additional blood tests[2]

*In April 2016, the US Food and Drug Administration withdrew the indication of extended-release niacin and delayed-release fenofibrate when used in combination with a statin.

Elevated Myeloperoxidase (MPO) Level

Inflammatory Disorders

Myeloperoxidase (MPO) is a vascular-specific inflammatory enzyme released by the leukocytes into the bloodstream in response to vulnerable plaque, erosions, or fissures in the endothelium of the arterial wall. MPO is involved in (1) lipid peroxidation converting LDL to an atherogenic form and HDL to a dysfunctional form, (2) destabilization and rupture of atherosclerosis plaque, and (3) vasoconstriction and endothelial dysfunction.

Elevated MPO level is an independent risk factor for CVD and is associated with a 2.0-fold increased risk for CVD events. MPO levels increase with clinical severity of known CAD.

Contributing Factors

Genetics/demographics

- Increasing age[96]

Lifestyle

- Overweight or obese[97]
- Tobacco use[98]
- Extreme athletes (marathon runners) seen after strenuous exercise[99]

Illness

- Hypertension[100]
- Vascular damage[101]
- Vasculitis[102]
- Autoimmune disorders[103]
- Chronic inflammatory disease[104] (rheumatoid arthritis,[104] lupus[105])
- Chronic lymphocytic leukemia[106]
- Bone marrow dyscrasias[107]

Treatment Considerations

Dietary/lifestyle intervention

- Fat weight loss[108]
- Regular exercise[109]
- Smoking cessation[98]
- Cardioprotective diet[110]

Pharmacological intervention

- Statins[111]

Disease intervention

- Antiplatelet therapy[112]
- Antihypertensive therapy for optimal BP control[100]
- Additional blood test (NT-proBNP)[113]
- Noninvasive imaging[114]

Elevated Insulin Level

Metabolic Disorders

Insulin is a polypeptide produced by specialized beta cells of the islets of Langerhans in the body and tail of the pancreas. An elevated fasting insulin level is associated with a 3.2-fold increased risk for CVD events.

Contributing Factors

Genetics/demographics

- Genetic predisposition[2]
- Elderly people[115]

Lifestyle

- Obese[116]
- Visceral adiposity[117]
- Sedentary lifestyle[118]
- High carbohydrate diet[26]
- Stress[119]

Illness

- Menopausal drop in estrogen[120]
- Chronic inflammation with elevated inflammatory markers[121]
- Illnesses such as:
  - Polycystic ovarian syndrome[2]
  - Cushing's disease[122]
  - Hemochromatosis, insulinoma[123]
  - Insulin resistance/diabetes[124]
  - Diabetes mellitus/metabolic syndrome[1]

Drugs

- Rifampin,[125] progesterone,[126] antiretrovirals,[127] corticosteroids[128]
- Elevations may be caused by postprandial blood sample or exogenous administration of insulin[129]

Treatment Considerations

Dietary/lifestyle intervention

- Fat restricted, cardioprotective diet[130]
- Limit simple carbohydrates, utilize high-fiber sources[131]
- Fat weight loss[132]
- Regular exercise[133]

Disease intervention

- Recommended pharmacologic methods of meeting insulin requirements or regulating insulin sensitivity[2]

Elevated Homocysteine Level

Metabolic Disorders

Homocysteine is a metabolic by-product of methionine metabolism. An elevated homocysteine level increases oxidative stress, may cause endothelial dysfunction and vascular injury, and enhances thrombogenicity. Patients with elevated homocysteine levels have a 1.5-fold increased risk for CVD events.

Contributing Factors

Genetics/demographics

- Genetic predisposition[3]

Lifestyle

- Deficiencies of vitamins folic acid, B6, and B12[1]
- Excess alcohol,[134] caffeine,[135] or nicotine[136]
- Diet low in greens, high in meats[137]

Illness

- Renal insufficiency/failure,[138] pernicious anemia,[139] megaloblastic anemia,[140] hypothyroidism[2]

Drugs

- Nicotinic acid (dose dependent),[141] fenofibrates,[141] sulfonamides,[141] metformin,[141] anticonvulsants,[141] methotrexate,[141] theophylline,[141] cyclosporine[142]

Treatment Considerations

Dietary/lifestyle intervention

- Diet high in green leafy vegetables[137]
- Traditional treatment has been folic acid, B6, and B12 vitamins[2]

Disease intervention

- Identify and treat any underlying abnormality such as renal insufficiency/pernicious anemia[2]
- Initiating treatment of elevated homocysteine continues to be controversial in reducing risk for CVD events versus increased risk for other conditions[2]

Abnormal Omega-3 & -6 Index/Abnormal EPA/AA Ratio

Omega-3 & -6 Fatty Acids

The 3 major omega-3 fatty acids are eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha-linolenic acid. Omega-6 fatty acids are proinflammatory and prothrombotic. The major omega-6 fatty acid is arachidonic acid (AA).

The omega-3 index (EPA and DHA expressed as a percentage of phospholipid fatty acids) is an indicator of risk for sudden cardiac death and nonfatal cardiovascular events and helps measure response over time to recommended therapy target. The EPA/AA ratio is a marker of cardiovascular risk, with higher ratios being associated with lower cardiac risk.

Contributing Factors

Genetics/demographics

- Genetic polymorphisms in the Fatty acid desaturase (FAD) genes[143]

Lifestyle

- Low dietary consumption of omega-3 fatty acids[144]
- High dietary consumption of omega-6 fatty acids[144]
- Dietary deficiency of omega-3 fatty acids[145]

Treatment Considerations

Dietary/lifestyle intervention

- Two primary omega-3 fatty acids are EPA and DHA. Dietary sources are:
  - Fish oil[2]
  - Fatty fish[2]
- ALA, 1 of the 3 major omega-3 fatty acids, is found in plant-based foods. It is converted to EPA and DHA after being ingested[2]

Decreased Vitamin D, 25 Hydroxy, LC/MS/MS

Metabolic Disorders

Vitamin D and its metabolites are hormones and hormone precursors. A deficiency of 25-hydroxyvitamin D is associated with development of atherosclerosis and increased risk for cardiovascular events. Decreased vitamin D level is associated with a 1.8-fold increased risk for cardiovascular mortality and a 1.6-fold to 5.0-fold increased risk for CVD events.

Contributing Factors

Genetics/demographics

- Elderly and newborns[1]

Lifestyle

- Inadequate sun exposure[1]:
  - People with more skin pigment are at higher risk for vitamin D deficiency[1]

Illness

- Obesity[1]
- Malabsorption[3]
- Renal disease[2]
- Liver disease[146]

Drugs

- Corticosteroids,[147] anticonvulsants,[1] antirejection medications,[148] HIV medications[148]

Treatment Considerations

Dietary/lifestyle intervention

- Vitamin D supplementation[3]

Disease intervention

- Initial loading therapy:
  - 50,000 IU vitamin D_2 weekly for 2 months[3]
- Maintenance therapy:
  - 50,000 IU vitamin D_2 once or twice monthly[3]
  - 2000-4000 IU vitamin D_3 daily and/or appropriate sun exposure and/or high vitamin D diet (eg, salmon, tuna fish, shiitake mushrooms)[3]

Elevated NT-proBNP Level

Heart Failure

NT-proBNP is an endogenously produced neurohormone secreted from the cardiac ventricular myocytes in response to cardiac stress. As a sensitive marker for cardiac dysfunction, elevated NT-proBNP levels provide aid in diagnosis of heart failure (HF) and assessment of response to therapy, prediction of chronic HF progression (which is associated with a 1.9-fold to 2.9-fold* increased risk for CVD events) and incidence of CVD death or HF after ACS, which carries a 2.4-fold to 6.6-fold* increased risk for CVD.

Contributing Factors

Illness

Cardic and Pulmonary

- Medical conditions that may be associated with myocardial stress[149]
- Systemic hypertension[150]
- HF of any etiology[2]
- Left or right ventricular hypertrophy[151]
- Diastolic dysfunction[152]
- Myocardial infarction[153]
- Acute coronary syndrome[154]
- Cardiac arrhythmias, especially atrial fibrillation[155]
- Cardiomyopathy[155]
- Myocarditis, possibly endocarditis[155]
- COPD[156]
- Pulmonary embolism[157]

Other

- Sepsis[158]
- Diabetes mellitus[159]
- Renal disease[160]

Treatment Considerations

Pharmacological intervention

- Dependent on etiology, consider:
  - Preload medications: nitrates,[161] diuretics[162]
  - Rate-control medications: beta blockers[163]
  - Afterload medications: ACE inhibitors,[164] ARBs,[70] alpha blockers,[70] calcium channel blockers,[165] direct vasodilators[166]
  - Cardiac pacing[167]

Disease intervention

- Complete evaluation of cardiometabolic function to exclude causes of cardiac dysfunction[2]
- Echocardiography[168]
- Other noninvasive imaging[2]
- Additional blood tests[2]

*Risk for HF progression is substantially increased in patients when both NT-proBNP and ST2 levels are elevated.

Elevated Soluble ST2 Level

Heart Failure

ST2 is an interleukin-1 family receptor that is expressed in cardiomyocytes. There are 2 isoforms: transmembrane-bound ST2 and soluble, ie, circulating, ST2 (sST2). The sST2 biomarker binds and removes interleukin(IL)-33 from the circulation, thus eliminating the protective effect that IL-33 provides to the cardiac muscle.

Patients with HF who have elevated sST2 levels >35 ng/mL have a worse prognosis, and are at increased risk for HF progression, rehospitalization, need for heart transplantation, and death. sST2 level is not affected by confounding factors as is BNP/NT-proBNP. Measuring both sST2 and NT-proBNP levels can help improve the risk stratification of patients with chronic HF.*

Contributing Factors

Illness

Cardic and Pulmonary

- Systemic hypertension[169]
- Ventricular hypertrophy[170]
- Diastolic dysfunction[171]
- Myocardial infarction / Acute coronary syndrome[172]
- Cardiomyopathy[173]
- Pulmonary embolism[174]

Other

- Diabetes mellitus[175]
- Renal disease[176]

Treatment Considerations

Pharmacological intervention

- Dependent on etiology, consider:
  - Diuretics[177]
  - Beta blockers[178]
  - ACE inhibitors[179]
  - Angiotensin Receptor Blockers[180]
  - Direct vasodilators[181]

Disease intervention

- Complete evaluation of cardiometabolic function:
  - Electrolytes/renal function/ CK-MB[2]
- Echocardiography[177]
- Additional blood tests:
  - NT-proBNP[182]

*Risk for HF progression is substantially increased in patients when both NT-proBNP and ST2 levels are elevated.

References

1. Kasper D, Fauci A, Hauser S, et al. Harrison's Principles of Internal Medicine. 19th ed: McGraw-Hill Education. 2015.
2. Mann DL, Zipes DP, Libby P, Bonow RO. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 10th ed: Saunders. 2015.
3. Brunton L, Chabner B, Knollman B. Goodman and Gillman's The Pharmacological Basis of Therapeutics. 12th ed: McGraw-Hill Education. 2011.
4. Wahl P, Walden C, Knopp R, et al. Effect of estrogen/progestin potency on lipid/lipoprotein cholesterol. *N Engl J Med*. 1983;308:862-867.
5. Shirzadi AA, Ghaemi SN. Side effects of atypical antipsychotics: Extrapyramidal symptoms and the metabolic syndrome. *Harv Rev Psychiatry*. 2006;14: 152-164.
6. Wei F, Crain AL, Whitebird RR, Godlevsky OV, O'Connor PJ. Effects of paroxetine and sertraline on low-density lipoprotein cholesterol: An observational cohort study. *CNS Drugs*. 2009;23:857-865.
7. Siri PW, Krauss RM. Influence of dietary carbohydrate and fat on LDL and HDL particle distributions. *Curr Atheroscler Rep*. 2005;7:455-459.
8. Windler E, Schöffauer M, Zyriax BC. The significance of low HDL-cholesterol levels in an ageing society at increased risk for cardiovascular disease. *Diab Vasc Dis Res*. 2007;4:136-142.
9. Ghadir MR, Riahin AA, Havaspour A, Nooranipour M, Habibinejad AA. The relationship between lipid profile and severity of liver damage in cirrhotic patients. *Hepat Mon*. 2010;10:285-288.
10. Chen J, Muntner P, Hamm LL, et al. The metabolic syndrome and chronic kidney disease in U.S. adults. *Ann Intern Med*. 2004;140:167-174.
11. Rizos CV, Elisaf MS, Liberopoulos EN. Effects of thyroid dysfunction on lipid profile. *Open Cardiovasc Med J*. 2011;5:76-84.
12. Mooradian AD, Haas MJ. The effect of nutritional supplements on serum high-density lipoprotein cholesterol and apolipoprotein A-I. *Am J Cardiovasc Drugs*. 2014;14:253-274.
13. Forey BA, Fry JS, Lee PN, Thornton AJ, Coombs KJ. The effect of quitting smoking on HDL-cholesterol – a review based on within-subject changes. *Biomark Res*. 2013;1:26.
14. Trevisan R, Dodesini AR, Lepore G. Lipids and renal disease. *J Am Soc Nephrol*. 2006;17:S145-147.
15. Pesant Y, Marc-Aurele J, Bielmann P, et al. Metabolic and antihypertensive effects of nebivolol and atenolol in normometabolic patients with mild-to-moderate hypertension. *Am J Ther*. 1999;6:137-147.
16. Kesim M, Tiryaki A, Kadioglu M, et al. The effects of sertraline on blood lipids, glucose, insulin and HBA1C levels: A prospective clinical trial on depressive patients. *J Res Med Sci*. 2011;16:1525-1531.
17. Vieira AS, Beijamini V, Melchiors AC. The effect of isotretinoin on triglycerides and liver aminotransferases. *An Bras Dermatol*. 2012;87:382-387.
18. Chang HH, Yang YK, Gean PW, et al. The role of valproate in metabolic disturbances in bipolar disorder patients. *J Affect Disord*. 2010;124:319-323.
19. Christogiannis LG, Kostapanos MS, Tellis CC, et al. Distinct effects of fixed combinations of valsartan with either amlodipine or hydrochlorothiazide on lipoprotein subfraction profile in patients with hypertension. *J Hum Hypertens*. 2013;27:44-50.
20. Siirtola A, Antikainen M, Ala-Houhala M, et al. Studies of LDL particle size and susceptibility to oxidation and association with glucose metabolism in children after heart transplantation. *J Heart Lung Transplant*. 2004;23:418-426.
21. Cofan F, Zambon D, Laguna JC, et al. Oxidation of low-density lipoproteins in renal transplant recipients treated with tacrolimus. *Transplant Proc*. 2002;34:377-378.
22. Kopf D, Westphal S, Luley CW, et al. Lipid metabolism and insulin resistance in depressed patients: Significance of weight, hypercortisolism, and antidepressant treatment. *J Clin Psychopharmacol*. 2004;24:527-531.
23. Olfson M, Marcus SC, Corey-Lisle P, et al. Hyperlipidemia following treatment with antipsychotic medications. *Am J Psychiatry*. 2006;163:1821-1825.

References

24. Dreon DM, Fernstrom HA, Williams PT, Krauss RM. A very low-fat diet is not associated with improved lipoprotein profiles in men with a predominance of large, low-density lipoproteins. *Am J Clin Nutr*. 1999;69:411-418.

25. Hoogeveen RC, Gaubatz JW, Sun W, et al. Small dense low-density lipoprotein-cholesterol concentrations predict risk for coronary heart disease: The Atherosclerosis Risk In Communities (ARIC) study. *Arterioscler Thromb Vasc Biol*. 2014;34:1069-1077.

26. Krauss RM. Dietary and genetic effects on low-density lipoprotein heterogeneity. *Annu Rev Nutr*. 2001;21: 283-295.

27. Iacobellis G. Obesity and Cardiovascular Disease: Oxford University Press. 2009.

28. Slentz CA, Houmard JA, Johnson JL, et al. Inactivity, exercise training and detraining, and plasma lipoproteins. STRRIDE: a randomized, controlled study of exercise intensity and amount. *J Appl Physiol (1985)*. 2007;103:432-442.

29. Campos H, Genest JJ, Jr., Blijlevens E, et al. Low density lipoprotein particle size and coronary artery disease. *Arterioscler Thromb*. 1992;12:187-195.

30. Griffin BA, Caslake MJ, Yip B, et al. Rapid isolation of low density lipoprotein (LDL) subfractions from plasma by density gradient ultracentrifugation. *Atherosclerosis*. 1990;83:59-67.

31. Betteridge DJ. Effects of pioglitazone on lipid and lipoprotein metabolism. *Diabetes Obes Metab*. 2007;9:640-647.

32. Superko HR, Krauss RM. Differential effects of nicotinic acid in subjects with different LDL subclass patterns. *Atherosclerosis*. 1992;95:69-76.

33. Staels B, Dallongeville J, Auwerx J, et al. Mechanism of action of fibrates on lipid and lipoprotein metabolism. *Circulation*. 1998;98:2088-2093.

34. Sniderman AD. Differential response of cholesterol and particle measures of atherogenic lipoproteins to LDL-lowering therapy: Implications for clinical practice. *J Clin Lipidol*. 2008;2:36-42.

35. Brunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk: Consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. *Diabetes Care*. 2008;31:811-822.

36. Marzullo P, Mariani G. From Basic Cardiac Imaging to Image Fusion. Core Competencies Versus Technological Progress: Springer. 2013.

37. Nishina PM, Johnson JP, Naggert JK, Krauss RM. Linkage of atherogenic lipoprotein phenotype to the low density lipoprotein receptor locus on the short arm of chromosome 19. *Proc Natl Acad Sci U S A*. 1992;89: 708-712.

38. Siri-Tarino PW, Williams PT, Fernstrom HS, Rawlings RS, Krauss RM. Reversal of small, dense LDL subclass phenotype by normalization of adiposity. *Obesity (Silver Spring)*. 2009;17:1768-1775.

39. Katzel LI, Coon PJ, Rogus E, Krauss RM, Goldberg AP. Persistence of low HDL-C levels after weight reduction in older men with small LDL particles. *Arterioscler Thromb Vasc Biol*. 1995;15:299-305.

40. Reaven GM, Chen YD, Jeppesen J, Maheux P, Krauss RM. Insulin resistance and hyperinsulinemia in individuals with small, dense low density lipoprotein particles. *J Clin Invest*. 1993;92:141-146.

41. Williams PT, Krauss RM, Vranizan KM, et al. Effects of exercise-induced weight loss on low density lipoprotein subfractions in healthy men. *Arteriosclerosis*. 1989;9:623-632.

42. Sorrentino MJ. Hyperlipidemia in Primary Care: A Practical Guide to Risk Reduction: Humana Press. 2011.

43. Rajman I, Eacho PI, Chowienczyk PJ, Ritter JM. LDL particle size: An important drug target? *Br J Clin Pharmacol*. 1999;48:125-133.

44. Rizzo M, Berneis K. Low-density lipoprotein size and cardiovascular risk assessment. *QJM*. 2006;99:1-14.

45. Mora S. Advanced lipoprotein testing and subfractionation are not (yet) ready for routine clinical use. *Circulation*. 2009;119:2396-2404.

References

46. Mora S, Szklo M, Otvos JD, et al. LDL particle subclasses, LDL particle size, and carotid atherosclerosis in the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2007;192:211-217.

47. Griffin BA. The effect of n-3 fatty acids on low density lipoprotein subfractions. *Lipids*. 2001;36 Suppl:S91-S97.

48. Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Saturated fatty acids and risk of coronary heart disease: Modulation by replacement nutrients. *Curr Atheroscler Rep*. 2010;12:384-390.

49. Page ST, Krauss RM, Gross C, et al. Impact of mifepristone, a glucocorticoid/progesterone antagonist, on HDL cholesterol, HDL particle concentration, and HDL function. *J Clin Endocrinol Metab*. 2012;97:1598-1605.

50. Annuzzi G, Rivellese AA, Wang H, et al. Lipoprotein subfractions and dietary intake of n-3 fatty acid: The Genetics of Coronary Artery Disease in Alaska Natives study. *Am J Clin Nutr*. 2012;95:1315-1322.

51. Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: A meta-analysis of 60 controlled trials. *Am J Clin Nutr*. 2003;77:1146-1155.

52. Lu M, Lu Q, Zhang Y, Tian G. ApoB/apoA1 is an effective predictor of coronary heart disease risk in overweight and obesity. *J Biomed Res*. 2011;25:266-273.

53. Behre C, Bergstrom G, Schmidt C. Moderate physical activity is associated with lower ApoB/ApoA-I ratios independently of other risk factors in healthy, middle-aged men. *Angiology*. 2010;61:775-779.

54. Marsh JB, Welty FK, Lichtenstein AH, Lamon-Fava S, Schaefer EJ. Apolipoprotein B metabolism in humans: Studies with stable isotope-labeled amino acid precursors. *Atherosclerosis*. 2002;162:227-244.

55. Klausen IC, Nielsen FE, Hegedus L, et al. Treatment of hypothyroidism reduces low-density lipoproteins but not lipoprotein(a). *Metabolism*. 1992;41:911-914.

56. Hartgens F, Rietjens G, Keizer HA, Kuipers H, Wolffenbuttel BH. Effects of androgenic-anabolic steroids on apolipoproteins and lipoprotein (a). *Br J Sports Med*. 2004;38:253-259.

57. Wolfe BM, Huff MW. Effects of low dosage progestin-only administration upon plasma triglycerides and lipoprotein metabolism in postmenopausal women. *J Clin Invest*. 1993;92:456-461.

58. Lakshman MR, Reda DJ, Materson BJ, Cushman WC, Freis ED. Diuretics and beta-blockers do not have adverse effects at 1 year on plasma lipid and lipoprotein profiles in men with hypertension. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *Arch Intern Med*. 1999;159:551-558.

59. Frank S, Kostner G (eds). Lipoproteins – Role in Health and Diseases. InTech. 2012.

60. McCune TR, Thacker LR, II, Peters TG, et al. Effects of tacrolimus on hyperlipidemia after successful renal transplantation: a Southeastern Organ Procurement Foundation multicenter clinical study. *Transplantation*. 1998;65:87-92.

61. Hardy TA, Marquez E, Kryzhanovskaya L, Taylor CC, Cavazzoni P. Cross-sectional comparison of fasting lipids in normoglycemic patients with schizophrenia during chronic treatment with olanzapine, risperidone, or typical antipsychotics. *J Clin Psychopharmacol*. 2006;26:405-408.

62. Furtado JD, Campos H, Appel LJ, et al. Effect of protein, unsaturated fat, and carbohydrate intakes on plasma apolipoprotein B and VLDL and LDL containing apolipoprotein C-III: Results from the OmniHeart Trial. *Am J Clin Nutr*. 2008;87:1623-1630.

63. Gille A, Bodor ET, Ahmed K, Offermanns S. Nicotinic acid: Pharmacological effects and mechanisms of action. *Annu Rev Pharmacol Toxicol*. 2008;48:79-106.

64. Berg G, Mesch V, Boero L, et al. Lipid and lipoprotein profile in menopausal transition. Effects of hormones, age and fat distribution. *Horm Metab Res*. 2004;36:215-220.

65. Haffner SM, Gruber KK, Aldrete G, Jr., et al. Increased lipoprotein(a) concentrations in chronic renal failure. *J Am Soc Nephrol*. 1992;3:1156-1162.

66. Wanner C, Rader D, Bartens W, et al. Elevated plasma lipoprotein(a) in patients with the nephrotic syndrome. *Ann Intern Med*. 1993;119:263-269.

References

67. Kaliaperumal R, William E, Selvam T, Krishnan SM. Relationship between lipoprotein(a) and thyroid hormones in hypothyroid patients. *J Clin Diagn Res*. 2014;8:37-39.

68. Chandni R, Ramamoorthy KP. Lipoprotein(a) in type 2 diabetic subjects and its relationship to diabetic microvascular complications. *World J Diabetes*. 2012;3:105-109.

69. Lippi G, Targher G. Optimal therapy for reduction of lipoprotein(a). *J Clin Pharm Ther*. 2012;37:1-3.

70. Ballantyne CM. Clinical Lipidology: A Companion to Braunwald's Heart Disease. 2nd ed: Saunders. 2014.

71. Tehrani DM, Wong ND. Cardiovascular disease risk assessment: Review of established and newer modalities. *Curr Treat Options Cardiovasc Med*. 2015;17:57.

72. Kamath S, Lip GY. Fibrinogen: Biochemistry, epidemiology and determinants. *QJM*. 2003;96:711-729.

73. Raynaud E, Perez-Martin A, Brun J, et al. Relationships between fibrinogen and insulin resistance. *Atherosclerosis*. 2000;150:365-370.

74. Shankar A, Wang JJ, Rochtchina E, Mitchell P. Positive association between plasma fibrinogen level and incident hypertension among men: Population-based cohort study. *Hypertension*. 2006;48:1043-1049.

75. Lee AJ, Lowe GD, Smith WC, Tunstall-Pedoe H. Plasma fibrinogen in women: relationships with oral contraception, the menopause and hormone replacement therapy. *Br J Haematol*. 1993;83:616-621.

76. de Maat MP, Knipscheer HC, Kastelein JJ, Kluft C. Modulation of plasma fibrinogen levels by ciprofibrate and gemfibrozil in primary hyperlipidaemia. *Thromb Haemost*. 1997;77:75-79.

77. Aziz CB, Omar N, Abdullah WZ, et al. Reduced fibrinogen, fibrinolytic biomarkers, and physical parameters after a weight-loss program in obese subjects. *N Am J Med Sci*. 2014;6:377-382.

78. Philipp CS, Cisar LA, Saidi P, Kostis JB. Effect of niacin supplementation on fibrinogen levels in patients with peripheral vascular disease. *Am J Cardiol*. 1998;82:697-699, A699.

79. Xu W, Chen B, Guo L, et al. High-sensitivity CRP: Possible link between job stress and atherosclerosis. *Am J Ind Med*. 2015;58:773-779.

80. Liukkonen T, Vanhala M, Jokelainen J, et al. Effect of menopause and use of contraceptives/hormone therapy on association of C-reactive protein and depression: A population-based study. *J Psychosom Res*. 2010;68:573-579.

81. Abramson BL, Benlian P, Hanson ME, et al. Response by sex to statin plus ezetimibe or statin monotherapy: A pooled analysis of 22,231 hyperlipidemic patients. *Lipids Health Dis*. 2011;10:146.

82. Coban E, Ozdogan M, Yazicioglu G, Sari R. The effect of fenofibrate on the levels of high sensitivity C-reactive protein in dyslipidaemic hypertensive patients. *Int J Clin Pract*. 2005;59:415-418.

83. Wi J, Kim JY, Park S, et al. Optimal pharmacologic approach to patients with hypertriglyceridemia and low high-density lipoprotein-cholesterol: Randomized comparison of fenofibrate 160 mg and niacin 1500 mg. *Atherosclerosis*. 2010;213:235-240.

84. Parildar H, Gulmez O, Cigerli O, et al. Carotid artery intima media thickness and HsCRP; predictors for atherosclerosis in prediabetic patients? *Pak J Med Sci*. 2013;29:495-499.

85. Daniels LB, Laughlin GA, Sarno MJ, et al. Lipoprotein-associated phospholipase A2 is an independent predictor of incident coronary heart disease in an apparently healthy older population: the Rancho Bernardo Study. *J Am Coll Cardiol*. 2008;51:913-919.

86. Hargens TA, Rhodes PG, VanReenen J, Kaminsky LA. Lipoprotein-associated phospholipase A2 and carotid intima-media thickness in individuals classified as low-risk according to Framingham. *Cardiovasc Diagn Ther*. 2014;4:487-494.

87. Charniot JC, Khani-Bittar R, Albertini JP, et al. Interpretation of lipoprotein-associated phospholipase A2 levels is influenced by cardiac disease, comorbidities, extension of atherosclerosis and treatments. *Int J Cardiol*. 2013;168:132-138.

References

88. Tzotzas T, Filippatos TD, Triantos A, et al. Effects of a low-calorie diet associated with weight loss on lipoprotein-associated phospholipase A2 (Lp-PLA2) activity in healthy obese women. *Nutr Metab Cardiovasc Dis*. 2008;18:477-482.

89. Noto H, Chitkara P, Raskin P. The role of lipoprotein-associated phospholipase A(2) in the metabolic syndrome and diabetes. *J Diabetes Complications*. 2006;20:343-348.

90. Gajos G, Zalewski J, Mostowik M, et al. Polyunsaturated omega-3 fatty acids reduce lipoprotein-associated phospholipase A(2) in patients with stable angina. *Nutr Metab Cardiovasc Dis*. 2014;24:434-439.

91. Kuvin JT, Dave DM, Sliney KA, et al. Effects of extended-release niacin on lipoprotein particle size, distribution, and inflammatory markers in patients with coronary artery disease. *Am J Cardiol*. 2006;98:743-745.

92. Saougos VG, Tambaki AP, Kalogirou M, et al. Differential effect of hypolipidemic drugs on lipoprotein-associated phospholipase A2. *Arterioscler Thromb Vasc Biol*. 2007;27:2236-2243.

93. Reddy KJ, Singh M, Batsell RR, et al. Lipoprotein-associated phospholipase A2 mass is significantly reduced in dyslipidemic patients treated with lifestyle modification and combination lipid-modifying drug therapy. *Prev Cardiol*. 2010;13:130-134.

94. Colley KJ, Wolfert RL, Cobble ME. Lipoprotein associated phospholipase A(2): Role in atherosclerosis and utility as a biomarker for cardiovascular risk. *EPMA J*. 2011;2:27-38.

95. Davidson MH, Corson MA, Alberts MJ, et al. Consensus panel recommendation for incorporating lipoprotein-associated phospholipase A2 testing into cardiovascular disease risk assessment guidelines. *Am J Cardiol*. 2008;101:51F-57F.

96. Giovannini S, Onder G, Leeuwenburgh C, et al. Myeloperoxidase levels and mortality in frail community-living elderly individuals. *J Gerontol A Biol Sci Med Sci*. 2010;65:369-376.

97. Zur B, Look M, Holdenrieder S, Stoffel-Wagner B. Elevated plasma myeloperoxidase concentration in adults with obesity. *Clin Chim Acta*. 2011;412:1891-1892.

98. Andelid K, Bake B, Rak S, et al. Myeloperoxidase as a marker of increasing systemic inflammation in smokers without severe airway symptoms. *Respir Med*. 2007;101:888-895.

99. Melanson SE, Green SM, Wood MJ, Neilan TG, Lewandrowski EL. Elevation of myeloperoxidase in conjunction with cardiac-specific markers after marathon running. *Am J Clin Pathol*. 2006;126:888-893.

100. Van der Zwan LP, Scheffer PG, Dekker JM, et al. Hyperglycemia and oxidative stress strengthen the association between myeloperoxidase and blood pressure. *Hypertension*. 2010;55:1366-1372.

101. Pitanga TN, de Aragao Franca L, Rocha VC, et al. Neutrophil-derived microparticles induce myeloperoxidase-mediated damage of vascular endothelial cells. *BMC Cell Biol*. 2014;15:21.

102. Rutgers A, Heeringa P, Tervaert JW. The role of myeloperoxidase in the pathogenesis of systemic vasculitis. *Clin Exp Rheumatol*. 2003;21:S55-63.

103. Castro C, Gourley M. Diagnostic testing and interpretation of tests for autoimmunity. *J Allergy Clin Immunol*. 2010;125(2 Suppl 2):S238-S247.

104. Fernandes RM, da Silva NP, Sato EI. Increased myeloperoxidase plasma levels in rheumatoid arthritis. *Rheumatol Int*. 2012;32:1605-1609.

105. Telles RW, Ferreira GA, da Silva NP, Sato EI. Increased plasma myeloperoxidase levels in systemic lupus erythematosus. *Rheumatol Int*. 2010;30:779-784.

106. Saygili EI, Aksoy N, Pehlivan M, et al. Enzyme levels and G-463A polymorphism of myeloperoxidase in chronic lymphocytic leukemia and multiple myeloma. *Leuk Lymphoma*. 2009;50:2030-2037.

107. Ip J, Uetrecht JP. In vitro and animal models of drug-induced blood dyscrasias. *Environ Toxicol Pharmacol*. 2006;21:135-140.

108. Tumova E, Sun W, Jones PH, et al. The impact of rapid weight loss on oxidative stress markers and the expression of the metabolic syndrome in obese individuals. *J Obes*. 2013;2013:729515.

109. Youssef H, Groussard C, Lemoine-Morel S, et al. Aerobic training suppresses exercise-induced lipid peroxidation and inflammation in overweight/obese adolescent girls. *Pediatr Exerc Sci*. 2015;27:67-76.

References

110. Lerman RH, Desai A, Lamb JJ, et al. A phytochemical-rich multivitamin-multimineral supplement is bioavailable and reduces serum oxidized low-density lipoprotein, myeloperoxidase, and plasminogen activator inhibitor-1 in a four-week pilot trial of healthy individuals. *Glob Adv Health Med*. 2014;3:34-39.

111. Kumar AP, Reynolds WF. Statins downregulate myeloperoxidase gene expression in macrophages. *Biochem Biophys Res Commun*. 2005;331:442-451.

112. de Lemos JA. Biomarkers in Heart Disease: Blackwell Publishing. 2008.

113. Michowitz Y, Kisil S, Guzner-Gur H, et al. Usefulness of serum myeloperoxidase in prediction of mortality in patients with severe heart failure. *Isr Med Assoc J*. 2008;10:884-888.

114. Gounis MJ, van der Marel K, Marosfoi M, et al. Imaging inflammation in cerebrovascular disease. *Stroke*. 2015;46:2991-2997.

115. Gumbiner B, Polonsky KS, Beltz WF, et al. Effects of aging on insulin secretion. *Diabetes*. 1989;38:1549-1556.

116. Modan M, Halkin H, Almog S, et al. Hyperinsulinemia. A link between hypertension obesity and glucose intolerance. *J Clin Invest*. 1985;75:809-817.

117. Seidell JC, Bjorntorp P, Sjostrom L, Kvist H, Sannerstedt R. Visceral fat accumulation in men is positively associated with insulin, glucose, and C-peptide levels, but negatively with testosterone levels. *Metabolism*. 1990;39:897-901.

118. Wang PT, Chiang IT, Lin CY, et al. Effect of a two-month detraining on glucose tolerance and insulin sensitivity in athletes—link to adrenal steroid hormones. *Chin J Physiol*. 2006;49:251-257.

119. Rostamkhani F, Zardooz H, Zahediasl S, Farrokhi B. Comparison of the effects of acute and chronic psychological stress on metabolic features in rats. *J Zhejiang Univ Sci B*. 2012;13:904-912.

120. Maturana MA, Spritzer PM. Association between hyperinsulinemia and endogenous androgen levels in peri- and postmenopausal women. *Metabolism*. 2002;51:238-243.

121. Dandona P, Aljada A, Bandyopadhyay A. Inflammation: The link between insulin resistance, obesity and diabetes. *Trends Immunol*. 2004;25:4-7.

122. Colao A, Pivonello R, Spiezia S, et al. Persistence of increased cardiovascular risk in patients with Cushing's disease after five years of successful cure. *J Clin Endocrinol Metab*. 1999;84:2664-2672.

123. Hramiak IM, Finegood DT, Adams PC. Factors affecting glucose tolerance in hereditary hemochromatosis. *Clin Invest Med*. 1997;20:110-118.

124. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28:412-419.

125. Takasu N, Yamada T, Miura H, et al. Rifampicin-induced early phase hyperglycemia in humans. *Am Rev Respir Dis*. 1982;125:23-27.

126. Wada T, Hori S, Sugiyama M, et al. Progesterone inhibits glucose uptake by affecting diverse steps of insulin signaling in 3T3-L1 adipocytes. *Am J Physiol Endocrinol Metab*. 2010;298:E881-888.

127. Lo JC, Kazemi MR, Hsue PY, et al. The relationship between nucleoside analogue treatment duration, insulin resistance, and fasting arterialized lactate level in patients with HIV infection. *Clin Infect Dis*. 2005;41:1335-1340.

128. Hoogwerf BJ, Goetz FC. Urinary C-peptide: A simple measure of integrated insulin production with emphasis on the effects of body size, diet, and corticosteroids. *J Clin Endocrinol Metab*. 1983;56:60-67.

129. Lautt WW. Postprandial insulin resistance as an early predictor of cardiovascular risk. *Ther Clin Risk Manag*. 2007;3:761-770.

130. Mozaffarian D, Appel LJ, Van Horn L. Components of a cardioprotective diet: New insights. *Circulation*. 2011;123:2870-2891.

131. Lattimer JM, Haub MD. Effects of dietary fiber and its components on metabolic health. *Nutrients*. 2010;2:1266-1289.

References

132. Gumbiner B, Polonsky KS, Beltz WF, et al. Effects of weight loss and reduced hyperglycemia on the kinetics of insulin secretion in obese non-insulin dependent diabetes mellitus. *J Clin Endocrinol Metab*. 1990;70:1594-1602.

133. Karacabey K. The effect of exercise on leptin, insulin, cortisol and lipid profiles in obese children. *J Int Med Res*. 2009;37:1472-1478.

134. Gibson A, Woodside JV, Young IS, et al. Alcohol increases homocysteine and reduces B vitamin concentration in healthy male volunteers—a randomized, crossover intervention study. *QJM*. 2008;101:881-887.

135. Verhoef P, Pasman WJ, Van Vliet T, Urgert R, Katan MB. Contribution of caffeine to the homocysteine-raising effect of coffee: A randomized controlled trial in humans. *Am J Clin Nutr*. 2002;76:1244-1248.

136. Jarvis CM, Hayman LL, Braun LT, et al. Cardiovascular risk factors and metabolic syndrome in alcohol- and nicotine-dependent men and women. *J Cardiovasc Nurs*. 2007;22:429-435.

137. Moll S, Varga EA. Homocysteine and MTHFR mutations. *Circulation*. 2015;132:e6-9.

138. van Guldener C. Why is homocysteine elevated in renal failure and what can be expected from homocysteine-lowering? *Nephrol Dial Transplant*. 2006;21:1161-1166.

139. Klee GG. Cobalamin and folate evaluation: Measurement of methylmalonic acid and homocysteine vs vitamin B(12) and folate. *Clin Chem*. 2000;46:1277-1283.

140. Acharya U, Gau JT, Horvath W, et al. Hemolysis and hyperhomocysteinemia caused by cobalamin deficiency: Three case reports and review of the literature. *J Hematol Oncol*. 2008;1:26.

141. Desouza C, Keebler M, McNamara DB, Fonseca V. Drugs affecting homocysteine metabolism: Impact on cardiovascular risk. *Drugs*. 2002;62:605-616.

142. Cook RC, Tupper JK, Parker S, et al. Effect of immunosuppressive therapy, serum creatinine, and time after transplant on plasma total homocysteine in patients following heart transplantation. *J Heart Lung Transplant*. 1999;18:420-424.

143. Jump DB, Depner CM, Tripathy S. Omega-3 fatty acid supplementation and cardiovascular disease. *J Lipid Res*. 2012;53:2525-2545.

144. Simopoulos AP. Dietary omega-3 fatty acid deficiency and high fructose intake in the development of metabolic syndrome, brain metabolic abnormalities, and non-alcoholic fatty liver disease. *Nutrients*. 2013;5:2901-2923.

145. Simopoulos AP. The importance of the ratio of omega-6/omega-3 essential fatty acids. *Biomed Pharmacother*. 2002;56:365-379.

146. Nair S. Vitamin d deficiency and liver disease. *Gastroenterol Hepatol (N Y)*. 2010;6:491-493.

147. Skversky AL, Kumar J, Abramowitz MK, Kaskel FJ, Melamed ML. Association of glucocorticoid use and low 25-hydroxyvitamin D levels: Results from the National Health and Nutrition Examination Survey (NHANES): 2001-2006. *J Clin Endocrinol Metab*. 2011;96:3838-3845.

148. Powrie R, Greene M, Camann W. de Swiet's Medical Disorders in Obstetric Practice. 5th ed: Wiley-Blackwell. 2010.

149. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. *Heart*. 2006;92:843-849.

150. Toda K, Sato Y, Hara T, et al. Correlates of NT-proBNP concentration in patients with essential hypertension in absence of congestive heart failure. *J Clin Lab Anal*. 2010;24:12-16.

151. Kim SW, Park SW, Lim SH, et al. Amount of left ventricular hypertrophy determines the plasma N-terminal pro-brain natriuretic peptide level in patients with hypertrophic cardiomyopathy and normal left ventricular ejection fraction. *Clin Cardiol*. 2006;29:155-160.

References

152. Ikonomidis I, Nikolaou M, Dimopoulou I, et al. Association of left ventricular diastolic dysfunction with elevated NT-pro-BNP in general intensive care unit patients with preserved ejection fraction: A complementary role of tissue Doppler imaging parameters and NT-pro-BNP levels for adverse outcome. *Shock*. 2010;33:141-148.

153. Mayr A, Mair J, Schocke M, et al. Predictive value of NT-pro BNP after acute myocardial infarction: Relation with acute and chronic infarct size and myocardial function. *Int J Cardiol*. 2011;147:118-123.

154. James SK, Lindahl B, Siegbahn A, et al. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: A Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy. *Circulation*. 2003;108:275-281.

155. Wu AH. Cardiac Markers. 2nd ed: Humana Press. 2003.

156. Hoiseth AD, Omland T, Hagve TA, Brekke PH, Soyseth V. NT-proBNP independently predicts long term mortality after acute exacerbation of COPD - a prospective cohort study. *Respir Res*. 2012;13:97.

157. Coutance G, Le Page O, Lo T, Hamon M. Prognostic value of brain natriuretic peptide in acute pulmonary embolism. *Crit Care*. 2008;12:R109.

158. Varpula M, Pulkki K, Karlsson S, et al. Predictive value of N-terminal pro-brain natriuretic peptide in severe sepsis and septic shock. *Crit Care Med*. 2007;35:1277-1283.

159. Magnusson M, Melander O, Israelsson B, et al. Elevated plasma levels of NT-proBNP in patients with type 2 diabetes without overt cardiovascular disease. *Diabetes Care*. 2004;27:1929-1935.

160. Vickery S, Price CP, John RI, et al. B-type natriuretic peptide (BNP) and amino-terminal proBNP in patients with CKD: relationship to renal function and left ventricular hypertrophy. *Am J Kidney Dis*. 2005;46: 610-620.

161. Scolletta S, Carlucci F, Biagioli B, et al. NT-proBNP changes, oxidative stress, and energy status of hypertrophic myocardium following ischemia/ reperfusion injury. *Biomed Pharmacother*. 2007;61: 160-166.

162. Cooper LB, Mentz RJ, Gallup D, et al. Serum bicarbonate in acute heart failure: Relationship to treatment strategies and clinical outcomes [published online ahead of print Jan 14, 2016]. *J Card Fail*. doi: 10.1016/j. cardfail.2016.01.007.

163. Gundogdu F, Bozkurt E, Kiziltunc A, et al. The effect of beta-blocker (carvedilol) therapy on N-terminal pro-brain natriuretic peptide levels and echocardiographic findings in patients with congestive heart failure. *Echocardiography*. 2007;24:113-117.

164. Squire I, Quinn P, Narayan H, et al. Identification of potential outcome benefit from ACE inhibition after acute coronary syndrome: a biomarker approach using N-terminal proBNP. *Heart*. 2010;96:831-837.

165. Ulimoen SR, Enger S, Pripp AH, et al. Calcium channel blockers improve exercise capacity and reduce N-terminal Pro-B-type natriuretic peptide levels compared with beta-blockers in patients with permanent atrial fibrillation. *Eur Heart J*. 2014;35: 517-524.

166. Sharif-Kashani B, Hamraghani A, Salamzadeh J, et al. The effect of amlodipine and sildenafil on the NT-proBNP level of patients with COPD-induced pulmonary hypertension. *Iran J Pharm Res*. 2014; 13(Suppl):161-168.

167. Wang RX, Guo T, Li XR. BNP/NT-proBNP and cardiac pacing: A review. *Pacing Clin Electrophysiol*. 2009;32:794-799.

168. Grewal J, McKelvie R, Lonn E, et al. BNP and NT-proBNP predict echocardiographic severity of diastolic dysfunction. *Eur J Heart Fail*. 2008;10:252-259.

169. Coglianese EE, Larson MG, Vasan RS, et al. Distribution and clinical correlates of the interleukin receptor family member soluble ST2 in the Framingham Heart Study. *Clin Chem*. 2012;58:1673-1681.

References

170. Ojji DB, Opie LH, Lecour S, et al. Relationship between left ventricular geometry and soluble ST2 in a cohort of hypertensive patients. *J Clin Hypertens (Greenwich)*. 2013;15:899-904.

171. Seliger SL, Ginsberg E, Gottdiener J, Christenson R, DeFilippi C. Soluble ST2 and galectin-3 are associated with subclinical diastolic dysfunction in older adults [abstract]. *J Am Coll Cardiol*. 2014;63(12_S):A769.

172. Kohli P, Bonaca MP, Kakkar R, et al. Role of ST2 in non-ST-elevation acute coronary syndrome in the MERLIN-TIMI 36 trial. *Clin Chem*. 2012;58:257-266.

173. Bartunek J, Delrue L, Van Durme F, et al. Nonmyocardial production of ST2 protein in human hypertrophy and failure is related to diastolic load. *J Am Coll Cardiol*. 2008;52:2166-2174.

174. Brown AM, Wu AH, Clopton P, Robey JL, Hollander JE. ST2 in emergency department chest pain patients with potential acute coronary syndromes. *Ann Emerg Med*. 2007;50:153-158, 158 e151.

175. Miller AM, Purves D, McConnachie A, et al. Soluble ST2 associates with diabetes but not established cardiovascular risk factors: a new inflammatory pathway of relevance to diabetes? *PLoS One*. 2012;7:e47830.

176. Bao YS, Na SP, Zhang P, et al. Characterization of interleukin-33 and soluble ST2 in serum and their association with disease severity in patients with chronic kidney disease. *J Clin Immunol*. 2012;32:587-594.

177. Daniels LB, Clopton P, Iqbal N, Tran K, Maisel AS. Association of ST2 levels with cardiac structure and function and mortality in outpatients. *Am Heart J*. 2010;160:721-728.

178. Gaggin H, Motiwala S, Bhardwaj A, et al. Cirulating concentration of soluble ST2 identify benefit of high dose beta blocker in chronic heart failure: results from the proBNP outpatient tailored chronic heart failure therapy (PROTECT) study [abstract]. *J Am Coll Cardiol*. 2013;61(10_S):E746.

179. Ky B, French B, McCloskey K, et al. High-sensitivity ST2 for prediction of adverse outcomes in chronic heart failure. *Circ Heart Fail*. 2011;4:180-187.

180. Breidthardt T, Balmelli C, Twerenbold R, et al. Heart failure therapy-induced early ST2 changes may offer long-term therapy guidance. *J Card Fail*. 2013;19: 821-828.

181. Wagner A, Köhm M, Nordin A, et al. Increased serum levels of the IL-33 neutralizing sST2 in limited cutaneous systemic sclerosis. *Scand J Immunol*. 2015;82:269-274.

182. Iqbal N, Wentworth B, Choudhary R, et al. Cardiac biomarkers: new tools for heart failure management. *Cardiovasc Diagn Ther*. 2012;2:147-164.

QuestDiagnostics.com

Quest, Quest Diagnostics, any associated logos, and all associated Quest Diagnostics registered or unregistered trademarks are the property of Quest Diagnostics.
All third party marks - ® and ™ - are the property of their respective owners. © 2015 Quest Diagnostics Incorporated. All rights reserved. MD83 4/2016