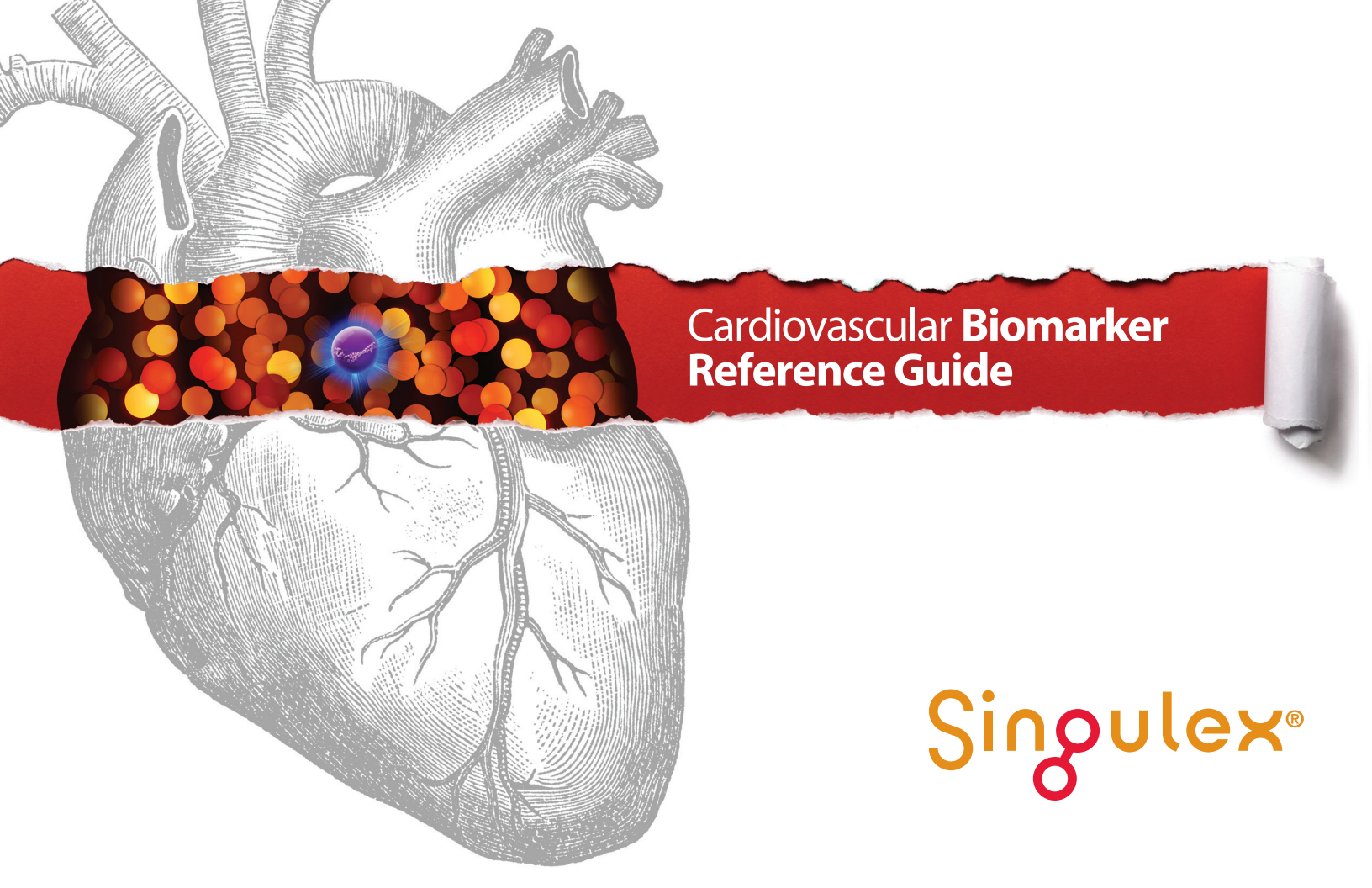

Cardiovascular **Biomarker Reference Guide**

Singulex®

Biomarker Reference Guide for Advanced Cardiovascular Testing

TABLE OF CONTENTS

97-0041-07

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
CARDIAC DYSFUNCTION MARKERS			
Elevated High Definition Cardiac Troponin (cTnI)	Cardiac troponin-I is a contractile protein found in cadiomyocytes. In the primary prevention setting, even slight elevations indicate risk for incident heart failure (HF), and cardiovascular (CV) death.[1,2,3] In secondary prevention patients, elevations are risk for future non-fatal myocardial infarction, HF, or CV death.[4,5] **8.5X increased risk of cardiovascular death in an apparently healthy population.[3]**	Elevations of cTnI are seen in cardiomyocyte injury or death, cardiac and vascular disease, and infection.[6] Causative factors for chronic cTnI elevations include hypertension (HTN), left ventricular hypertrophy and systolic dysfunction, type 2 diabetes, hypothyroidism, end-stage renal disease (ESRD), and cardiac inflammation.[7,8,9]	Evaluate baseline cardiac function to determine ischemic versus non-ischemic pathology.[9] Therapies that have been shown to improve cardiac function (e.g. decrease cardiac workload and/or blood pressure) include nitrates, calcium channel blockers, beta blockers, ACE inhibitors, angiotensin receptor blockers (ARBs), aspirin, and lipid-lowering agents.[9]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
CARDIAC DYSFUNCTION MARKERS			
Elevated N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP)	Peptide released in response to cardiac wall stress or stretch. Elevations in NT-proBNP may indicate risk for developing atherosclerosis, cardiac dysfunction and heart failure, and are independently associated with cardiac events in both primary and secondary prevention patient populations.[1,2,3] **Up to a 6X increased risk of mortality and cardiovascular hospitalization in an apparently healthy population;**[1] **In treated heart failure patients, increasing NT-proBNP concentrations over time, are associated with 2X increased occurrence of cardiovascular events, compared with stable or decreasing NT-proBNP concentrations below 1,000 pg/mL.**[4]	Elevated in medical conditions that impart stress on heart muscle or stretch on cardiac chambers, such as congestive heart failure, ischemic heart disease, atrial fibrillation and valvular disease.[1,2,5] Elevated levels are also seen in patients of advanced age, and in the presence of hyperthyroidism, sleep apnea, renal failure, cirrhosis of the liver and chronic lung disease.[5]	Evaluate underlying causes of cardiac dysfunction. Consider EKG, echocardiogram stress EKG, and angiogram. Once cause is determined, address underlying conditions. Both resistance training and aerobic exercise have been shown to reduce NT-proBNP.[5,6]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
VASCULAR INFLAMMATION AND DYSFUNCTION MARKERS			
Elevated High Definition Endothelin (ET)	Endothelin is a pro-inflammatory peptide, secreted by vascular endothelial cells and vascular smooth muscle cells, that regulates arterial vasomotor tone and thus blood pressure.[1] In addition, it is secreted by and exerts its effects on renal, pulmonary, cardiac, hepatic, and adipose cells.[1] ET promotes the development of atherosclerotic vascular disease by stimulating inflammatory cytokine release, platelet aggregation, cell adhesion molecule expression, and vascular smooth muscle cell proliferation.[2] **Elevated endothelin is a predictor of 10-year mortality in apparently healthy individuals.[3]**	The renal vasculature is much more sensitive to ET than other vascular beds, and in such, elevations are associated with an upregulation of the renin-angiotensin-aldosterone system (RAAS), hypertension, and renal dysfunction.[4,5] Excess endothelin production is also associated with chronic heart failure, cancer, obesity, insulin resistance, type 2 diabetes, and allograft rejection.[6,7,8,9]	Endothelin elevations reflect advanced disease and a worsening prognosis. Due to its multisystem effects, endothelin elevations should be considered in conjunction with other biomarker abnormalities to determine the cause or causes of the increased endothelin levels. In general, therapies for elevated endothelin levels are targeted at improving vasomotor tone and the endothelial health of the organ or organ systems affected. Multiple treatment options exist, including moderate exercise, dietary flavonoids, hormone replacement therapy, fenofibrate therapy in type 2 diabetics, and endothelin receptor blockers for pulmonary hypertension.[10,11,12,13]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
VASCULAR INFLAMMATION AND DYSFUNCTION MARKERS			
Elevated High Definition Interleukin-6 (IL-6)	Pro-inflammatory cytokine that may increase platelet aggregation and synthesis of C-reactive protein (CRP), and is associated with increased severity of cardiovascular disease (CVD).[1] IL-6 is involved in the pathogenesis of atherosclerosis, as elevated IL-6 concentrations are found in atheromatous arterial plaques.[2,3] There is a strong independent association between elevated IL-6 levels and the presence of clinical and subclinical CVD, including heart failure and mortality in the elderly.[4,6] **2X increased risk of cardiovascular (CV) event in women;[5]** **3X increased risk of CV death in men.[1]**	Elevations in IL-6 may be due to hyperlipidemia, cardiovascular disease, hypertension, heart failure, diabetes, sleep apnea, central adiposity, periodontal disease, smoking, active inflammation/ infection and autoimmune disease (e.g. rheumatoid arthritis, thyroid dysfunction).[3,4,7,8,9,10,11,12,13,14]	Lifestyle habits that have been shown to reduce IL-6 and other markers of inflammation include maintaining a healthy weight and dietary habits, a regular exercise routine that incorporates aerobic and strength training, adequate sleep, and stress management.[14,15]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
VASCULAR INFLAMMATION AND DYSFUNCTION MARKERS			
Elevated High Definition Interleukin-17A (IL-17A)	IL-17A is a T-cell derived cytokine that stimulates stromal cells and macrophages to secrete pro-inflammatory cytokines.[1] It is responsible for inducing and mediating immune and inflammatory responses.[2] Elevations are seen in cardiovascular disease and it has been shown that IL-17A plays a role in atherosclerosis and plaque instability.[2,3]	Elevations are associated with cardiovascular disease, periodontal disease, inflammatory bowel disease, systemic lupus erythematosus, osteoporosis, and other autoimmune diseases such as rheumatoid arthritis, and thyroid diseases.[4,5]	Lifestyle habits that decrease inflammation include maintaining a healthy weight and dietary habits, a regular exercise routine that incorporates aerobic and strength training, adequate sleep, and stress management.[6,7]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
VASCULAR INFLAMMATION AND DYSFUNCTION MARKERS			
Elevated High Definition Tumor Necrosis Factor-Alpha (TNF-α)	TNF-α is a pro-inflammatory cytokine secreted by macrophages. Elevated levels may contribute to insulin resistance and endothelial dysfunction.[1,2] There is a strong independent association between elevated TNF-α levels and the presence of clinical and subclinical cardiovascular disease, and heart failure (HF).[3,4,5] **2X increased risk of death in a HF population;[3]** **2X incident HF risk if level doubles over time.[4]**	Elevated TNF-α levels are often due to increased body fat, specifically visceral fat. Elevated levels may also be seen in dyslipidemia, atherosclerosis, HF, rheumatoid arthritis, Cushing's disease, kidney disease, insulin resistance, type 2 diabetes, obstructive sleep apnea, and in those who smoke.[2,6,7]	Reduction of body fat (particularly visceral fat) to optimal levels, strict weight management, regular exercise, smoking cessation, and healthy dietary habits have been shown to reduce circulating TNF-α levels.[2,6]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
VASCULAR INFLAMMATION AND DYSFUNCTION MARKERS			
Elevated Lipoprotein-associated Phospholipase A2 ($Lp\text{-}PLA_2$)	Vascular-specific inflammatory enzyme that is associated with the formation of rupture-prone plaque. $Lp\text{-}PLA_2$ has been identified as a strong and independent predictor of cardiovascular disease events and stroke in patients with and without clinically evident coronary artery disease, as well as in patients with low density lipoprotein cholesterol (LDL-C).[1] Studies have shown that increased levels of $Lp\text{-}PLA_2$ are associated with increased risk for cardiovascular outcomes, and that measuring $Lp\text{-}PLA_2$ improves risk stratification.[2,3] **Elevated levels of $Lp\text{-}PLA_2$ and high-sensitivity C-reactive protein (hs-CRP) together carry up to a 11X greater risk of ischemic stroke.[4]**	Primarily related to LDL, with increased $Lp\text{-}PLA_2$ enzyme activity present in small dense LDL (sdLDL). Values increase with plaque progression, particularly that of rupture-prone plaque.[1]	Medications that have been shown to reduce $Lp\text{-}PLA_2$ levels include niacin, statins, fibrates, ezetimibe, and fish oil.[5,6] Healthy dietary habits with reduced carbohydrate consumption, moderate alcohol intake, maintenace of a healthy weight and regular physical activity have also demonstrated an $Lp\text{-}PLA_2$ lowering effect. Smoking cessation should also be advised.[7,8]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
VASCULAR INFLAMMATION AND DYSFUNCTION MARKERS			
Elevated High Sensitivity C-Reactive Protein (hs-CRP)	Primarily an acute phase reactant produced in the liver that is associated with generalized inflammatory response and atherogenesis. Elevated concentrations are predictive of recurrent ischemia, myocardial infarction, and stroke.[1] **1.5-3.0 relative risk of a cardiovascular event when hs-CRP is elevated in apparently healthy men and women.[2,3]**	hs-CRP is released from activated leukocytes in response to infection or trauma, and from vascular smooth muscle cells in response to atherosclerosis. Elevations are also seen in overweight individuals, those with insulin resistance, type 2 diabetes, periodontal disease, sleep-disordered breathing, autoimmune disorders, women on birth control pills and smokers.[1,4,5,6]	Treat underlying causes of inflammation with lifestyle modification: weight loss, glucose and insulin control, and smoking cessation.[4,7] Medications to consider include those that target inflammation and/or the underlying causes of inflammation, such as aspirin, lipid-lowering and anti-diabetic agents.[8]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
VASCULAR INFLAMMATION AND DYSFUNCTION MARKERS			
Elevated Homocysteine	Homocysteine is the by-product of methionine metabolism, a process that requires vitamin B6, vitamin B9 (folic acid), and vitamin B12. Elevated levels are an independent cardiovascular risk factor, and may contribute to cardiovascular disease by damaging endothelial cells, altering platelet aggregation, inhibiting vasodilation, and increasing oxidation of low-density lipoprotein (LDL) cholesterol.[1,2] **20-50% increase in coronary heart disease risk for each 5 umol/L increase in homocysteine.[3]**	Elevations in homocysteine may be seen with deficiencies of folic acid, B6 and B12, renal failure, pernicious anemia, hypothyroidism, acute lymphoblastic leukemia, psoriasis, Alzheimer's disease, vascular dementia, cognitive impairment, coronary artery disease, stroke, pregnancy complications and bone loss.[2,4,5] Excess alcohol, caffeine, or nicotine intake as well as lack of exercise or a diet deficient in fruits and vegetables may contribute to increases in homocysteine.[2]	Treatment of homocysteine is controversial, but treatment of associated causes of endothelial dysfunction is prudent. Identify and treat underlying abnormality such as renal insufficiency, vitamin deficiency and pernicious anemia with folic acid (L-methylfolate), vitamin B12, and vitamin B6 supplements. Consider diet high in green, leafy vegetables.[2,6]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
DYSLIPIDEMIA MARKERS			
Elevated Low Density Lipoprotein Cholesterol (LDL-C)	LDL-C is a measure of the cholesterol content of LDL particles. Elevated LDL-C may promote atherosclerosis, particularly when the LDL is oxidized.[1]	Elevated LDL-C may be found in inactive and/or obese individuals, and in those with an excessive intake of saturated fats, trans-fats, and carbohydrates.[2] Elevations may also be due to genetic factors, advancing age and the presence of other diseases, including hypothyroidism.[2]	A diet emphasizing monounsaturated fats, omega-3 fatty acids and moderate total carbohydrate consumption, combined with a regimen of regular moderate-to-intense physical activity, has been shown to reduce LDL.[3,4] Lipid-lowering therapies include statins, fibrates, niacin, fish oil, and cholesterol-absorption inhibitors.[5]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
DYSLIPIDEMIA MARKERS			
Elevated Apolipoprotein B (Apo B)	Apo B is the primary protein component in very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), lipoprotein(a) [Lp(a)], chylomicrons and chylomicron remnants. Because it is associated with each particle in a 1:1 ratio, it is considered a direct measure of atherogenic lipoproteins.[1] Elevated apo B is associated with the presence of carotid atherosclerosis, cardiovascular events, the metabolic syndrome and type 2 diabetes.[1] **2-3X increased risk of incident cardiovascular disease.[2]**	Genetic tendency, obesity, high carbohydrate/fat diet, sedentary lifestyle, other illness (e.g., hypothyroidism, kidney disease, cystic fibrosis), certain medications (e.g., beta blockers, estrogen, androgen, and glucocorticoids).[3]	A cardioprotective diet emphasizing a reduction in saturated fats, trans fats and carbohydrates (especially in the presence of elevated triglycerides), weight loss as appropriate, and regular aerobic exercise has been shown to reduce apo B.[3] Lipid-lowering medications, including statins, niacin, fibrates, cholesterol absorption inhibitors, bile acid sequesterants, and omega-3 fatty acids, may also be beneficial.[3]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
DYSLIPIDEMIA MARKERS			
Elevated Small Dense LDL (sdLDL)	The atherogenicity of sdLDL is related to its extended time in circulation, ability to more easily enter the arterial wall, and susceptibility to oxidation. Elevated sdLDL is independently associated with incident cardiovascular disease, as well as disease progression and severity.[1] **Up to 3.6X increased risk of incident ischemic heart disease in men;**[2,3] **3X increased risk of myocardial infarction in men and women.**[4]	Elevations in sdLDL are often seen with insulin resistance, metabolic syndrome, elevated triglycerides, type 2 diabetes, fatty liver, lack of physical activity and a high carbohydrate diet.[5,6]	Medications that have demonstrated a shift in particle size from small dense to larger LDL particles include pioglitazone, fibrates and niacin. Statins will lower total particle number, but have been variable in their ability to shift LDL size.[7,8] Lifestyle strategies to reduce sdLDL include moderation of carbohydrate intake, emphasis on monounsaturated fats and oils, regular physical activity, and stress management.[6]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
DYSLIPIDEMIA MARKERS			
Low High Density Lipoprotein-cholesterol (HDL-C)	HDL, which contains about equal amounts lipid and protein, mediates reverse cholesterol transport, in which cholesterol from the peripheral tissues is returned to the liver for excretion as bile.[1] HDL is additionally cardioprotective, due to its anti-inflammatory, anti-oxidative, and anti-thrombotic characteristics.[1,2] Low HDL is an independent risk factor for cardiovascular disease, while high HDL has been shown to be protective against the development of cardiovascular disease.[1,2] **For every 10% reduction in HDL, risk for coronary artery disease increases 13%.[3]**	Low HDL may be due to genetics, excess weight, inactivity, smoking, high carbohydrate intake, elevated triglycerides, insulin resistance, type 2 diabetes, liver, renal or thyroid disease, and certain medications (e.g., beta blockers, anabolic steroids, and progestational agents).[1,4,5,6]	Dietary strategies to improve HDL include adequate intake of monounsaturated fats and omega-3 fatty acids, and moderate alcohol intake.[2] Treat insulin resistance and type 2 diabetes. Encourage weight loss, regular exercise, and smoking cessation when appropriate. Medications that have been shown to increase HDL include statins, niacin, omega-3 fatty acids, thiazolidinediones, and fibrates.[1,4,6,7,8]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
DYSLIPIDEMIA MARKERS			
Low Apolipoprotein A1 (Apo A1)	Apo A1 is the major protein of high-density lipoprotein (HDL). Apo A1 containing particles mediate reverse cholesterol transport, returning excess cholesterol from peripheral tissues to the liver. Low levels indicate suboptimal reverse cholesterol transport.[1]	Causes of low apo A1 include genetic tendency, high-fat/high-carbohydrate diet, visceral obesity, insulin resistance, type 2 diabetes, inactive lifestyle, smoking, familial hypoalphalipoproteinemia, and liver, renal and thyroid disease.[2,3,4,5,6,7,8]	Strategies to improve HDL include adequate intake of monounsaturated fats and omega-3 fatty acids, and moderate alcohol intake. Treat insulin resistance and type 2 diabetes; encourage weight loss, regular exercise, and smoking cessation when appropriate. Medications that have been shown to increase HDL include statins, niacin, omega-3 fatty acids, thiazolidinediones, and fibrates.[9,10]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
DYSLIPIDEMIA MARKERS			
Low High-Density Lipoprotein 2b (HDL-2b)	The cardioprotective function and inverse relationship with cardiovascular disease seen in HDL comes mostly from the subclass HDL-2b.[1] Low HDL-2b is associated with adverse cardiovascular events.[1,2] **1.84X increased risk of acute ischemic stroke with depressed HDL-2b.[2]**	Low HDL-2b may be due to genetic tendency, elevated triglycerides, a high-carbohydrate diet, visceral obesity, insulin resistance, type 2 diabetes, smoking, liver and thyroid disease, renal failure and certain medications.[3,4]	Lifestyle modifications, including a healthy, low-to-moderate carbohydrate diet, moderate alcohol consumption, regular physical activity, weight management and smoking cessation.[5]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
DYSLIPIDEMIA MARKERS			
Elevated Triglycerides (TG)	Triglycerides are an important biological marker of cardiovascular disease risk, due to their association with remnant particles (such as very low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL)) and impaired reverse cholesterol transport. Elevated triglycerides are an independent cardiovascular risk, especially in those at risk for or diagnosed with type 2 diabetes.[1] **Odds ratio 1.72 incident coronary heart disease.**[2]	Causes of elevated triglycerides include genetic tendency, obesity, insulin resistance, type 2 diabetes, high-carbohydrate and/or high-fat diet, excessive alcohol consumption, sedentary lifestyle, hypothyroidism, renal disease, and medications such as beta blockers, thiazide diuretics, glucocorticosteroids, anabolic steroids and some HIV medications.[1]	Dietary strategies to reduce triglycerides include adoption of a Mediterranean-style diet (increased intake of monounsaturated fats and omega-3 fatty acids, elimination of trans fats, reduction of total carbohydrate to less than 50% of calories, emphasis on low glycemic-load foods and reduction of fructose).[1] Decreases in alcohol intake, loss of 5-10% of body weight and regular exercise have also been shown to reduce triglycerides. Triglyceride lowering medications include fibrates, niacin, omega-3 fatty acids, statins, and ezetimibe.[1]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
DYSLIPIDEMIA MARKERS			
Elevated Lipoprotein(a) (Lp[a])	Elevated Lp(a) is an independent, genetically linked causal risk factor for cardiovascular disease.[1] Structurally similar to plasminogen, it competes for plasminogen receptor sites, which results in increased coagulability and reduced fibrinolysis.[2] Lp(a) is a stable risk factor for coronary artery disease, peripheral vascular disease, ischemic stroke and abdominal aortic aneuryism.[1] **Up to 2.5X increased risk of myocardial infarction with elevations in Lp(a).[3]**	Elevations in Lp(a) are largely due to genetic factors and, to a lesser extent, to diseases of the liver and kidney, hormonal factors such as thyroid hormones and steroids, age, and cigarette smoking.[2,4]	Because Lp(a) is very resistant to treatment, it is important to aggressively treat all associated atherogenic lipoprotein abnormalities.[2] Lifestyle changes have no impact on Lp(a) levels.[1,2,4] Niacin is the only effective Lp(a)-lowering treatment, but therapeutic response may be gradual.[2] Fenofibrates have a limited effect. Statins may elevate Lp(a).[4] Female hormones, including hormone replacement therapy, appears to lower Lp(a) but remains controversial.[2]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
CARDIOMETABOLIC MARKERS			
Elevated Parathyroid Hormone (PTH)	Primary hyperparathyroidism is the unregulated overproduction of PTH associated with abnormal parathyroid function, resulting in abnormal calcium homeostasis. In secondary hyperparathyroidism, chronic vitamin D deficiency leads to a decrease in blood calcium, which stimulates increased PTH secretion. Excessive PTH levels have a pro-inflammatory effect, stimulating the release of cytokines by vascular smooth muscle cells, promoting cardiomyocyte hypertrophy and vascular remodeling.[1,2] **2.5X increased risk of death, coronary artery disease/myocardial infarction, or stroke.[3]**	Causes of elevated PTH include renal disease, low vitamin D status, and adenomas.[3,4] PTH elevations have been associated with insulin resistance, type 2 diabetes, hypertension and vascular inflammation.[3,5]	Distinguish between primary and secondary hyperparathyroidism. In secondary hyperparathyroidism, vitamin D supplementation may be considered, as well as treatment for kidney disease.[6]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
CARDIOMETABOLIC MARKERS			
Insufficient Vitamin D	The vascular effects of vitamin D include modulation of smooth muscle cell proliferation, inhibition of cytokine release, suppression of renin gene expression, and regulation of thrombosis.[1,2] Low levels of vitamin D are associated with endothelial dysfunction, inflammation, hypertension and left ventricular hypertrophy, elevated parathyroid hormone (PTH), insulin resistance and type 2 diabetes, and risk for cardiovascular events.[1,2] **For every 10 ng/mL decline in vitamin D, there is a 9% greater relative hazard of mortality, and a 25% greater relative hazard of myocardial infarction.[3]**	Low levels of vitamin D are caused by inadequate dietary intake of vitamin D, low sun exposure, a dark-skinned complexion, kidney and liver disease, impaired absorption (such as in Crohn's disease, celiac disease, and cystic fibrosis), obesity, smoking, and medications such as anticonvulsants, glucocorticoids, and HIV medications.[2]	Adequate sun exposure, high vitamin D containing foods (such as wild-caught salmon or fortified milk), and vitamin D supplementation have all been shown to increase vitamin D levels.[2]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
CARDIOMETABOLIC MARKERS			
Abnormal Leptin	Leptin is an adipokine that helps regulate appetite by signaling satiety to receptors in the hypothalamus. It also has peripheral actions that stimulate vascular inflammation, oxidative stress, and vascular smooth muscle hypertrophy.[1] These actions may contribute to the pathogenesis of type 2 diabetes, hypertension, and cardiovascular disease (CVD).[1] **3X increased risk of CVD;**[2] **2X increased risk of stroke.**[3]	Elevations in leptin are associated with insulin resistance, increased risk for type 2 diabetes, CVD, and stroke.[1,4] Leptin deficiency and resistance are associated with metabolically-reduced energy expenditure, and may be affected by inadequate sleep duration.[1,5]	Weight loss via a low-glycemic index diet, regular exercise, short-term fasting, and adequate sleep have been shown to decrease leptin levels.[1,4,5,6]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
CARDIOMETABOLIC MARKERS			
Elevated Ferritin	Ferritin is an iron-containing protein produced in the liver. Elevated iron stores may enhance the oxidation of lipids through the production of free radicals via the Fenton Reaction.[1] Additionally, iron deposits in the liver, beta cells, and peripheral muscle tissue may contribute to insulin resistance by interfering with the ability of insulin to suppress hepatic glucose production, and disrupting glucose metabolism in muscle.[2] **3X increased risk of incident type 2 diabetes;[3]** **2X increased risk of incident atherosclerosis and/or progression of pre-existing atherosclerosis.[4]**	Elevated ferritin is associated with abdominal obesity, inflammation, hemochromatosis, hepatic disease, inappropriate iron therapy, and lead poisoning.[5,6,7]	As elevated serum ferritin is often associated with obesity and the metabolic syndrome, weight loss to maintain a body mass index (BMI) of <25, achieved through a cardioprotective diet and exercise is recommended. Limit or eliminate iron-rich foods and supplements, if warranted, to reduce iron intake; consider phlebotomy to reduce iron levels.[1,8]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
CARDIOMETABOLIC MARKERS			
Abnormal Adiponectin	Adiponectin is a protein hormone secreted primarily by adipocytes. It has anti-inflammatory, anti-antiatherogenic, and insulin-sensitizing effects on the heart and blood vessels. Serum levels of adiponectin are **reduced** in patients with type 2 diabetes, insulin resistance, obesity, and coronary artery disease.[1] Paradoxically, **elevated** levels may be seen in post acute coronary syndrome and chronic heart failure (CHF) patients, and are predictive for mortality;[2] **3.2X increased risk of mortality in CHF patients, if elevated; also associated with elevated N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP) levels.[3]**	**Low** levels of adiponectin may be caused by obesity (increased body fat, waist-to-hip ratio, and intra-abdominal fat) and are associated with insulin resistance.[1,4] This may be due to transcriptional suppression or decreased secretion caused by inflammatory cytokines, or genetic factors.[1] **Elevated** adiponectin may be seen in chronic inflammatory conditions such as heart failure, type 1 diabetes, systemic lupus erythematosus, rheumatoid arthritis, and irritable bowel syndrome.[1,5] It is also theorized to be the result of compensatory response to stress, aberrant expression of receptors, or adiponectin resistance.[6]	Drug therapies that have been shown to increase adiponectin include pioglitazone, fenofibrates, beta blockers, certain angiotension receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors.[1,6] Lifestyle modifications that have been shown to increase low adiponectin include a reduction in body weight of >10%, consumption of a Mediterranean-type diet, increased physical activity, and moderate alcohol intake.[6]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
CARDIOMETABOLIC MARKERS			
Abnormal Cortisol	Cortisol is a hormone responsible for regulating blood sugar, energy production, inflammation, and immune response. Cortisol levels may elevate in a response to physical, mental, or environmental stress.[1] Cortisol directly affects the heart and blood vessels, influencing vascular function, atherogenesis, and vascular remodeling.[1,2] Elevations may also affect glucose and lipid metabolism, as well as blood pressure.[1] **5X increased risk of cardiovascular death.[3]**	Cortisol elevations may occur in response to physiologic (sepsis, trauma) and psychological stress, and are seen in Cushing's Syndrome, type 2 diabetes, and obstructive sleep apnea (OSA).[1,4,5,6]	Weight loss achieved through improved dietary intake and regular exercise has been shown to reduce cortisol in overweight individuals.[7] Adequate sleep, stress management, and continuous positive airway pressure (CPAP), in those with OSA also reduce cortisol levels.[8,9,10,11,12]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
CARDIOMETABOLIC MARKERS			
Low Testosterone (male)	Low testosterone in men is frequently accompanied by adverse health consequences, including decreased muscle mass, increased abdominal fat, insulin resistance, dyslipidemia, and hypertension.[1,2] Studies in men have also shown that low testosterone levels are associated with increased risk of mortality, cardiovascular events and future type 2 diabetes.[3,4,5]	Low testosterone in males may be due to genetic predisposition, injury, infection, cancer treatment, pituitary disorders, obesity, and aging.[8]	Exercise and weight loss have been shown to increase testosterone in males, and supplementation may be considered for significant declines in testosterone.[9]
Elevated Testosterone (female)	Elevated testosterone levels in women are associated with adverse metabolic features, including insulin resistance and type 2 diabetes, abdominal obesity, dyslipidemia, chronic inflammation, cardiovascular disease, and polycystic ovary syndrome (PCOS).[6,7]	The most frequent cause of elevated testosterone levels in women is PCOS.[7]	For women with PCOS, treatments include lifestyle modification and hormone-influencing medications, blood sugar regulation agents including insulin and metformin, and hormone supplementation.[10]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
CARDIOMETABOLIC MARKERS			
Sex Hormone Binding Globulin (SHBG)	Testosterone and oestradiol circulate in the bloodstream, bound mostly to SHBG. SHBG is a testosterone transport protein that affects the circulating levels of bioavailable testosterone, and has emerged as one of many factors associated with type 2 diabetes, metabolic syndrome, sleep apnea, and cardiovascular disease (especially in women).[1,2,3,4,5,6,7,8] Total testosterone and SHBG tests are ordered to evaluate free androgens by calculating the Free Testosterone Index (FTI), a method of quantifying the amount of testosterone, not bound to SHBG.	SHBG concentrations are affected by a number of different diseases, high values being found in hyperthyroidism, hypogonadism, androgen insensitivity and hepatic cirrhosis in men. Low concentrations are found in myxoedema, hyperprolactinaemia and syndromes of excessive androgen activity. Concentrations are also affected by drugs such as androgens, oestrogens, thyroid hormones and anticonvulsants. Measurement of SHBG enables identification of those women with hirsutism who are more likely to respond to estrogen therapy.[1]	SHBG assessment is particularly useful when the total testosterone value is inconsistent with clinical signs, or when monitoring testosterone replacement therapy.[9] Exercise and weight loss has been shown to increase SHBG in men and women but long term impact needs further evaluation.[10,11]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
CARDIOMETABOLIC MARKERS			
Elevated Cystatin C	Cystatin C is a serum protein produced at a steady rate by all nucleated cells. It is cleared only via glomerular filtration and is much less influenced by age, gender, race and body mass than creatinine, making it an ideal marker for assessing kidney function.[1] Studies have shown cystatin C to be a marker for early detection of kidney disease, and a superior risk marker to creatinine-based eGFR for cardiovascular morbidity and mortality.[1,2] **Hazard ratio 3.87 for cardiovascular mortality in a secondary prevention population.[3]**	Increases in cystatin C are seen with impaired renal function.[3,4]	Therapies for elevated cystatin C should target improving or protecting kidney function; this includes blood pressure control, cardioprotective diet, regular exercise, maintaining a healthy body weight, and smoking cessation.[5]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
CARDIOMETABOLIC MARKERS			
Elevated Hemoglobin A1c (HbA1c)	HbA1c represents the average level of blood glucose over the previous 3 months, and demonstrates the degree of glucose control.[1] **A 1% increase in HbA1c concentrations is associated with a 20–30% increase in cardiovascular events and all-cause mortality.[2]**	HbA1c is elevated in any condition where glucose control may be compromised; this includes metabolic syndrome and insulin resistance, type 1 and type 2 diabetes, and undiagnosed diabetes. Levels may also be acutely elevated during periods of illness, or by some medications.[3]	Weight management, regular exercise, and a carbohydrate-controlled diet have all been shown to reduce elevated HbA1c.[4] Medications used in the management of diabetes include biguanides, sulfonylureas, meglitinides, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors, and insulin.[3,5]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
CARDIOMETABOLIC MARKERS			
Elevated Fasting Glucose	Elevated glucose is a risk for both microvascular and macrovascular disease, and contributes to endothelial dysfunction and cardiovascular disease (CVD). Elevated fasting levels above 100 mg/dL are associated with an increased risk of developing type 2 diabetes and future CVD.[1]	Risk factors for elevated glucose include genetics, physical inactivity, poor diet, overweight status, and polycystic ovary syndrome (PCOS) in women.[1]	Weight management, regular exercise, and a carbohydrate-controlled diet have all been shown to reduce elevated glucose. Medications used in the management of diabetes and to maintain glucose control include biguanides, sulfonylureas, meglitinides, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors, and insulin.[1,2]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
CARDIOMETABOLIC MARKERS			
Elevated Fasting Insulin	Elevated fasting insulin levels are associated with pre-diabetes, type 2 diabetes, and future cardiovascular events.[1] Generally, elevated insulin levels are detected before changes in glucose levels.[1] **Ischemic heart disease risk increases 11X when both insulin and Apolipoprotein B (Apo B) are elevated.[1]**	Elevations in fasting insulin are multi-factorial, and include excess weight, increases in visceral fat, metabolic syndrome, insulin resistance, stress, illness, type 2 diabetes, polycystic ovary syndrome (PCOS), and Cushing's disease. Some medications, including corticosteroids, levodopa, and oral contraceptives, may also increase fasting insulin levels.[2]	Weight management, regular exercise, and a carbohydrate-controlled diet have all been shown to reduce the risk of type 2 diabetes.[3] Medications used in the management of diabetes and to maintain glucose control include biguanides, sulfonylureas, meglitinides, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors, and insulin.[4]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
CARDIOMETABOLIC MARKERS			
Abnormal Thyroid Tests: Thyroid Stimulating Hormone (TSH)	Both hyperthyroidism and hypothyroidism produce changes in cardiac contractility, myocardial oxygen consumption, cardiac output, blood pressure, and vascular resistance.[1] Hyperthyroidism and hypothyroidism may lead to cardiac arrhythmias, and hypothyroidism may contribute to hypercholesterolemia.[1] **2.5X-3.3X increased risk of incident congestive heart failure if TSH >7.0 mUI/L and >10.0 mIU/L, respectively;**[2] **3X increased risk of cardiovascular-related hospital admissions in Hashimoto's patients >50 years of age.**[3]	TSH **increases** with primary hypothyroidism, Hashimoto's thyroiditis, TSH antibodies, thyrotoxicosis, thyrotropin-producing tumors, and hypothyroid patients not receiving sufficient replacement hormone. Increases may also occur during treatment with lithium or dopamine.[4,5] TSH **decreases** in hyperthyroidism, secondary pituitary or hypothalamic hypothyroidism, euthyroid sick patients, treated Graves' disease, and over-replacement of thyroid hormone in treatment of hypothyroidism. TSH may decrease when treated with T3, aspirin, corticosteroids, and heparin.[5,6]	Determine the underlying cause of hypo/hyperthyroidism. Thyroid hormone replacement may be considered for hypothyroidism.[4,6] Restoration of thyroid function often reverses the abnormal cardiovascular hemodynamics and lipids.[1]

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
CARDIOMETABOLIC MARKERS			
Abnormal Thyroid Tests: T3 Total	T3 concentration in serum is more a reflection of the functional state of the peripheral tissue than the secretory performance of the thyroid gland. T3 works directly on the cardiomyocyte and systemic vasculature, affecting systemic vasculature resistance, blood volume, cardiac contractility, heart rate, and cardiac output.[1] **~30% of patients with congestive heart failure have low T3;**[1] **Reduced T3 is a predictor of all-cause and cardiovascular mortality.**[1]	**Increased** T3 values are associated with hyperthyroidism, T3 thyrotoxicosis, daily dosage of 25 µg or more of T3, or 300 µg or more of T4, acute thyroiditis, and thyroxine binding globulin (TBG) elevation from any cause.[1,2] **Decreased** T3 levels are associated with hypothyroidism (however, some will have normal levels), starvation and state of nutrition, acute illness, TBG decrease from any cause, and drugs such as glucocorticoids, androgens, large doses of aspirin, propranolol, phenytoin, and amiodarone.[1,2]	Treat underlying cause and consider further diagnostic testing.

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
CARDIOMETABOLIC MARKERS			
Abnormal Thyroid Tests: Free T3	Free T3 is the physiologically active form of T3.	Free T3 is **elevated** in hyperthyroidism and **lowered** in hypothyroidism, starvation, and acute illness.[1,2,3]	Determine and treat underlying cause.

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
CARDIOMETABOLIC MARKERS			
Abnormal Thyroid Tests: T4 Total	The determination of T4, which measures both bound, unbound and free thyroxine, can be utilized for detection of hyperthyroidism, primary and secondary hypothyroidism, and monitoring of thyroid stimulating hormone (TSH) suppression therapy.[1,2,3]	T4 total **increases** in hyperthyroidism, acute thyroiditis (first stage), and liver disease (hepatitis).[1,2,3] T4 total **decreases** in hypothyroidism, hypoproteinemia and treatment with triiodothyronine.[1,2,3]	Treat underlying cause (e.g., hyperthyroidism, primary and secondary hyperthyroidism) and adjust TSH suppression therapy if indicated.

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
CARDIOMETABOLIC MARKERS			
Abnormal Thyroid Tests: Free T4	Lower free thyroxine (T4) levels have been associated with increased cardiovascular risk, insulin resistance, hyperlipidemia, and metabolic syndrome.[1,2,3]	**Increased** free T4 levels are associated with Graves' disease (hyperthyroidism), hypothyroidism treated with thyroxine or I-131, and euthyroid sick syndrome.[1,2,3] **Decreased** free T4 levels are associated with primary hypothyroidism, secondary hypothyroidism (pituitary), tertiary hypothyroidism (hypothalamic), and hypothyroidism treated with triiodothyronine.[1,2,3]	Determine and treat underlying cause.

DISORDER	PATHOLOGY	CAUSATIVE FACTORS	CONSIDERATIONS
CARDIOMETABOLIC MARKERS			
Elevated Uric Acid (UA)	Uric acid is a product of purine metabolism. Risk factors associated with elevated UA include hypertension, metabolic syndrome, obstructive sleep apnea, vascular disease, endothelial dysfunction, and stroke. UA is a negative prognostic marker for stroke, and is associated with inflammatory markers such C-reactive protein (CRP), Interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α).[1,2,3]	Possible causes of elevations of uric acid include hypoparathyroidism, gout, alcoholism, type 2 diabetes, and kidney disease.[3,4,5,6,7]	Treat underlying cause and consider using medications to lower the uric acid levels to prevent gouty attacks.[4]

References

cTnI

1. Sundstrom J, et al. *Eur Heart J.* 2009; 30: 773-781.
2. Wang T, et al. *Circulation.* 2012; 126: 1596-604.
3. Apple F, et al. *Clin Chem.* 2012; 58: 930-935.
4. Omland T, et al. *J Am Coll Cardiol.* 2013; 61: 1240-9.
5. White H, et al. *J Am Coll Cardiol.* 2014; 63: 345-54.
6. Kelley W, et al. *Clin Chem.* 2009; 55: 2098-112.
7. de Lemos J, et al. *JAMA.* 2013; 309: 2262-9.
8. Tsutamoto T, et al. *Am Heart J.* 2010; 159: 63-7.
9. Jeremias A, et al. *Ann Intern Med.* 2005; 142: 786-791.

NT-proBNP

1. Rosenberg J, et al. *Euro Heart J.* 2009; 30: 66-73.
2. Tsai S, et al. *Yonsei Med J.* 2010; 51: 151-163.
3. Don-Wauchope A, et al. *Heart Fail Rev.* 2014; 19: 541-51.
4. Gaggin H, et al. *Cong Heart Fail.* 2013; 19: 135-42.
5. Struthers A, et al. *Eur Heart J.* 2007; 28: 1678-82.
6. Smart N, et al. *Eur J Prev Cardiol.* 2012; 19: 428-35.

Endothelin

1. Bohm F, et al. *Cardiovasc. Res.* 2007; 76: 8-18.
2. Weil B, et al. *Can J Cardiol.* 2012; 28: 347-53.
3. Yokoi K, et al. *Circ J.* 2012; 76: 2779-2784.
4. Pernow J, et al. *J of Cardiovas Pharmacol.* 1989; 13: Suppl 5, S205-206.
5. Denton K, et al. *Clin Exp Pharm & Phys.* 1990; 17: 861-872.
6. Rosano L, et al. *Nat Rev Cancer.* 2013; 13: 637-651.
7. Lteif A, et al. *Diabetes.* 2007; 56: 728-734.
8. Raina A, et al. *Transplantation.* 2012; 94: 885-893.
9. Moorehouse R, et al. *Curr Hypertens. Rep.* 2013; 15: 489-96.
10. Loke W, et al. *Am J Clin Nutr.* 2008; 88: 1018-25.
11. Saitta A, et al. *Arterioscler Thromb Vasc Biol.* 2001; 21: 1512-9.
12. Glineur C, et al. *Arterioscler Thromb Vasc Biol.* 2013; 33: 621-8.
13. Rubin L, et al. *N Engl J Med.* 2002; 346: 896-903.

IL-6

1. Luc G, et al. *Arterioscler Thromb Vasc Biol.* 2003; 23: 1255-1261.
2. Raaz-Schrauder D, et al. *Cytokine.* 2012; 57: 251-257.
3. Fisman E, et al. *Adv Cardiol.* 2008; 45: 44-64.
4. Kalogeropoulos A, et al. *J Am Coll Cardiol.* 2010; 55: 2129-37.
5. Arant C, et al. *Clin. Cardiol.* 2009; 32: 244-250.
6. Harris T, et al. *Am J Med.* 1999; 106: 506-512.
7. Spranger J, et al. *Diabetes.* 2003; 52: 812-817.
8. Geivelis M, et al. *J Periodontol.* 1993; 64: 980-983.
9. Bartold P, et al. *J Periodontal Res.* 1991; 26: 339-45.
10. Kuschner W, et al. *Eur Respir J.* 1996; 9: 1989-1994.
11. Yudkin J, et al. *Atherosclerosis.* 2000; 148: 209-214.
12. Ishihara K, et al. *Cytokine Growth Factor Rev.* 2002; 13: 357-68.
13. Kalogeropoulos A, et al. *Heart Fail Clin.* 2012; 8: 113-123.
14. Hong S, et al. *Brain Behav Immun.* 2005; 19: 165-72.
15. Giugliano D, et al. *J Am Coll Cardiol.* 2006; 48: 677- 85.

IL-17A

1. Fisman E, et al. *Adv Cardiol.* 2008; 45: 44-64.
2. Erbel C, et al. *Basic Res Cardiol.* 2011; 106: 125-134.
3. Zhu F, et al. *Clin Immunol.* 2011; 141: 152-60.
4. Ding H, et al. *Mol Biol Rep.* 2012; 39: 7473-7478.
5. Kramer J. *J Periodontol.* 2007; 78: 1083-1093.
6. Giugliano D, et al. *J Am Coll Cardiol.* 2006; 48: 677-85.
7. Myles I. *Nutrition Journal.* 2014; 13: 61.

TNF-α

1. Winkler G, et al. *Diabet Med.* 1999; 16: 207-11.
2. Zhang H, et al. *Clin Sci.* 2009; 116: 219-230.
3. Dunlay S, et al. *Circulation.* 2008; 118: 625-631.
4. Kalogeropoulos A, et al. *J Am Coll Cardiol.* 2010; 55: 2129-37.
5. Cesari M, et al. *Am J Cardiol.* 2003; 92: 522-8.
6. Kalogeropoulos A, et al. *Heart Fail Clin.* 2012; 8: 113-123.
7. Hansson G. *NEJM.* 2005; 352: 1685-95.

Lp-PLA$_2$

1. Ballantyne C, et al. *Circulation.* 2004; 109: 837-42.
2. Anderson J, et al. *Am J Cardiol.* 2008; 101: 23F–33F.
3. Nambi V, et al. *Stroke.* 2009; 40: 376-381.
4. Ballantyne C, et al. *Arch Int Med.* 2005; 165: 2479-2484.
5. Kuvin J, et al. *Am J Cardiol.* 2006; 98: 743-5.
6. Saougos V, et al. *Arterioscler Thromb Vasc Biol.* 2007; 27: 2236-43.
7. Reddy K, et al. *Prev Cardiol.* 2010; 13: 130-4.
8. Hatoum I, et al. *Am J Clin Nutr.* 2010; 91: 786-93.

hs-CRP

1. The Emerging Risk Factors Collaboration. *Lancet.* 2010; 375: 132-40.
2. Ridker P, et al. *N Engl J Med.* 1997; 336: 973-9.
3. Ridker P, et al. *N Engl J Med.* 2000; 342: 836-43.
4. Nicklas J, et al. *Obesity.* 2013; 21: 681-9.
5. Su M, et al. *Eur Arch Otorhinolaryngol.* 2013; 270: 749-754.
6. Bansal T, et al. *J Clin Diagn Res.* 2014; 8: ZE21-4.
7. Pfutzner A, et al. *Diabetes Technol Ther.* 2006; 8: 28-36.
8. Prasad K. *Cardiovasc Drug Rev.* 2006; 24: 33-50.

Homocysteine

1. Lipi G, et al. *Clin Chem Lab.* 2012; 50: 2075-2080.
2. Varga E, et al. *Circulation.* 2005; 111: e289-e293.
3. Humphrey L, et al. *Mayo Clin Proc.* 2008; 83: 1203-12.
4. Siri, P. et al. *Journal of the American College of Nutrition.* 1998; Vol. 17, No. 5, 435-441.
5. Mahalle N, et al. *Journal of Cardiology.* 2013; 61: 289-294.
6. Brattstrom L, et al. *Am J Clin Nutr.* 2000; 72: 315-23.

References

LDL-C

1. Medline Plus. "What is Cholesterol." Available at http://www.nhlbi.nih.gov/health/health-topics/topics/hbc. Accessibility verified October 23, 2014.
2. Medline Plus. "What is Cholesterol." Available at http://www.nhlbi.nih.gov/health/health-topics/topics/hbc/causes.html. Accessibility verified October 23, 2014.
3. Siri P, et al. *Curr Atheroscler Rep.* 2005; 7: 455-9.
4. Eckel R, et al. *J Am Coll Cardiol.* 2014; 63: 2960-2984.
5. http://www.nhlbi.nih.gov/health/health-topics/topics/hbc/treatment.html. Accessibility verified October 23, 2014.

Apo B

1. Cole T, et al. *Clinical Chemistry.* 2013; 59: 752-770.
2. Contois J, et al. *Clin Chem.* 2009; 55: 407-419.
3. Sniderman A, et al. *Nat Rev Endocrinol.* 2010; 6: 335–346.

sdLDL

1. Kwon S, et al. *Yonsei Med J.* 2006; 47: 405-14.
2. Lamarche B, et al. *Circulation.* 1997; 95: 69-75.
3. St-Pierre A, et al. *Arterioscler Thromb Vasc Biol.* 2005; 25: 553-559.
4. Austin M, et al. *JAMA.* 1988; 260: 1917-21.
5. Kim D, et al. *Diabetol Metab Syndr.* 2010; 2: 18.
6. Siri P, et al. *Curr Atheroscler Rep.* 2005; 7: 455-459.
7. Backes J, et al. *Ann Pharmacother.* 2005; 39: 523-6.
8. Emadzadeh M, et al. *Angiology.* 2013; 64: 216-22.

HDL-C

1. Assman G, Gotto A. *Circulation.* 2004; 109: III8-14.
2. Toth P. *Circulation.* 2004; 109: 1809-1812.
3. Despres J, et al. *Atherosclerosis.* 2000; 153: 263-272.
4. Siri P, et al. *Curr Atheroscler Rep.* 2005; 7: 455-459.
5. Kaysen G. *J Ren Nutr.* 2009; 19: 73-7.
6. National Cholesterol Education Program. "Third report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults." *Circulation.* 2002 Dec 17; 106(25): 3143-421.
7. Singh I, et al. *JAMA.* 2007; 298: 786-98.
8. Pirillo A, Catapano A. *Atheroscler Suppl.* 2013; 14: 237-42.

Apo A1

1. Barter P, Rye K. *J Intern Med.* 2006; 259: 447-54.
2. Goek O. et al. *Nephrol Dial Transplant.* 2012; 27: 2839-2847.
3. Assman G, Gotto A. *Circulation.* 2004; 109: III8-14.
4. Kim D, et al. *Diabetol Metab Syndr.* 2010; 2: 18.
5. Siri P, et al. *Curr Atheroscler Rep.* 2005; 7: 455-459.
6. Kaysen G. *J Ren Nutr.* 2009; 19: 73-7.
7. National Cholesterol Education Program. "Third report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults." *Circulation.* 2002 Dec 17; 106(25): 3143-421.
8. Lab Tests Online. "Apo A-1." Available at http://labtestsonline.org/understanding/analytes/apoa/tab/test. Accessibility verified October 14, 2014.
9. Singh I, et al. *JAMA.* 2007; 298: 786-98.
10. Pirillo A, Catapano A. *Atheroscler Suppl.* 2013; 14: 237-42.

HDL-2b

1. Zeljkovic A, et al. *Atherosclerosis.* 2010; 210: 548-54.
2. Jia L, et al. *Int J Cardiol.* 2007; 120: 331-7.
3. Tilly-Kiesi M, et al. *J Lipid Res.* 1996; 37: 1569-157.
4. Williams PT, et al. *Metabolism.* 1994; 43: 655-663.

Triglycerides

1. Miller M, et al. *Circulation.* 2011; 123: 2292-333.
2. Sarwar N, et al. *Circulation.* 2007; 115: 450-458.

Lp(a)

1. Jones G, et al. *Clin Chem.* 2007; 53: 679-685.
2. Kamstrup P, et al. *J Am Coll Cardiol.* 2013; 61: 1146-1156.
3. Jacobson T. *Mayo Clin Proc.* 2013; 88: 1294-1311.
4. Siekmeier R, et al. *The Open Clinical Chemistry Journal.* 2010; 3: 72-89.

PTH

1. Hagstrom E, et al. *Circulation.* 2009; 119: 2765-2771.
2. Deo R, et al. *Hypertension.* 2011; 58: 1021-1028.
3. Anderson J, et al. *Am Heart J.* 2011; 162: 331-339.e2.
4. Garcia de la Torre N, et al. *Endocr Relat Cancer.* 2003; 10: 309-22.
5. Cheng S, et al. *Mediators Inflamm.* 2014; 2014: 709024.
6. de Francisco A, et al. *NDT Plus.* 2008; 1 (suppl 1): i24-i28.

Vitamin D

1. Wang T, et al. *Circulation.* 2008; 117: 503-511.
2. Lee J, et al. *J Am Coll Cardiol.* 2008; 52: 1949-56.
3. Kestenbaum B, et al. *J Am Coll Cardiol.* 2011; 58: 1433-41.

Leptin

1. Koh K, et al. *Circulation.* 2008; 117: 3238-3249.
2. van der Vleuten G, et al. *Atherosclerosis.* 2005; 183: 355-360.
3. Wannamethee S, et al. *Stroke.* 2013; 44: 3-8.
4. Hajer G, et al. *Euro Heart J.* 2008; 29: 2959-2971.
5. Spiegel K, et al. *J Clin Endocrinol Metab.* 2004; 89: 5762-71.
6. Chan J, et al. *J Clin Invest.* 2003; 111: 1409-1421.

Ferritin

1. Basuli D, et al. *Front Pharmacol.* 2014; 5: 117.
2. Fernandez-Real J, et al. *Diabetes Care.* 1998; 21: 62-68.
3. Forouhi N, et al. *Diabetologia.* 2007; 50: 949-956.
4. Kiechl S, et al. *Circulation.* 1997; 96: 3300-3307.
5. Syrovatka P, et al. *Eur J Clin Invest.* 2011; 41: 846-853.
6. Iwasaki T, et al. *Diabetes Care.* 2005; 28: 2486-2491.
7. Fischbach F and Dunning M. *Nurses' Quick Reference to Common Laboratory & Diagnostic Tests,* 4th ed. (PA : Lippincott Williams & Wilkins, 2006).
8. Wrede C, et al. *Eur J Endocrinol.* 2006; 154: 333-40.

Adiponectin

1. Szmitko P, et al. *Am J Physiol Heart Circ Physiol.* 2007; 292: H1655-H1663.
2. Wilson S, et al. *Am Heart J.* 2011; 161: 1147-1155.
3. Kistorp C, et al. *Circulation.* 2005; 112: 1756-1762.
4. Kadowaki T, et al. *J Clin Invest.* 2006; 116: 1784-92.
5. Aprahamian T, et al. *Int J Inflam.* 2011; 2011: 376909.
6. Athyros V, et al. *Current Drug Targets.* 2010; 11: 122-135.

References

Cortisol

1. Walker B. *Eur J Endocrinol.* 2007; 157: 545-559.
2. Hamer M, et al. *PLoS One.* 2012; 7: e31356.
3. Vogelzangs N, et al. *J Clin Endocrinol Metab.* 2010; 95: 4959-4964.
4. Chiodini I, et al. *Eur J Endocrinol.* 2005; 153: 837-844.
5. Whitworth J, et al. *Vasc Health Risk Manag.* 2005; 1: 291-299.
6. Balbo M, et al. *Int J Endocrinol.* 2010; 2010: 759234.
7. Johnstone A, et al. *Eur J Endocrinol.* 2004; 150: 185-194.
8. Leproult R, et al. *Sleep.* 1997; 20: 865-70.
9. Turakitwanakan W, et al. *J Med Assoc Thai.* 2013; 96: S90-5.
10. Chan E, et al. *Complement Ther Clin Pract.* 2013; 19: 179-83.
11. Cox T, et al. *Health Educ Behav.* 2013; 40: 78-87.
12. Schmoller A, et al. *Metabolism.* 2009; 58: 848-53.

Testosterone

1. Laaksonen D, et al. *Eur J Endocrinol.* 2003; 149: 601-608.
2. Salenave S, et al. *Ann Endocrinol (Paris).* 2012; 73: 141-6.
3. Araujo A, et al. *J Clin Endocrin Metab.* 2011; 96: 3007-3019.
4. Khaw K, et al. *Circulation.* 2007; 116: 2694-2701.
5. Allan C, et al. *Asian J Andrology.* 2014; 16: 232-238.
6. Ding E, et al. *JAMA.* 2006; 295: 1288-1299.
7. Patel S, et al. *J Clin EndocrinMetab.* 2009; 94: 4776-4784.
8. Mayo Clinic. "Male hypogonadism." Available at http://www.mayoclinic.org/diseases-conditions/male-hypogonadism/basics/causes/con-20014235. Accessibility verified October 16, 2014.
9. Khoo J, et al. *J Sex Med.* 2013; 10: 1823-32.
10. Cobin R, et al. *Endocrine Practice.* 2005; 11:125-34.

SHBG

1. Selby, C. *Ann Clin Biochem.* 1990; 27 (Pt 6): 532-41.
2. Li C, et al. *Diabetes Care.* 2010; 33: 1618-24.
3. Maggio M, et al. *J Clin Endocrinol Metab.* 2011; 96: 1053-9.
4. Grunstein R, et al. *J Clin Endocrinol Metab.* 1989; 68: 352-8.
5. Michos E, et al. *Atherosclerosis.* 2008; 200: 432-8.
6. Joffe H, et al. *Ann Epidemiol.* 2006; 16: 105-12.
7. Le T, et al. *Trends in Endocrinology and Metabolism: TEM.* 2012; 23: 32-40.
8. El Khoudary S, et al. *Atherosclerosis.* 2012; 225: 180-186.
9. Lab Tests Online. "SHBG." Available at: http://labtestsonline.org/understanding/analytes/shbg/tab/test/. Accessibility verified November 5, 2014.
10. Stolzenberg-Solomon R, et al. *Breast Cancer Research.* 2012; 14: R141.
11. Roberts C, et al. *Metabolism: Clinical and Experimental.* 2013; 62: 725-733.

Cystatin C

1. Koenig W, et al. *Clinical Chemistry.* 2005; 51:321-327.
2. Svensson-Färbom P, et al. *J Intern Med.* 2014; 275: 506-21.
3. Keller T, et al. *Eur Heart J.* 2009; 30: 314-320.
4. Lab Tests Online. "Cystatin C." Available at: http://labtestsonline.org/understanding/analytes/shbg/tab/test/. Accessibility verified November 5, 2014.
5. National Kidney Foundation. "KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease." Available at: http://www2.kidney.org/professionals/KDOQI/guidelines_bp/. Accessibility verified December 2, 2014.

HbA1c

1. MedlinePlus. "A1c Test." Available at http://www.nlm.nih.gov/medlineplus/ency/article/003640.htm. Accessibility verified October 23, 2014.
2. Khaw K, et al. *Ann Intern Med.* 2004; 141: 413-420.
3. Benhalima K, et al. *J Diabetes Complications.* 2011; 25: 202-7.
4. Knowler W, et al. *N Engl J Med.* 2002; 346: 393-403.
5. Joslin Diabetes Center. "Oral Diabetes Medications Summary Chart." Available at http://www.joslin.org/info/oral_diabetes_medications_summary_chart.html. Accessibility verified October 23, 2014.

Glucose

1. American Diabetes Association. *Diabetes Care.* 2014; 37: Supplement 1 S14-S80.
2. Joslin Diabetes Center. "Oral Diabetes Medications Summary Chart." Available at http://www.joslin.org/info/oral_diabetes_medications_summary_chart.html. Accessibility verified October 23, 2014.

Insulin

1. Despres J, et al. *NEJM.* 1196; 334: 952-957.
2. Lab Tests Online. "Insulin." Available at http://labtestsonline.org/understanding/analytes/insulin/tab/test/. Accessibility verified July 29, 2014.
3. Knowler W, et al. *N Engl J Med.* 2002; 346: 393-403.
4. Joslin Diabetes Center. "Oral Diabetes Medications Summary Chart." Available at http://www.joslin.org/info/oral_diabetes_medications_summary_chart.html. Accessibility verified October 23, 2014.

TSH

1. Klein I, et al. *Circulation.* 2007; 116: 1725-1735.
2. Rodondi N, et al. *Arch Intern Med.* 2005; 165: 2460-2466.
3. Nyirenda M, et al. *Thyroid.* 2005; 15: 718-24.
4. Garber J, et al. *Endocr Pract.* 2012; 18: 988-1028.
5. Fischbach F and Dunning M. *Nurses' Quick Reference to Common Laboratory & Diagnostic Tests,* 4th ed. (PA : Lippincott Williams & Wilkins, 2006).
6. Bahn R, et al. *Endocr Pract.* 2011; 17: 456-520.

T3 Total

1. Klein I, et al. *Circulation.* 2007; 116: 1725-1735.
2. Fischbach F and Dunning M. *Nurses' Quick Reference to Common Laboratory & Diagnostic Tests,* 4th ed. (PA : Lippincott Williams & Wilkins, 2006).

References

Free T3

1. Fischbach F and Dunning M. *Nurses' Quick Reference to Common Laboratory & Diagnostic Tests,* 4th ed. (PA : Lippincott Williams & Wilkins, 2006).
2. Bahn R, et al. *Endocr Pract.* 2011; 17: 456-520.
3. Skugor M and Wilder J. *The Cleveland Clinic Guide to Thyroid Disorders* (New York: Kaplan Pub., 2009).

T4 Total

1. Klein I, et al. *Circulation.* 2007; 116: 1725-1735.
2. Fischbach F and Dunning M. *Nurses' Quick Reference to Common Laboratory & Diagnostic Tests,* 4th ed. (PA : Lippincott Williams & Wilkins, 2006).
3. Duntas L, et al. *Thyroid.* 2007; 17: 1075-84.

Free T4

1. Klein I, et al. *Circulation.* 2007; 116: 1725-1735.
2. Fischbach F and Dunning M. *Nurses' Quick Reference to Common Laboratory & Diagnostic Tests,* 4th ed. (PA : Lippincott Williams & Wilkins, 2006).
3. Duntas L, et al. *Thyroid.* 2007; 17: 1075-84.

Uric Acid

1. Ruggiero C, et al. *Eur Heart J.* 2006; 27: 1174–1181.
2. Fang J, Alderman M. *JAMA.* 2000; 283: 2404-2410.
3. Feig D, et al. *N Engl J Med.* 2008; 359: 1811-21.
4. Roddy E. *BMJ.* 2013; 347: f5648.
5. Krishnan E, et al. *Ann Intern Med.* 2012; 157: 233-41.
6. Medscape. "Uric Acid." Available at: http://emedicine.medscape.com/ article/2088516-overview#aw2aab6b3. Accessibility verified November 3, 2014.
7. Medline Plus. "Uric Acid- blood." Available at: http://www.nlm.nih.gov/medlineplus/ency/article/003476.htm. Accessibility verified November 3, 2014.

Singulex®

Power to Prevent, **One Molecule at a Time.**