

Evolving Treatments for Cardiometabolic Syndrome

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Summary

Forty-seven million adult Americans are estimated to have cardiometabolic syndrome. This syndrome greatly increases risk of developing both type 2 diabetes and cardiovascular disease. Current management typically treats each element of the constellation of cardiometabolic risk factors individually. Treatment of this syndrome is evolving to consideration of the patient as a whole and the probable cause—insulin resistance secondary to excess visceral fat.

Key Points

- The number of Americans who have metabolic syndrome is much larger than the number who have diabetes.
- Cardiometabolic syndrome increases risk of developing type 2 diabetes.
- Cardiometabolic syndrome increases cardiovascular morbidity and mortality by three- to fourfold.
- Cardiovascular risks factors in the patient with cardiometabolic syndrome should be addressed as a whole entity rather than individually.

AS DEFINED BY THE American Diabetes Association, a normal fasting glucose is between 70 and 100 mg/dL.¹ A fasting glucose between 100 and 126 mg/dl is impaired fasting glucose, or pre-diabetes.¹ Forty million Americans have pre-diabetes. A fasting glucose greater than 126 or a random glucose of greater than 200 mg/dl on two separate occasions is diagnostic for diabetes.¹ About 18.2 million people in the U.S. have diabetes of which 90 to 95 percent is type 2, and the other 5 to 10 percent is type 1. People in the U.S. are converting from pre-diabetes to diabetes at the rate of 11 percent a year. The fastest growing population of people with diabetes in this country are children. The prevalence of type 2 diabetes in children has gone up approximately a thousandfold over the last 10 years.

One study demonstrating the important relationship between glucose and health found that when hemoglobin A_{1c} (A1C) increases above 5 percent, the risk for cardiovascular disease increases.² If the risk of macrovascular disease really begins when A1C increases above 5 percent, then control of cardiovascular risk factors in the past has not been aggressive enough. Current treatment guidelines for diabetes suggest a target A1C of less than 7 percent, which may not be fully minimizing risk.³ Over the last two decades, while deaths secondary to cancer, stroke, and cardiovascular

disease in the U.S. have gone down, deaths in patients with diabetes have increased.⁴

Cardiometabolic Risk Factors

Cardiometabolic syndrome is a clustering of modifiable risk factors predisposing individuals to cardiovascular and metabolic disease (type 2 diabetes). These risk factors include elevated blood pressure, elevated triglycerides, low high-density lipoprotein cholesterol (HDL-C), abdominal obesity, inflammation, insulin resistance, and elevated blood glucose. The criteria for identifying a patient with metabolic syndrome are given in Exhibit 1.^{5,6} Although there is controversy about cardiometabolic syndrome, most clinicians find it a useful designation for identifying patients at high risk of cardiovascular disease and type 2 diabetes.^{7,8} It is important to look at the individual with high blood pressure, dyslipidemia, and raised glucose as an entity, as opposed to focusing on blood pressure one year at an annual visit, blood glucose the next year, and lipids the year after that.

Cardiometabolic syndrome increases cardiovascular morbidity, and also mortality, by three- to fourfold (see Exhibit 2).⁹ Approximately 47 million adult Americans have metabolic syndrome. As the U.S.

population continues to gain weight, the number of people estimated to have metabolic syndrome is increasing every year.

The root cause of metabolic syndrome is insulin resistance, which is most likely secondary to excess abdominal or visceral adipose tissue. Excess visceral fat is accumulation of visceral adipose tissue defined as intra-abdominal fat bounded by parietal peritoneum or transversalis fascia. Subcutaneous fat is the other major fat in the body. This is superficial to the abdominal and back muscles. Visceral fat is more metabolically active than subcutaneous fat, has greater endocrine activity, and causes greater adverse effect on metabolism and cardiovascular risk.¹⁰ Visceral fat has a greater ability to release cytokines and adipokines than does subcutaneous fat.

Fat in the liver and muscle can also cause metabolic dysfunction. The breakdown of stored triglycerides into its constituent, fatty acids of glycerol leads to insulin resistance. Increased free fatty acids reduce insulin signaling, signal transduction in muscle, and change the metabolism of glucose. Free fatty acids are the cause of metabolic insulin-resistant muscle, which empowers fat cells to have major effects on muscle.

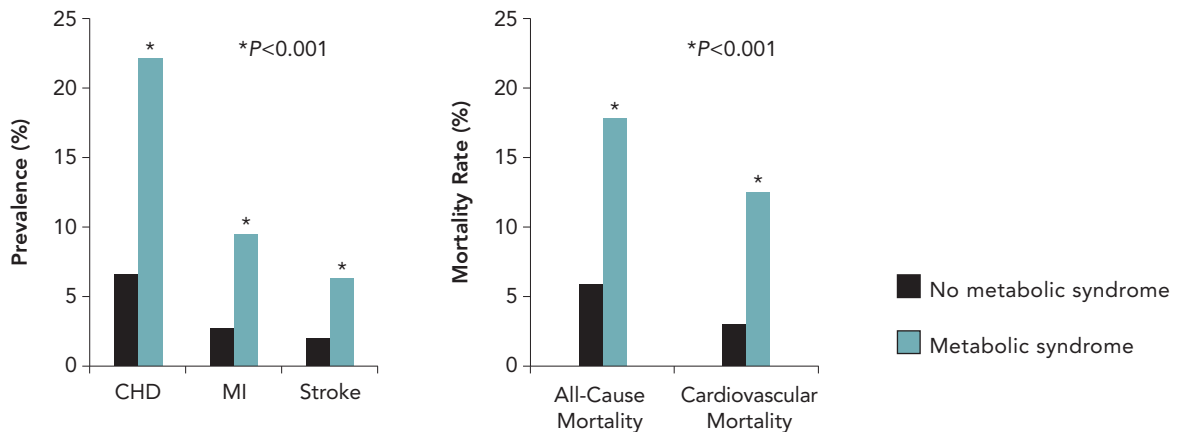
There is a clear, significant increase in cardiovascular (CV) death, myocardial infarction, and all-cause deaths, with increasing central adiposity. Waist circumference, as a marker of visceral fat and central adiposity, is directly related to CV death, MI, and type 2 diabetes; all cause mortality. As waist circumference increases, so does the risk of each indicator (see Exhibit 3).^{11,12} Body weight is also a predictor of disease. As body mass index

Exhibit 1: Diagnostic Criteria for Cardiometabolic Syndrome^{5,6}

Presence of any three of five criteria constitute diagnosis of cardiometabolic syndrome

Measure	Categorical Cut Points
Elevated waist circumference	≥35 inches (88 cm) in women (≥31 for Asian Americans) ≥40 inches (102 cm) in men (≥35 for Asian Americans)
Elevated triglycerides	≥150 mg/dl or drug treatment for elevated TG
Reduced HDL-C	<40 mg/dl in men, <50 mg/dl in women or drug treatment for reduced HDL-C
Elevated BP	≥130 mm Hg systolic BP or ≥85 mm Hg diastolic BP or drug treatment for hypertension
Elevated fasting glucose	≥100 mg/dl or drug treatment for elevated glucose

Exhibit 2: Metabolic Syndrome Associated With Increased CV Morbidity and Mortality⁹



*Cardiovascular mortality was defined using ICD-9 (codes 390-459) before 1997 and ICD-10 (codes 100-199) thereafter.

increases in men and women, type 2 diabetes, gallstones, hypertension, and coronary artery disease incidence increases dramatically.¹³

Treatment of Cardiometabolic Syndrome

Current therapies for cardiometabolic syndrome often address individual cardiovascular disease risk factors instead of the root cause (see Exhibit 4). To effectively manage cardiometabolic syndrome, it's important to

- Identify at-risk patients
- Recommend a weight-loss diet
- Design an exercise plan
- Encourage behavior modification
- Explore pharmacotherapy options.

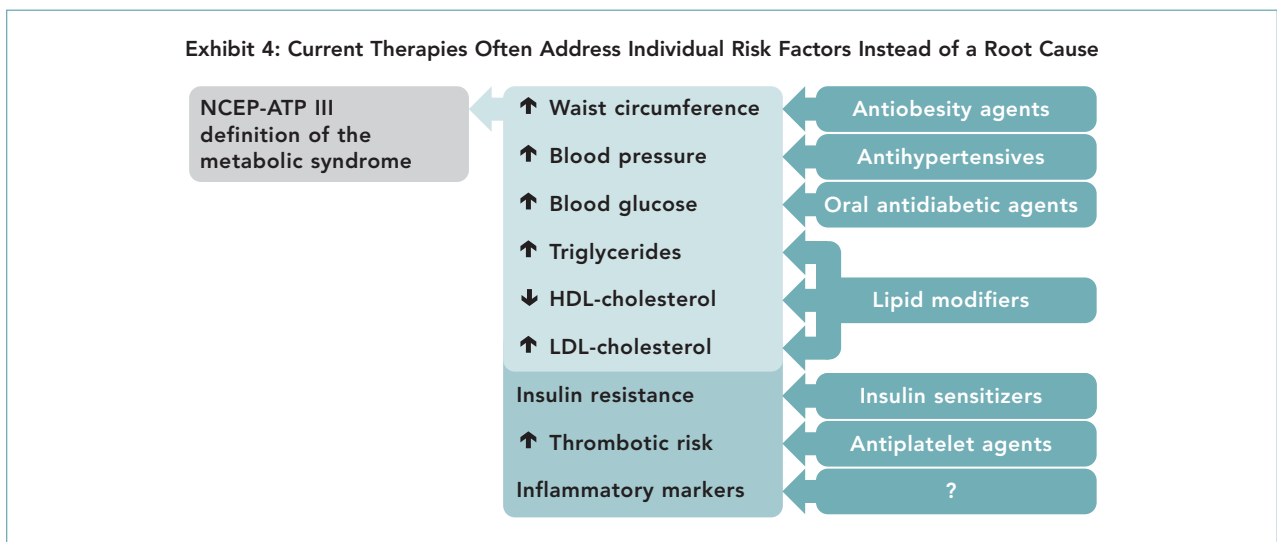
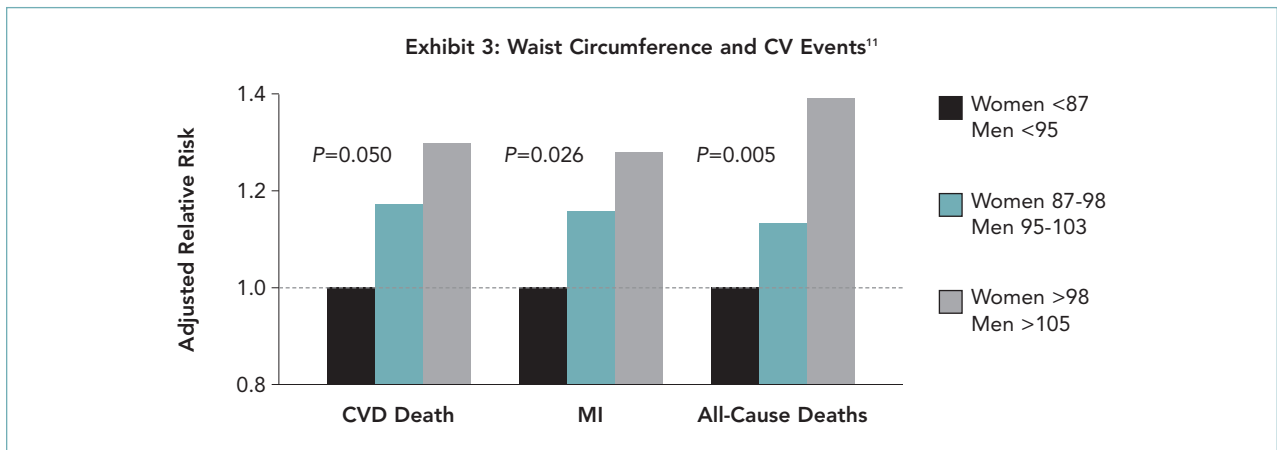
Weight loss through dietary changes is important, but visceral fat loss is also critical. Helping patients make appropriate lifestyle changes to lose weight is a significant challenge for all of healthcare.

Another important aspect of treatment is exercise. Whether taken in one 30- or 45- minute session, or

in bursts of 10 or 15 minutes at multiple times during the day, exercise adds up. Patients can get discouraged when told they need to exercise for long periods of time; breaking this into smaller chunks of time may make fitting exercise into daily life easier. Ultimately, patients should get 60 to 120 minutes of physical activity five days a week to lose weight.

Currently available pharmacotherapies for weight loss, orlistat (Xenical[®]) and sibutramine (Meridia[®]), can induce weight loss of between 5 and 10 percent over two years or more.¹⁴⁻¹⁶ However, drug-induced weight loss with these agents tends to be only 4 to 9 pounds greater than that produced by dietary changes alone.¹⁴ Despite this, in the XENDOS trial, the modest weight-loss difference from placebo produced by orlistat (6 pounds) reduced the incidence of diabetes by over a third.¹⁷ Adverse effects such as blood pressure increases with sibutramine, and gastrointestinal issues can complicate therapy in many patients.

An investigational agent being studied for weight loss is rimonabant. This agent blocks the CB1 receptor of the endocannabinoid system (ECS). The



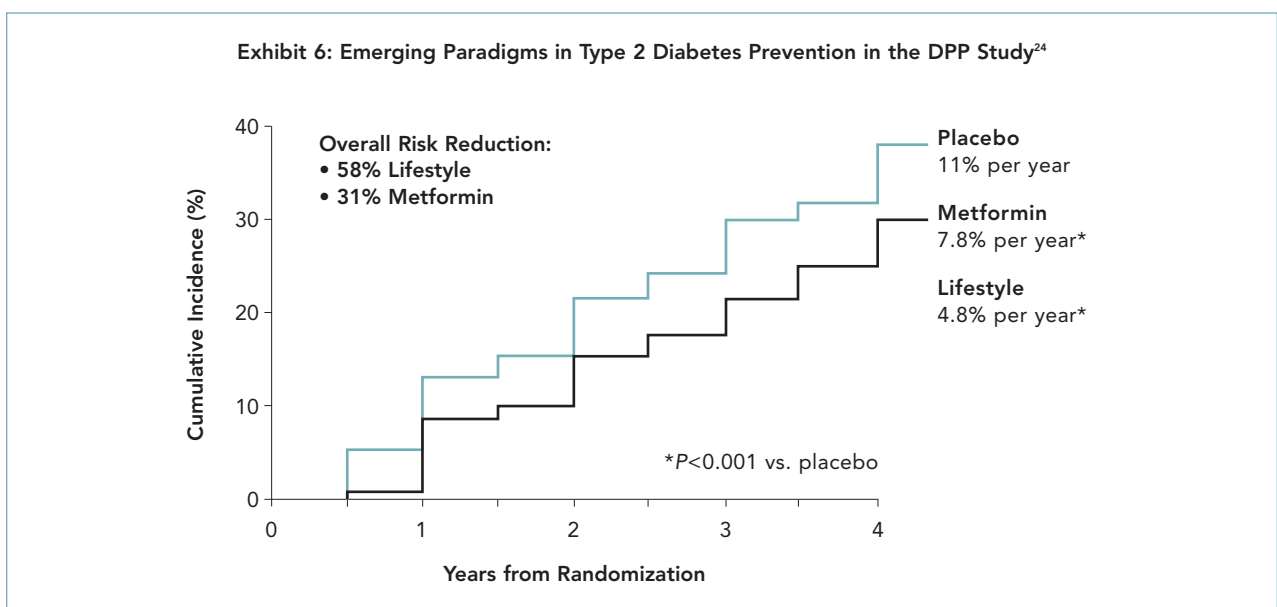
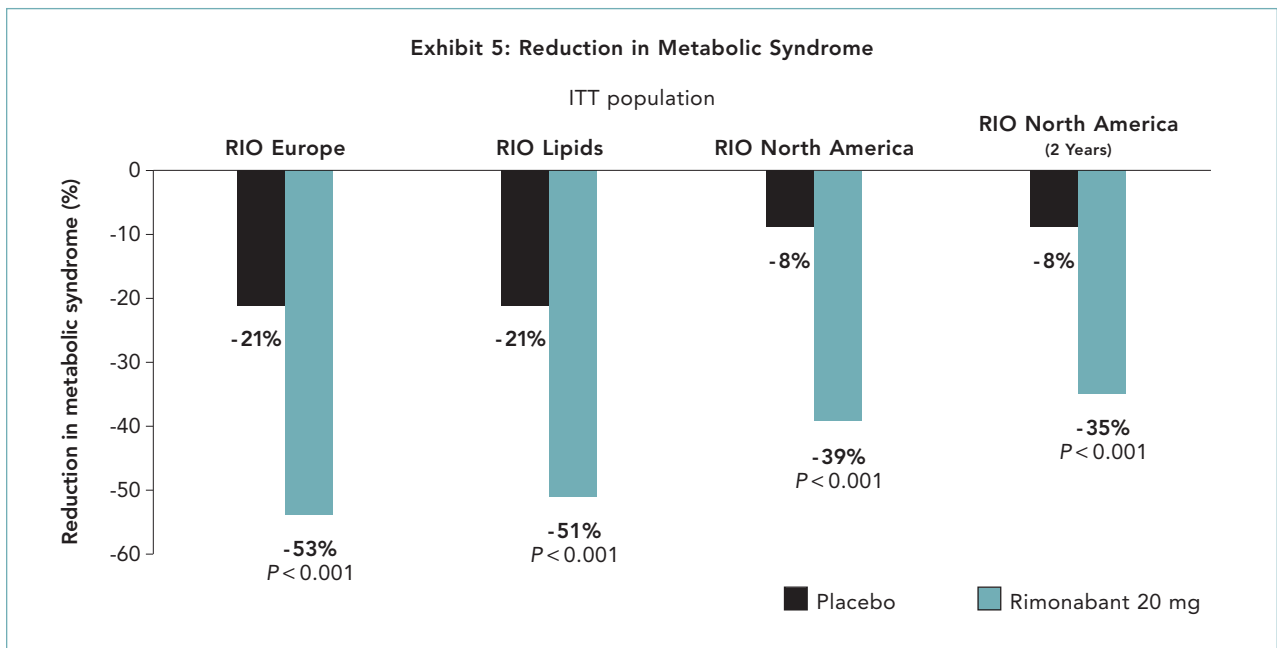
ECS is a physiologic neuromodulatory signaling system that plays a role in a number of physiologic processes. Increased ECS activity is associated with excessive food intake.¹⁸

Four weight-loss trials have been conducted with rimonabant.¹⁹⁻²³ Overall, this agent produces a significant reduction in waist circumference and weight, and significant improvement in metabolic profile (decreased triglycerides, increased HDL-C, and improved insulin sensitivity). The trials found significant decreases in the presence of cardiometabolic syndrome in patients treated with rimonabant (see Exhibit 5). Efficacy has been maintained in the trials for up to two years of therapy. Like all weight-loss medications, weight regain

occurs when therapy is stopped. The most common adverse effect is a transient self-limiting increase in GI side effects, which goes away after two to three weeks.

Effective weight loss likely requires combination medication therapy and lifestyle changes, as has proven the case in successfully treating hypertension or type 2 diabetes. It's unlikely that one drug will result in a 50-pound weight loss by the patient, but it may well be that a combination of two or three will be effective.

Bariatric surgery, while effective for weight loss and altering metabolic risk factors, has typically been utilized as a last-resort option. This is primarily because of the expense, potential for significant adverse effects, and limitations on third-party coverage.



Preventing Conversion From Pre-Diabetes to Diabetes

Research from multiple prevention studies of type 2 diabetes has been published in recent years. An important point to note about earlier studies is that they have not focused on prevention but on delaying disease development. Within the next five years, many of the medications currently used to treat type 2 diabetes and various cardiovascular risks (i.e., angiotensin converting enzyme inhibitors) likely will show indications for pre-diabetes treatment as well.

One of the largest trials was the Diabetes Prevention Program (DPP) conducted by the National Institutes of Health.²⁴ This study enrolled individuals with impaired glucose tolerance and randomized them to lifestyle modifications or metformin. With dietary changes and exercise for 30 minutes per day for five days per week, the subjects in the lifestyle modification group lost an average of 7 percent of their starting weight.²⁴ With lifestyle changes, the progression from pre-diabetes to diabetes was reduced by 58 percent (see Exhibit 6). Metformin reduced the progression from pre-diabetes to diabetes by about one-third.

Exenatide (Byetta®), a new antidiabetic agent, is a glucagon-like peptide 1 (GLP-1) analogue that is 53 percent analogous with human GLP-1. GLP-1 slows down gastric emptying. It antagonizes the effect of glucagon on glucose production. Thus, it lowers glucose production, decreases appetite and, in animal models, increases pancreatic beta cells.²⁵ Exenatide is injected twice a day. Many patients experience a profound weight loss of 13 to 26 lbs.²⁶ Pramlintide (Smylin®) is another new antidiabetic agent that is an amylin analog. Amylin is co-secreted with insulin. When a patient is insulin deficient, amylin goes down. Pramlintide is similar to exenatide in that it slows gastric emptying and decreases appetite. It does not have any effect on beta cells nor does it produce as much weight loss as exenatide. Patients can lose 4 to 7 pounds when treated with pramlintide.²⁷ Exenatide and pramlintide, like other antidiabetic agents, may have a role in preventing the conversion from pre-diabetes to diabetes mellitus.

Conclusion

Despite extensive advances in cardiovascular risk management, patients are still experiencing cardiovascular events and developing type 2 diabetes. Cardiometabolic syndrome is a significant problem that increases risk of cardiovascular events and type 2 diabetes. Current treatment paradigms tend to treat only a single element of the constellation of cardiometabolic syndrome risk factors. New therapeutic advances combined with lifestyle changes reduce cardiometabolic risk factors and offer sustained health benefits. By reducing all of the cardiovascular

risk factors found in the patient with cardiometabolic syndrome, better patient outcomes will result. *JMCM*

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