

EDITORIAL COMMENT

Cardiometabolic Risk

Shifting the Paradigm Toward Comprehensive Assessment*



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Despite research achievements in understanding the pathophysiology of disease, improvements in prevention and management of risk factors, and innovations in the management of atherosclerosis, cardiovascular disease remains the leading cause of death in the United States.¹ After 40 years of success in reducing cardiovascular disease burden, mortality rates attributable to cardiovascular disease are now increasing.² Future projections further indicate that the burden of cardiovascular disease, along with major cardiovascular risk factors, including hypertension, hyperlipidemia, and type 2 diabetes, will continue to rise in the coming decades.²

The key reason for the increase in cardiovascular disease is the rise in obesity and associated modifiable cardiometabolic risk factors.³ More than 70% of the U.S. population is overweight or obese, a number expected to rise in the coming decades.⁴ The prevalence of obesity is also increasing in younger people, affecting approximately 20% of children and adolescents and 40% of young adults.⁴ Because obesity is inherently linked to insulin resistance, the prevalence of prediabetes and type 2 diabetes is also increasing, with over half the U.S. population having prediabetes or diabetes.⁵ Alarmingly, 1 in 5 U.S. adolescents already have prediabetes, and more than half of young adults have dyslipidemia.⁶

It comes as no surprise that the incidence of premature atherosclerotic cardiovascular disease (ASCVD) and myocardial infarction in the United States is rising.⁷ A recent large meta-analysis corroborated that prediabetes is associated with both all-cause mortality and cardiovascular disease.⁸ In addition, data from the UK Biobank indicated that people with prediabetes have a 2-fold increase in incident ASCVD, chronic kidney disease, and heart failure, major comorbidities that may develop prior to the progression from prediabetes to type 2 diabetes.⁹ This is further supported by anatomic correlation, with over 58% of asymptomatic adults with prediabetes having evidence of coronary artery disease on coronary computed tomography angiography.¹⁰

Cardiovascular risk factor prevalence is shifting from traditionally recognizing smoking, hypertension, diabetes, and elevated low density lipoprotein cholesterol to an increased appreciation of obesity, insulin resistance, inflammation, and social determinants of health.^{11,12} Cardiovascular risk associated with early metabolic deterioration of overweight and obesity remains frequently undiagnosed and untreated. For example, a recent retrospective analysis using electronic health records demonstrated that 80% of patients with newly diagnosed prediabetes did not receive treatment.¹³ Although there is wide heterogeneity in cardiometabolic risk, early risk assessment for future diabetes development, cardiovascular risk factor progression, and cardiovascular disease development may inform key decisions for pharmacological and other preventive strategies. Earlier and broader risk assessment is needed, as the risk of obesity, diabetes, and hypertension causing a first cardiovascular event is in fact higher at a younger age and declines with advancing age.¹⁴ People at increased cardiovascular risk due to early metabolic risk may be stratified as low ASCVD risk using the Framingham risk models and pooled cohort equations. For example, among people who

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experience a myocardial infarction before age 50 years, half did not meet current guideline-based treatment thresholds for statin therapy prior to their index event.¹⁵ Current limitations in risk prediction models may result in a substantial number of people not receiving appropriate preventative care.

In this issue of *JACC: Advances*, Howell et al.¹⁶ describe a novel risk prediction model. The modified Cardiometabolic Disease Staging System (CMDS) was developed and validated using data from 2 independent prospective cohorts consisting of more than 48,000 U.S. adults. This model utilizes both established cardiovascular risk factors (cholesterol levels, presence of diabetes, blood pressure control, smoking status) and specific markers of cardiometabolic health (fasting blood glucose, triglyceride levels, body mass index). The model predicted a 10-year risk of major adverse cardiovascular events, performing superiorly to the Framingham risk score and comparably to the ACC/AHA pooled cohort equations in this group of patients.

The use of such a model to predict cardiovascular outcomes expands on previous work by the authors, in which a similar CMDS score showed promise in identifying the patients at highest risk for developing diabetes and also those in whom weight loss therapy was likely to be effective at preventing the disease.^{17,18} Considering the rapid rise of obesity and insulin resistance in the U.S. population, the current CMDS model, which can predict the risk of both diabetes and cardiovascular disease, may identify and risk stratify candidates for more aggressive early intervention and treatment, including both lifestyle management and pharmacological treatment. From a practical standpoint, the model utilizes information readily accessible in the electronic medical record, allowing for its widespread utility. As the authors note, the modified CMDS includes the presence and severity of metabolic syndrome traits, extending and refining our current ASCVD risk prediction by incorporating cardiometabolic risk.

Comprehensive cardiometabolic risk assessment is highlighted by recent guidance from the American Heart Association, which advocates for the holistic assessment of risk factors, staging of cardiometabolic disease, and ultimately earlier detection and prevention of cardiovascular disease.¹¹ In an era of

rapidly expanding pharmacological approaches to treat obesity and cardiometabolic risk with cardioprotective glucagon-like peptide 1 receptor agonists (GLP-1 receptor agonists) and sodium-glucose transport protein 2 inhibitors (SGLT2 inhibitors), identifying and prioritizing those people who may benefit the most may need to be considered. The Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity trial confirmed for the first time a pharmacological approach to reduce cardiovascular risk in people with overweight or obesity.¹⁹ Despite the overwhelming cardiovascular benefit, only few people are receiving appropriate and guideline-recommended treatment. A recent analysis confirmed that only 2.8% and 3.9% of people with type 2 diabetes and cardiovascular disease receive recommended GLP-1 receptor agonist and SGLT2 inhibitor, respectively, highlighting a major discrepancy between evidence-based guideline recommendations and real-world pharmacotherapy use.²⁰

In summary, we applaud Howell et al.¹⁶ for creating a comprehensive cardiometabolic risk prediction tool. The CMDS model was previously developed to predict future risk of type 2 diabetes and has now been shown to also predict the risk of major adverse cardiovascular events. Identification of people at high risk for cardiovascular disease may guide important preventive care and pharmacological approaches for treatment. Practical use of the CMDS model to guide clinical decision-making in patients at highest risk for type 2 diabetes progression and cardiovascular disease development should be next evaluated and may hold promise for a more comprehensive approach to cardiometabolic risk assessment.

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