Diabetes is still a CAD risk equivalent, now what?

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Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of mortality worldwide with an estimated 19 million deaths attributed annually. Coronary artery disease (CAD) accounts for roughly 50% of these deaths.¹ Diabetes mellitus (DM) has long been recognized as potent ASCVD risk factor and clinical predictor of major adverse cardiovascular events (MACE). Abundant evidence across multiple racial and ethnic groups has continually shown this to be true. Overall, patients with diabetes are two to four times more likely to experience MACE than those without diabetes, and cardiovascular disease is the leading cause of early death in adults with diabetes.²

Haffner et al described the concept of diabetes mellitus as a “CAD risk equivalent” based on the results of their landmark 1998 study that demonstrated a similar risk of MACE for patients with diabetes mellitus without known CAD and patients with established CAD and no diabetes.³ Multiple subsequent studies have yielded similar findings; however, some have suggested a more heterogeneous nature to ASCVD risk in diabetic patients.^{4,5} While some controversy remains regarding the concept of diabetes as a “CAD risk equivalent,” the current guidelines recommend similar prevention

strategies for both patients with diabetes and those with established CAD.

In this issue of the Journal, Han et al. re-examine the potency of diabetes as a risk factor for ASCVD. To further elaborate on the existing literature, they have performed an elegant, propensity-matched retrospective analysis of a large contemporary cohort of patients undergoing SPECT-MPI utilizing cadmium-zinc-telluride nuclear perfusion imaging technology. Although studies in the past have employed propensity matching to examine the relationship of patients with and without diabetes and the risk of ASCVD, this study is unique as it balances risk factors and SPECT-MPI parameters using propensity score weighting in a contemporary imaging registry.⁴ Findings are consistent with prior studies in that diabetes remains the most potent risk factor for MACE when compared to other conventional ASCVD risk factors. An interesting novel finding from this study was the interplay of diabetes with the mode of stress testing and total perfusion deficit in prediction of MACE. Put another way, the patient’s mode of stress, exercise versus pharmacologic, was the most potent predictor of clinical outcome regardless of diabetes or cardiovascular disease status.⁴ Those who were able to exercise, presumably corresponding with a higher baseline functional status, exhibited better outcomes over the designated follow-up period.

Based on their observations, Han et al have re-established that diabetes is a potent risk factor for the development of ASCVD. So why do we need to revisit a principle such as diabetes is a “CAD risk equivalent”? Investigations such as these are important to periodically re-evaluate long held dogmas as contemporary medicine advances. For example, beta blockers were once considered vital chronic therapy for those with ischemic heart disease; however, we now understand the benefits likely do not exceed one to two years following myocardial infarction.⁶ Class 1 antiarrhythmic agents

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were commonly used in the post-infarction setting to suppress premature ventricular contractions until the Cardiac Arrhythmia Suppression Trial demonstrated a higher risk of mortality with this practice.⁷ In this case, Han et al have not produced a medical reversal. Their data recapitulate that when scrupulously balancing for risk factors, patients with diabetes and without known CAD do seem to have a similar risk of MACE as patients without diabetes and with established CAD. With these facts about diabetes and ASCVD risk reconfirmed, the question for clinicians is, what can and will we do about it?

Since the first observation of diabetes as a “CAD risk equivalent,” our understanding of diabetes and options for treatment has grown. We know more about the effects of longstanding insulin resistance and persistent hyperglycemia, and how this promotes endothelial dysfunction, oxidative stress, and accelerated atherosclerosis leading to the development of cardiovascular disease.^{4,5} Diabetes is often associated with compounding comorbidities, such as hypertension and dyslipidemia, which serve to further heighten ASCVD risk. Unfortunately, tight glycemic control has only shown a modest reduction in risk of MACE without significant benefit in all-cause mortality.⁸ More recent trials suggest additional cardiovascular benefit from agents in anti-glycemic classes, including the sodium–glucose cotransporter 2 (SGLT-2) and glucagon-like peptide 1 receptor agonists (GLP-1). Both of these classes have been shown to improve CV outcomes, independent of their glucose lowering effects.⁹ Overall, the cardio-protective benefits of glucose lowering therapies appear more pronounced in patients with shorter duration of DM and without CAD,⁵ therefore efforts in ASCVD risk reduction should ideally focus on early detection and treatment of diabetes.

The data from Han et al add to a growing body of literature demonstrating a strong association between capacity to exercise and reduced risk of ASCVD events. Subjects who underwent pharmacologic in lieu of exercise stress imaging were more likely to suffer an ASCVD event regardless of diabetes or CAD status. A 2004 meta-analysis of over 14 thousand subjects demonstrated that inability to exercise was associated with poor outcomes. Normal perfusion in this group was actually associated with a > 1% risk of ASCVD. Meta-regression in this study found exercise capacity to be the strongest predictor of ASCVD events.¹⁰ When viewed through another methodology, Bourque et al showed that among subjects achieving > 10 metabolic equivalents on exercise testing, both ischemia and ASCVD events were rare.¹¹ All of these data must be taken in the context that choice of

exercise or pharmacological stressor is not always made based on a definitive assessment of the patient’s exercise capacity, but rather on the potentially biased assessment of the ordering clinician.

Despite this limitation, Han et al. reaffirm the importance of preserving one’s physical capacity, a fact that clinicians should perhaps pay more attention to than reflexively ordering perfusion studies for any patient with anginal symptoms. Substantial evidence exists supporting routine physical activity and exercise as fundamental in the prevention and treatment of cardiovascular disease and diabetes. Furthermore, numerous epidemiological studies have shown that a sedentary lifestyle is associated with a higher prevalence of most all ASCVD risk factors. Currently, recommendations are for at least 150 minutes of moderate intensity aerobic exercise or 75 minutes of vigorous exercise per week, with the addition of resistance training two days per week.¹² Yet, according to the Centers for Disease Control and Prevention National Center for Health Statistics, only 23% of the American population are exercising in an amount to meet these guideline recommendations.¹³ Despite widespread recognition of the risks of physical inactivity, it is estimated that less than 40% of all physicians counsel their patients on the benefits of regular physical activity. Interestingly, studies have shown that physician’s own physical activity behavior can predict how likely they were to recommend physical activity to patients.¹⁴ In addition having room to improve on engaging in adequate physical activity, patients with diabetes are often not adequately treated with proven medical therapies. A large-scale analysis of patients with diabetes across the Veterans Administration showed that, on average, only 68.3% were on moderate intensity statin therapy.¹⁵ Similar findings were observed among residents of Olmsted County, Minnesota with only 47% of patients being prescribed a moderate or high intensity statin within 3 months of diagnosis.¹⁶

Our understanding of disease states and risk has benefited from the development of large registries and payer databases that span states and nations. These data can be readily investigated to uncover a great many observations with high precision and replicability. The much larger challenge is how we as clinicians respond to the findings. We need to move beyond observations of risk into developing the interventions that mitigate that risk or preferably prevent the risk in the first place.

Disclosures

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