Predicting and Preventing Myocardial Infarction in the Young

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In this issue of *Diabetes Care*, Divakaran et al. (1) report on patients from the Partners YOUNG-MI registry who suffered a first myocardial infarction (MI) at or before the age of 50 years. They describe diabetes prevalence and long-term cardiovascular outcomes stratified by diabetes status. Diabetes is a well-established risk factor for major adverse cardiovascular events (MACE) such as MI, stroke, or cardiovascular death. However, most existing data are in older patients. Thus, this article offers an opportunity to gain insight into an important and understudied population.

The mean age of this study cohort was 44 years, 19% were women, and 73% were white. Patients were enrolled between 2000 and 2016, and median follow-up was just over 11 years. Of the 2,097 patients in this cohort, 416 (20%) had diabetes, 39 (2%) of whom had type 1 diabetes. In 81 patients (20% of the patients with diabetes, 4% of the overall cohort), this was a new diabetes diagnosis. Although young, the risk factor burden in these patients was substantial. Half the cohort reported current smoking, 9 in 10 carried a diagnosis of hyperlipidemia, and 1 in 4 reported a family history of premature cardiovascular disease. Despite this significant risk factor burden, the median atherosclerotic cardiovascular disease (ASCVD) 10-year risk score was just under 10% in study patients with diabetes.

Despite the young age of this cohort, the cumulative incidence curves shown in Fig. 1 of the article show all-cause mortality >20% at 10 years in patients on insulin and >10% in patients with diabetes not on insulin. Cardiovascular mortality was ~10% in patients with diabetes, over threefold higher than that for patients without diabetes. In multivariable models controlling for baseline covariates, prevalent diabetes at the time of index MI was associated with a 65% higher all-cause mortality and a 110% higher cardiovascular mortality compared with patients with MI but without diabetes.

This study highlights that diabetes is not rare in young patients with MI and that it is associated with significantly worse cardiovascular outcomes. In any observational cohort, no matter how carefully collected, caution must be used in interpreting outcome effects, due to residual confounding. As is also common with registries, the patients enrolled may not be reflective of the broader population of interest. The YOUNG-MI registry is drawn from two large tertiary-care academic medical centers in Boston, MA. Registry patients are mostly white and male. The median income of enrolled patients was well above the U.S.'s national median, and 9 out of 10 patients were insured. This is illustrated by the very high prevalence of diagnosed dyslipidemia, allowing us to infer these patients had access to care, at least for lipid screening.

Despite these potential limitations, this is an important study. An MI at a young age is a preventable tragedy that has potentially devastating implications for patients and their families. A trial of screening or treatment in a cohort with low event rates would require large numbers or long follow-up, both of which can be prohibitively expensive. Absent robust randomized trial data to guide care, and with the need to prevent adverse cardiovascular outcomes in our patients, we must rely on observational data.

Risk stratifying young adults is challenging. Although the 2019 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on the Primary Prevention of Cardiovascular Disease recommends assessment of cardiovascular risk beginning at age 20 years (2), the published ACC/AHA ASCVD risk calculator (3) does not apply before age 40. Calculated short-term risk is heavily influenced by age, but a high risk factor burden translates into a significantly higher lifetime risk of cardiovascular disease. A 40-year-old with a 10-year ASCVD risk of 5% may well carry a lifetime risk of 50% or more (4). Comorbidities not included in risk calculators, such as chronic kidney disease, systemic inflammatory disorders, or a history of pregnancy-related complications, can be markers

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of higher risk in young patients. Two potentially useful factors to augment risk estimation in these patients are computed tomography–derived coronary artery calcium (CAC), a measure of coronary atherosclerosis, and cardiorespiratory fitness, a measure of cardiac functional performance. Easily obtained and interpreted, both may offer clinical utility.

Well-done population epidemiology studies have shown that the burden of CAC predicts an increased risk of fatal and nonfatal coronary heart disease events (5). Nasir et al. (6) showed that nearly 1 in 10 patients screened in routine practice had a coronary calcium score $\geq$400, a marker of significantly increased risk. More than half of those patients were not identified as high risk by traditional risk calculators. In a prior study from the Partners YOUNG-MI registry (7), Singh et al. showed that the median calculated 10-year ASCVD risk score was 5%, and half the men and nearly 2 in 3 women presenting with MI would not have been eligible for statin therapy prior to that event by the 2013 ACC/AHA guidelines.

Cardiorespiratory fitness is another useful risk marker, proven to substantially improve prediction of mortality (8). Patients at low cardiorespiratory fitness are at increased lifetime risk of adverse cardiovascular events. Unfortunately, there are no compelling data to support exercise interventions to improve ASCVD outcomes, with a large well-done trial in the space being negative (9). Both high coronary calcium and low cardiorespiratory fitness independently predict adverse cardiovascular events (10).

The Know Diabetes by Heart initiative (11) was created to increase awareness of cardiovascular disease and stroke among the general population of patients with diabetes. Young patients may be more focused on glycemic control and preventing microvascular disease rather than on the risk for adverse cardiovascular events that they may perceive as a problem limited to older patients. The high prevalence of risk factors in this cohort suggest an opportunity for more aggressive risk factor control to prevent a first MI. Among these patients with diabetes, half were current smokers, nearly all had dyslipidemia, and two-thirds had hypertension. These established prevention targets are thoroughly addressed in the current American Diabetes Association *Standards of Medical Care in Diabetes* (12).

In addition to lifestyle modification, risk factor control, statin therapy, and aspirin in selected patients, the diabetes treatment paradigm to reduce cardiovascular risk now includes glucagon-like peptide 1 receptor agonists (GLP-1RA) and sodium–glucose cotransporter 2 (SGLT2) inhibitors. These drugs have shown a consistent secondary prevention benefit for prevention of MACE in patients with established ASCVD (13). Data in primary prevention are less robust. In the Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) trial (14) of the GLP-1RA dulaglutide, most trial participants did not have established ASCVD. The point estimates for MACE in primary and secondary prevention were equal, although the trial was not powered to definitively evaluate those subgroups. A large meta-analysis showed no heterogeneity in the effects of GLP-1RA by the presence of ASCVD (15). Dulaglutide is currently the only GLP-1RA approved for cardiovascular disease risk reduction in patients both with and without established ASCVD (16). In terms of SGLT2 inhibitors, the Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE) trial (17) did not demonstrate heterogeneity by baseline ASCVD (primary prevention hazard ratio 0.68, 95% CI 0.49–0.94; secondary prevention hazard ratio 0.85, 95% CI 0.69–1.06; *P*-interaction = 0.25).

This important and well-done study further elucidates an important problem. Potentially important avenues for future clinical investigation include improving risk stratification in young adults, especially those at higher expected risk, perhaps via CAC or other biomarkers. This would potentially allow us to identify patients who may benefit from interventions to improve cardiovascular outcomes. We must also investigate why risk factor control is suboptimal in these young adults. This would allow us to better align patient and provider understanding and preferences with best practice. And finally, we must further explore the role of GLP-1RA and SGLT2 inhibitors in the primary prevention of ASCVD.

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