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EDITORIAL COMMENT

Identifying and Treating Young Patients at Risk for Cardiovascular Events*

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Remarkable progress in the prevention of acute myocardial infarction (MI) has been achieved in the past 2 decades (1). Improved primary prevention, focusing on modifiable risk factors such as smoking, cholesterol, blood pressure, diet, and physical activity, has accounted for much of this decline (2). Despite this, >500,000 Americans, and many more globally, still experience a new MI every year and 210,000 will have a recurrent MI (1). The majority of these events occur in older individuals, with a mean age of 65 years in men and 72 years in women (1). Individuals under 50 years of age are thought to account for approximately 10% of all MIs (3). Younger patients tend to have a lower in-hospital mortality (3), but the longer-term consequences in terms of morbidity from heart failure, angina, need for revascularization procedures, and quality of life can be devastating. Cardiovascular risk prediction in this population is particularly tricky because the atherosclerotic cardiovascular disease (ASCVD) risk score, the main tool recommended to determine statin eligibility, weighs age as the single most powerful predictor of risk. For the overall population, this is probably appropriate, but for younger patients the ASCVD score likely underestimates risk.

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In this issue of the *Journal*, Singh et al. (4) present results from the YOUNG-MI registry evaluating the performance of 2 commonly used risk assessment tools to determine statin eligibility from the 2013 American College of Cardiology/American Heart Association guidelines for treatment of blood cholesterol and 2016 U.S. Preventive Services Task Force recommendations for statin use in primary prevention in a retrospective cohort of young adults under 50 years of age who experienced a first-time MI. This study included patients with only type 1 MI, of which about one-half were ST-segment elevation MIs. They estimated the ASCVD risk score based on data available before MI or at the time of presentation. If a risk factor was discovered after hospitalization, it was not included. The median age of patients was 45 years (17% were under 30 years of age), 80% were men, and the vast majority (83%) had at least 1 traditional cardiovascular risk factor. Despite this, the median 10-year ASCVD risk score of the cohort was surprisingly low, at 4.8%, meaning that only 49% and 29% would have met criteria for statin eligibility as per the 2013 American College of Cardiology/American Heart Association guidelines and 2016 U.S. Preventive Services Task Force recommendations, respectively. The recommendations performed especially poorly in younger at-risk women, where 63% were not eligible for statins by either guideline.

There are some important limitations of the registry that merit consideration. The study sample is not representative of the U.S. population as a whole (it was predominantly white from hospitals located in high socioeconomic status communities). The design of the registry is retrospective, and the findings may be overstated. Data collection using electronic medical records faces the challenge of missing data. Finally, the lack of a control group does not allow us to know the prevalence of risk factors in people who did not have an MI. Notwithstanding these limitations, there are some important implications of this study.

First, the fact that most patients in the registry (83%) had at least 1 traditional risk factor (i.e.,

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dyslipidemia, smoking, hypertension, or diabetes) before their MI suggests that aggressively treating these risk factors is probably as important in young patients as it is in older patients. In the INTERHEART study for example, these risk factors plus 5 other modifiable risk factors accounted for 90% of the population attributable risk (PAR) of MI in adult men and 94% of the PAR in adult women (5,6). These associations were also consistent across multiple ethnicities and geographic regions, and were consistent in young versus older patients. Specifically, in the INTERHEART study, the PAR of the 9 risk factors was greater in the younger men (93.0%) and women (96.5%) compared with the older men and women, strongly suggesting that when a traditional risk factor is present in a person <50 years of age, its impact is greater. This calls for early screening in young patients who are at risk for MI, including in those who are overweight, have a family history of MI, are from high-risk ethnic groups (e.g., South-Asians), and are smokers. Thus, primary care physicians and specialists should realize that even when a single MI risk factor is present in a young person, aggressive risk factor modification is warranted.

Second, the ASCVD risk is highly dependent on age and likely underestimates risk in patients <50 years of age. This means that identifying younger patients likely to benefit from statin therapy is more challenging. Other outcomes, such as the presence of subclinical atherosclerosis, may be a useful risk marker in younger patients. In the CARDIA (Coronary Artery Risk Development in Young Adults) prospective cohort study (N = 3,538 individuals from 4 U.S. cities), modification of 5 healthy lifestyle factors in young adults between 18 and 30 years of age (overweight or obese, low alcohol intake, healthy diet, physical activity, nonsmoker) was associated with a lower risk of subclinical atherosclerosis after 20 years of follow-up (7). More recently, simple non-lab-based risk scores have been developed and validated for CVD risk prediction. The non-lab-based Fuster-BEWAT score that includes information on smoking, physical activity, diet (fruit and vegetable consumption), body weight, and blood pressure predicts the presence of subclinical atherosclerosis (8), as does the INTERHEART risk score (9) incorporating hypertension, smoking, diabetes, and abdominal obesity, among other factors, and both reliably estimate cardiovascular disease risk across a diverse range of community-based populations from low- to high-income countries. Because these risk scores do not rely on laboratory results, they can be used as simple screening tools to identify younger patients who should be targeted for more aggressive primary prevention treatments.

Third, the importance of family history of MI in younger patients is an important predictor of risk and often underemphasized in classic risk scores. It is often assumed that family history refers to a genetic predisposition to heart disease (10). However, family history may also refer to exposure to shared environmental factors, including socioeconomic status, dietary intake, physical activity, and sedentary behavior patterns, that tend to be similar within families. If a patient <50 years of age has a strong family history of premature coronary artery disease it should prompt further screening for modifiable risk factors, at the very least a lipid profile, followed by a discussion with the patient about initiating statin therapy. Although there is a legitimate concern about overtreatment, the benefit-risk ratio for statins, even in lower-risk individuals, seems favorable. For every 1-mmol/l (39 mg/dl) reduction in low-density lipoprotein cholesterol, the risk of a major cardiovascular event is reduced by about 9% in the first year then 24% for each treatment year thereafter (average treatment effect over 5 years is about 20%) (11). This means that for every 10,000 higher-risk individuals (5-year risk ≥30%) who have a 2 mmol/l drop in low-density lipoprotein cholesterol, approximately 1,140 events would be prevented with statin therapy, whereas in low-risk patients (5-year risk 5% to 9%) approximately 310 events would be prevented. By contrast, the downsides are few, such that for every 10,000 patients treated with a statin for 5 years there would be an excess of about 5 cases of myopathy, 50 to 100 new cases of diabetes, and 5 to 10 hemorrhagic strokes (11). When considering a lifetime risk of events, the presence of traditional risk factors in younger patients should be treated aggressively, and that includes statins for those <50 years of age.

For the future, we should place greater emphasis on primordial prevention of risk factors in youths, that is, preventing or minimizing overweight, obesity, and type 2 diabetes (which is on the rise in youths), and when these risk factors exist, they should be treated aggressively. Smoking, which is a dynamic risk factor that may change with popular culture, is particularly damaging in women, and public health programs and policy measures to prevent young women from smoking is critically important. Beyond this, evaluating inflammatory risk in young patients at risk of MI may add value, especially for the 5% to 10% of patients in whom no traditional risk factors are apparent, particularly because new therapeutic options now exist for these patients (12). Newer biomarkers, including markers of