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EDITORIAL COMMENT

Cholesterol Guidelines

A Missed Opportunity for Young Adults?*

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Older age has long been recognized as one of the strongest risk factors for cardiovascular disease. Accordingly, even in the presence of risk factors, young individuals are rarely considered for statin therapy. In 2002, Akosah et al. (1) evaluated the National Cholesterol Education Panel III guidelines using a cohort of 222 young adults who experienced a myocardial infarction (MI) and found that 82% would not have been eligible for statin therapy before their event. In 2017, the Young-MI registry (2) evaluated the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol guidelines (3) using a cohort of 1,685 adults who experienced an MI at age 50 years or younger and found that only 51% of them would have been eligible for statin therapy before their MI. Strikingly, the number of patients who were actually on statin therapy before their MIs was only 12%, a finding that reflects that even among individuals who are eligible for therapy, far fewer are actually prescribed or adhere with such therapy.

When considering these findings, a plausible conclusion might be that we need a lower threshold to initiate statin therapy among at-risk young individuals. Yet, newer guidelines have also been criticized for increasing the number of individuals who are deemed eligible for statin therapy; an increase that has mostly occurred in older adults (4). Because of the inherent imprecision of current risk assessment approaches, the treatment of more individuals who may ultimately experience an event requires us to treat a much larger segment of the population. Recognizing these challenges, the latest 2018 Multisociety Cholesterol Guideline has expanded the various approaches that can be used to determine statin eligibility while stressing the importance of shared decision-making. Notably, this guideline has also emphasized that at any age group, it is important to adhere to a healthy lifestyle.

There are key differences between the 2013 and 2018 cholesterol guidelines with respect to young adults. According to the 2013 ACC/AHA guideline, statins could be considered for patients with atherosclerotic cardiovascular disease (ASCVD) risk of 5% to 7.5% (Class IIa), whereas the 2018 guideline requires the presence of a risk enhancer for individuals within this group (Class IIb). Among patients younger than 40 years, in whom the pooled cohort equations cannot be used, the 2018 guideline suggests considering statin therapy among those with low-density lipoprotein cholesterol (LDL-C) of ≥160 mg/dl and a family history of ASCVD. One may posit if these changes enhance our ability to identify and treat young individuals who are at risk of ASCVD events.

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In this issue of the *Journal*, Zeitouni et al. (5) evaluated the 2018 Multisociety Cholesterol Guideline (6) among patients hospitalized with a first MI and found that only 46% of adults younger than 55 years of age would have been eligible for statin therapy based on having a Class I or IIa recommendation before their event. In contrast, approximately 90% of older adults were eligible. In addition, the

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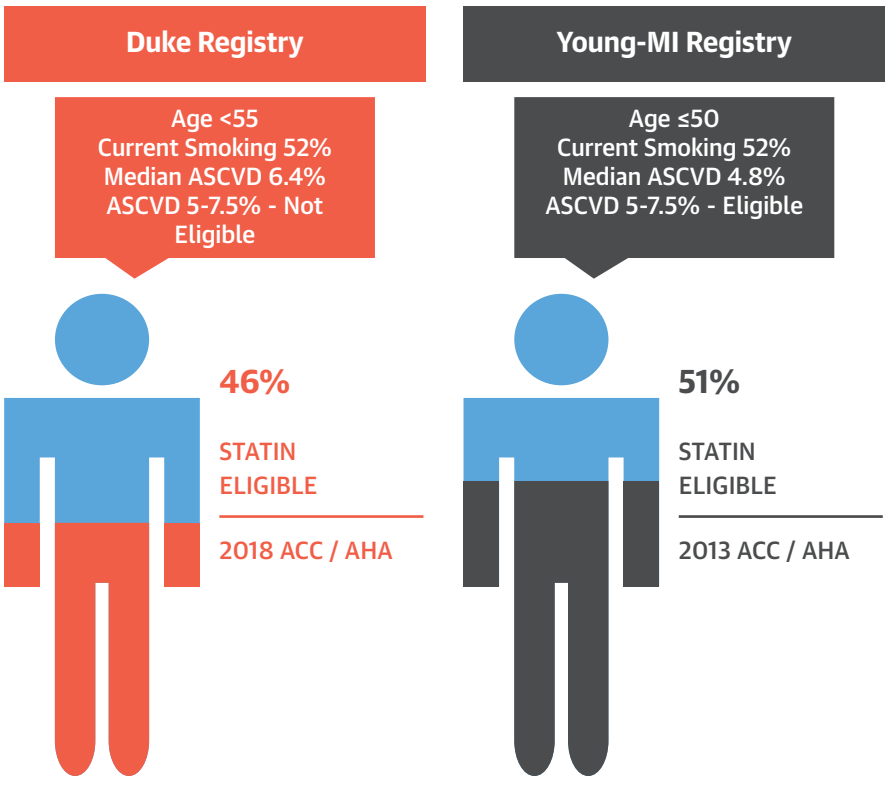
FIGURE 1 Statin Eligibility Among Young Adults in the Duke and Young-MI Registries



Shaded area of stick figure represents proportion of young adults eligible for statin therapy according to the 2018 Multisociety Cholesterol Guideline and the 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guideline (**red:** Duke Registry; **gray**: Young-MI Registry). ASCVD = atherosclerotic cardiovascular disease.

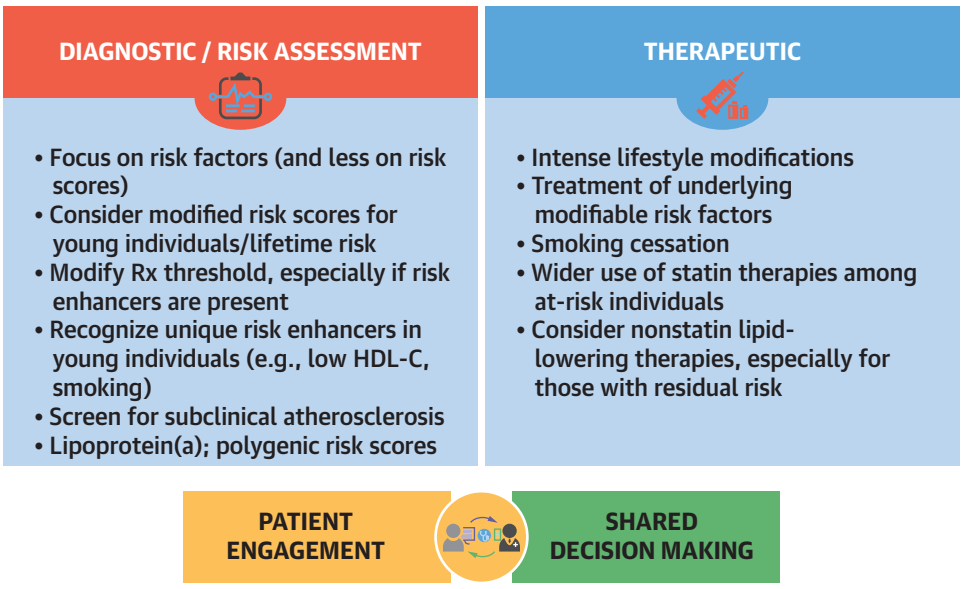
study found that most young patients did not meet the criteria for aggressive secondary prevention following their MI. When compared with the 2013 ACC/AHA guideline, and despite the addition of risk enhancers, the 2018 guideline identified fewer young adults. The investigators suggested that this decrement might be due to the fact that the 2013 guidelines considered patients with a 10-year ASCVD risk of 5% to 7.5% as being eligible to receive statins, whereas the 2018 guideline only provided a Class IIb indication and only when risk-enhancing factors were present.

The current study provides important evidence that nearly 1 in 2 adults who experienced a MI at a young age were not eligible for primary prevention statin therapy per the 2018 Cholesterol Guideline. Even when including patients with borderline risk (ASCVD 5% to 7.5%) and a risk enhancer, the proportion of statin-eligible patients only increased by 6.2%. A key factor accounting for this deficiency is that current risk scores are heavily based on age.

Data from both the Duke and Young-MI registries (**Figure 1**) should force us to re-examine how we allocate statin use among young individuals. Young adults have a greater risk to lose productive life years yet remain undertreated both before and after their events (7). Even those who experience an event often remain at considerable risk of a recurrent nonfatal or fatal cardiovascular event (8). Because the prevalence of traditional cardiovascular risk factors in young adults who experience an MI is high, one approach to improved primary prevention is to identify those who have risk factors for ASCVD events. Such an approach could consist of treatment of underlying risk factors, while also recommending LDL-C lowering therapies in those who have such risk factors. When considering risk factors, it is important to highlight that smoking was reported in more than one-half of young patients, which was similar in the Young-MI registry (9).

The findings of Zeitouni et al. (5) are extremely important but need to be considered in the context of

FIGURE 2 Opportunities for Enhanced Cardiovascular Disease Prevention in Young Adults



Various methods that may be helpful in improving risk assessment and expanding diagnostic and therapeutic approaches for cardiovascular disease prevention. HDL-C = high-density lipoprotein cholesterol; Rx = prescription.

several limitations. When evaluating risk enhancers, any family history of CAD was used rather than family history of premature CAD. If data on lipids before MI data were not available, the investigators used the first available values from the following year, a time when patients might have already been on a high-intensity stains, and thus, the calculated ASCVD risk would be lower. The investigators did not further stratify statin eligibility by sex, but previous data (2) showed that the proportion of young women eligible for statin therapy was significantly lower than the proportion of young men. Also, biomarkers such as high-sensitivity C-reactive protein, lipoprotein(a), and coronary artery calcium (CAC) were not routinely available. CAC testing is increasingly used in the context of shared decision-making, and the identification of coronary atherosclerosis, which possibly can also be achieved with 3-dimensional femoral ultrasound (10), may be particularly important among young individuals (11–13).

Because current diagnostic and therapeutic approaches may not adequately identify at-risk young adults, it is useful to consider a few alternative approaches (**Figure 2**). The ASCVD risk score calculator underestimates risk in some young adults, and statin therapy should be more strongly considered among young adults with borderline risk (5% to 7.5%), especially when either traditional or nontraditional risk factors are present. It is important to recognize that certain risk factors may be particularly important among young individuals, including tobacco use, low high-density lipoprotein cholesterol, obesity, and substance abuse (14). When considering these factors, it is apparent that there are many more opportunities to reduce the risk of MI beyond just cholesterol-lowering agents. Ultimately, greater primordial and primary prevention efforts are needed. If our goal is to achieve the greatest possible reduction in cardiovascular events, we should not miss any opportunities to improve prevention.

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