JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 74, NO. 15, 2019

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

# Coronary Artery Disease in Young Adults

## A Hard Lesson But a Good Teacher*

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The consequences of premature coronary artery disease (CAD) are devastating. Although atherosclerotic cardiovascular disease (ASCVD) events have been declining in older adults, these gains have not extended to younger adults (1). In fact, acute myocardial infarction (AMI) rates have increased among young adults age 35 to 54 years, particularly in women (2). More attention needs to be paid to this younger population.

Although any CAD before age 55 years for men or 65 years for women is labeled "premature," it is particularly alarming when CAD occurs in the young, defined as onset before age 45 years. CAD in young adults carries a poor long-term prognosis, and as many as 4% to 10% of AMI events occur in this age group (3). It is paramount to better understand conventional and unique risk factors to prevent ASCVD events in this population. An adage states "If experience is the best teacher, the worst experiences teach us the best lessons." Thus, what can survivors of early onset CAD teach us about risk, not only for their initial event but for future events?

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In this issue of the *Journal*, the study by Collet et al. (4) describes a unique cohort of 880 adults who experienced symptomatic CAD at a young age (<45 years), predominantly presenting as obstructive (stenosis: ≥70%) AMI (excluding myocarditis, Takotsubo cardiomyopathy and coronary vasospasm), who then were followed for up to 20 subsequent years. This observational study, called the AFIJI (Appraisal of risk Factors in young Ischemic patients Justifying aggressive Intervention) registry, had the 3 following objectives: 1) to evaluate the rate of first recurrent major adverse cardiovascular event (MACE) and associated risk factors; 2) to determine the relationship between the initial lesion and the new lesions; and 3) to determine the rate of repeated recurrences. At initial presentation, the average age was 40 years. These patients were mainly smokers with a family history of CAD or hyperlipidemia; 87% were male; and 10% had chronic inflammatory or immunosuppressive disease. During follow-up, despite initial prescription of aspirin (98%) and statins (93%), one-third of these patients had a recurrent MACE, and of these, 36% had at least a second recurrence.

Key study findings were as follows: 1) recurrence rates remained high, despite medical therapy; 2) recurrent events generally occurred from new coronary lesions, which confirms prior work showing that nonobstructive plaques are the vulnerable ones, more prone to rapid progression (5); and 3) clinical factors associated with recurrence were insufficient control of conventional risk factors (diabetes, hypertension, and smoking), multivessel disease, Asian or sub-Saharan African ethnicity, and inflammatory disease. Smoking was the strongest modifiable factor for recurrent MACE. In sum, this study helped shed light on factors associated with progression and opportunities for enhanced prevention (4).

How can the cardiovascular community apply the findings from this important study? First, using a team-based care and patient-centered approach (6), there is a critical imperative to better implement guideline-recommend care. This entire AFIJI cohort had premature CAD, yet 48% with a first recurrence were not taking a high-intensity statin agent, and

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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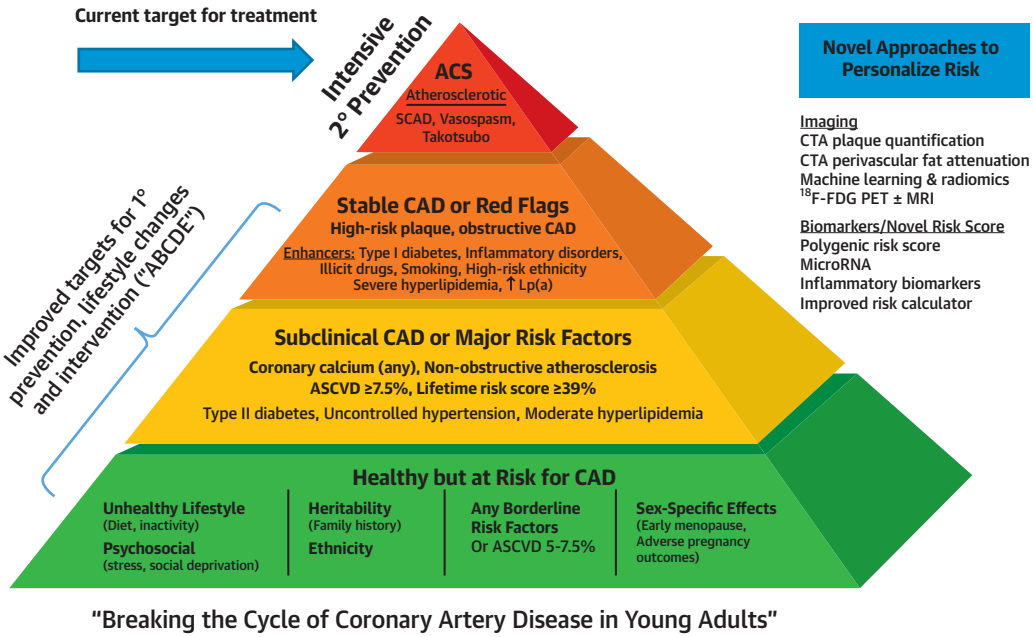
ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2019.08.1023

**FIGURE 1 Breaking the Cycle of Coronary Artery Disease in Young Adults**




A multipronged approach is required to break the cycle from CAD "at-risk" to ACS in young adults. More intensive secondary prevention in stable CAD is needed, particularly in the setting of "red flags." Enhanced primary prevention includes better identification of subclinical CAD or major risk factors. Patients should be screened for conventional ASCVD risk factors and managed with an "ABCDE" approach. Novel imaging, biomarkers, and risk scoring will enhance personalized risk prediction. Healthy lifestyle remains the foundation for prevention for all.
1° = primary; 2° = secondary; $^{18}$F-FDG-PET = fluorine-18-labeled fluorodeoxyglucose-positron emission tomography; ACS = acute coronary syndromes; ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; CTA = computed tomography angiography; Lp(a) = lipoprotein (a); MRI = magnetic resonance imaging.

7.2% were not taking a statin drug at all. Ezetimibe should be considered for established ASCVD if the low-density lipoprotein-cholesterol (LDL-C) threshold is ≥70 mg/dl, despite maximally tolerated statin dosage; but 83% of patients with first recurrence were not taking ezetimibe. Second, because recurrence rates are so high, even more efforts needed to be directed toward preventing the development of CAD in the first place through primordial and primary prevention efforts, as outlined in the "ABCDE" approach in the 2019 American College of Cardiology (ACC)/American Heart Association (AHA) Primary Prevention Guidelines (6).

Identifying which young, healthy adults are at risk for CAD remains challenging due to the limitations in risk calculators, the limited sensitivity for established screening modalities, and the insufficient observational data for this age group. Young adults age <40 years are less likely to be treated with preventive therapies because 10-year ASCVD risk estimators, used to guide statin therapy recommendations, do not include this age group (6). In the YOUNG-MI registry, most adults who presented with AMI before age 50 years would not have been guideline-eligible for statin therapy prior to their event (7).

The AFIJI study found that ethnicity, inflammatory disease, and behavior-related risk factors were the major contributors to poor prognosis in this secondary prevention population. Similarly, the 2019 ACC/AHA guidelines identified "risk-enhancing factors" for adults age 40 to 75 years that would upgrade risk estimates and favor initiation and intensification of statin therapy in primary prevention, such as the presence of family history of premature ASCVD, inflammatory and autoimmune disorders, HIV infection, chronic kidney disease, history of preeclampsia, South Asian ethnicity, and elevated lipoprotein(a) (6). The AFIJI study observed that several of these factors are linked to early onset CAD, and thus, should be "red flags" in younger adults too. For adults age 20 to 59 years, a lifetime risk score can be

calculated from the ACC/AHA Risk Estimator, to promote intensification of lifestyle measures and track improvements in risk factors (6).

Determination of the presence of atherosclerosis in younger adults is of paramount importance. The initial studies of atherosclerosis in young adults were limited to autopsy studies in war veterans from the 1950s (8). Now, both invasive and noninvasive imaging can be used to identify atherosclerosis burden and progression. For persons age 40 to 75 years, if risk-based decisions to initiate statin therapy for primary prevention are uncertain, the 2019 ACC/AHA guidelines state that it is reasonable to use coronary artery calcium (CAC) assessment by noncontrast computed tomography (CT) to refine risk estimation as a shared decision-making tool (6). While CAC imaging is generally not typically performed in young adults age <40 years, studies have shown that the presence of CAC (>0) ranged from 10% to 34% in young adults and carried a significant increased risk for future cardiovascular and all-cause mortality (9,10).

Coronary CT angiography (CCTA) is currently not endorsed as a decision aide in asymptomatic adults. However, as a noninvasive strategy, it does provide a potential role to guide prevention recommendations in younger adults. In prior studies of symptomatic middle- to older-aged adults undergoing CCTA, the presence of nonobstructive, noncalcified high-risk plaques, and obstructive CAD all correlated with an increased risk of future MACE and mortality (11). These findings have been extended to patients at low estimated 10-year risk, those without conventional risk factors, and in younger adults (<45 years) (11). Perhaps most importantly, demonstration of atherosclerosis by CCTA has been associated with increased implementation of preventive lifestyle modifications and pharmacotherapies (e.g., statin, aspirin, antihypertensive therapy).

Looking to the future, the key to aging well is to start young (12). The ACC/AHA guidelines endorse treating severe primary hypercholesterolemia in young adults (6), but even moderate hyperlipidemia in young adulthood is associated with increased future ASCVD risk (12). The ECAD (Eliminate Coronary Artery Diseases; NCT02245087) trial is recruiting 10,000 participants in early to mid-adulthood (men age 35 to 50 years; women age 45 to 59 years) with LDL-C ≥70 mg/dl who are not statin candidates by current guidelines, to determine whether lowering LDL-C with atorvastatin, 20 mg/day, versus guideline-directed care alone can reduce MACE. The SCOT-HEART 2 (Computed Tomography Coronary Angiography for the Prevention of Myocardial Infarction; NCT03920176) trial plans to enroll 6,000 individuals at risk for ASCVD and determine if a risk score-guided versus a CCTA-guided approach reduces MACE. These important studies will help shape subsequent prevention strategies.

Breaking the cycle of CAD in young adults is going to take a multipronged approach (**Figure 1**). This approach involves recognizing young adults at risk (including those with "red flags") to improve targets and adherence to established prevention approaches. Further opportunities remain to enhance personalized medicine through emerging novel multimodality imaging, inflammatory biomarkers, refinement of polygenic risk scores, and improved lifetime risk calculation. Let us also learn from the lessons that the young adults with early-onset CAD from the AFIJI study have taught us about lesions and factors associated with progression so that we can better ensure history does not repeat itself for the next generation of young adults.

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**KEY WORDS** long-term outcomes, myocardial infarction, premature coronary artery disease, recurrent event, young