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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Managing Atherosclerotic Cardiovascular Risk in Young Adults

JACC State-of-the-Art Review

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ABSTRACT

There is a need to identify high-risk features that predict early-onset atherosclerotic cardiovascular disease (ASCVD). The authors provide insights to help clinicians identify and address high-risk conditions in the 20- to 39-year age range (young adults). These include tobacco use, elevated blood pressure/hypertension, family history of premature ASCVD, primary severe hypercholesterolemia such as familial hypercholesterolemia, diabetes with diabetes-specific risk-enhancing factors, or the presence of multiple other risk-enhancing factors, including in females, a history of pre-eclampsia or menopause under age 40. The authors update current thinking on lipid risk factors such as triglycerides, non–high-density lipoprotein cholesterol, apolipoprotein B, or lipoprotein (a) that are useful in understanding an individual's long-term ASCVD risk. The authors review emerging strategies, such as coronary artery calcium and polygenic risk scores in this age group, that have potential clinical utility, but whose best use remains uncertain. Finally, the authors discuss both the obstacles and opportunities for addressing prevention in early adulthood.
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Atherosclerotic cardiovascular disease (ASCVD) comprises approximately two-thirds of cardiovascular disease (CVD) deaths worldwide as coronary artery disease and ischemic atherosclerotic stroke, which are major contributors to disability over the life course.[1-3] In addition, rising mortality rates in mid- and later adulthood reflect underlying ASCVD and contribute to declines in life expectancy. Because most individuals with premature ASCVD have modifiable risk factors that predate their disease, early intervention is a priority.[4] Indeed, in a series of consecutive patients aged ≤50 years admitted with a type I myocardial infarction (MI), approximately 1 in 5 patients were aged ≤40 years.[5] They had similar risk profiles except for more substance abuse and spontaneous coronary artery dissection and less hypertension. **Figure 1** identifies at-risk groups with high lifetime risk of ASCVD who should be candidates for more intensive evaluation and management. Those with tobacco use, hypertension, family history of premature coronary heart disease (CHD), primary severe hypercholesterolemia, diabetes mellitus (DM) with diabetes risk factors, and multiple major enhancing risk factors benefit from more intensive evaluation

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ABBREVIATIONS AND ACRONYMS

AHA = American Heart Association

apoB = apolipoprotein B

ASCVD = atherosclerotic cardiovascular disease

BP = blood pressure

CAC = coronary artery calcium

CHD = coronary heart disease

CT = computed tomography

CVD = cardiovascular disease

DM = diabetes mellitus

FamHx = family history

FH = familial hypercholesterolemia

HDL-C = high-density lipoprotein cholesterol

LDL-C = low-density lipoprotein cholesterol

Lp(a) = lipoprotein (a)

MetS = metabolic syndrome

MI = myocardial infarction

PCE = pooled cohort equations

PRS = polygenic risk score

RCT = randomized controlled trial

and treatment. In many of these cases, the relative risks of risk factors are greater when young. We also discuss modalities to determine risk such as 30-year risk assessments and lipid risk factors such as non-high-density lipoprotein-cholesterol (HDL-C), apolipoprotein B (apoB), triglycerides, and lipoprotein (a) [Lp(a)]. We review the role that a family history of premature ASCVD, polygenic risk score (PRS), and noninvasive imaging can play to determine whether subclinical atherosclerosis is present. The important "payoff" is identifying those most likely to have progression of atherosclerotic plaques in their coronary arteries and who require more aggressive management.

HIGHLIGHTS

- Addressing risk factors in individuals aged 20-39 years can reduce premature atherosclerotic cardiovascular disease.
- Tobacco cessation and managing hypertension, hypercholesterolemia, diabetes, sex-specific risk factors, and metabolic syndrome are essential.
- Measuring nonfasting lipids, triglycerides, Lp(a), and apoB levels can identify high-risk patients.

TOBACCO USE

CIGARETTE SMOKING INCREASES VIRTUALLY ALL CLINICAL MANIFESTATIONS OF ASCVD. Smoking acts synergistically with hypertension, DM, and hyperlipidemia to increase ASCVD risk.[6,7] Smoking doubles the risk of CHD and stroke, triples the risk of sudden cardiac death, and increases 5-fold the risk of peripheral arterial disease and abdominal aortic aneurysm.[6,7] The absolute and relative risks of MI due to smoking differ by age.[6,7] The relative risk of MI is much higher in younger smokers, providing a compelling rationale to prioritize tobacco cessation in efforts to reduce CVD events among younger adults.

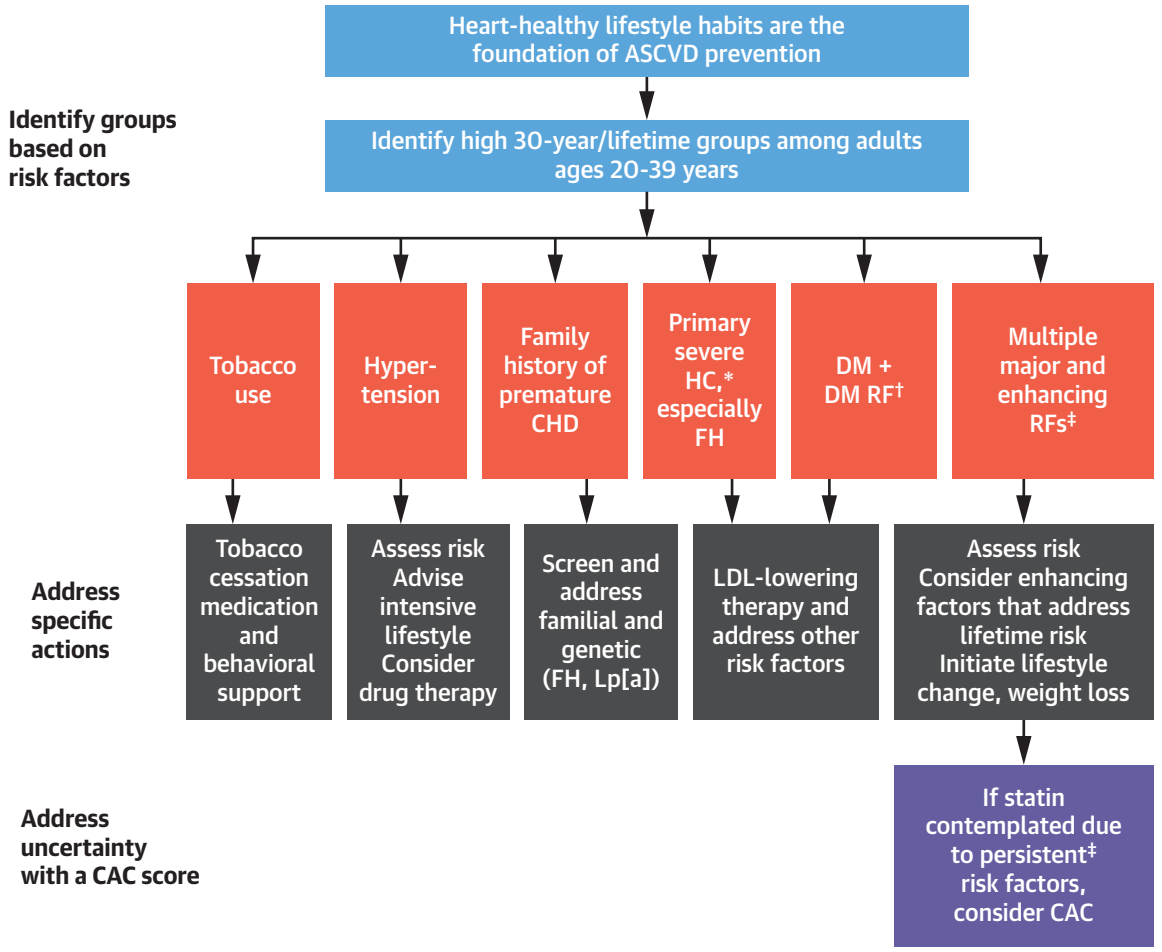
Although the prevalence of tobacco smoking in the United States has declined since its peak in 1965, 14% of U.S. adults reported smoking cigarettes in 2019.[8] Smoking prevalence varies by age, being highest among those aged 25-44 years (16.7%) and 45-64 years (17.0%), and lower among young adults 18-24 years (8.0%) or adults over 65 years (8.2%).[8] Social determinants and psychosocial factors help explain smoking rates that are still too high. The prevalence of smoking is higher among individuals with less education; lower incomes; lesbian, gay, or bisexual sexual orientation; and those with serious psychological distress[9] as well as those living with HIV, substance use disorders, and psychiatric comorbidities.

Combustible tobacco products other than cigarettes also increase CVD risk.[9] In 2019, 16.7% of U.S. adults reported combustible tobacco use, which includes cigarettes, cigars, cigarillos, pipes, and water pipes.[9] Electronic cigarettes (e-cigarettes) are noncombustible alternative tobacco products that, unlike cigarettes, do not burn tobacco to generate the products of combustion that are primarily responsible for the pathogenesis of CVD.[10] Instead, e-cigarettes heat a nicotine-containing liquid to generate an aerosol that users inhale.[10] The prevalence of e-cigarette use among all U.S. adults was 4.5% in 2019, with higher rates among younger age groups (9.3% and 6.4% prevalence among young adults aged 18-24 years and 25-44 years, respectively).[8] Although e-cigarettes have lesser toxic material than cigarettes, there are some studies that document negative effects on ASCVD factors.[10] We await data, however, to determine whether e-cigarettes are safer than cigarettes and to measure their overall impact on cardiovascular morbidity and mortality. However, e-cigarette use has demonstrated some negative effects on ASCVD biomarkers, although there is no prospective epidemiologic evidence of the effect on ASCVD morbidity and mortality of switching to e-cigarettes.[11]

THE BENEFITS OF SMOKING CESSATION ARE SUBSTANTIAL, ESPECIALLY EARLY IN LIFE. Smoking decreases an individual's life expectancy by approximately 10 years. Clinicians should emphasize that excess overall and CVD mortality attributable to cigarette smoking is rapidly reversible after smoking cessation.[8] This is a potentially fixable cause of premature and recurrent MI.[9] Furthermore, the life expectancy benefit is greater when smoking stops earlier in life. Smokers who stop before 40 years of age reduce their risk of smoking-attributable death by 90%.[8]

EFFECTIVE TOBACCO CESSATION TREATMENT PLANS AND PATHWAYS ARE AVAILABLE BUT UNDERUSED. A robust evidence base supports the effectiveness of brief clinician interventions, behavioral counseling, and Food and Drug Administration-approved cessation medications (which include 5 nicotine replacement products, varenicline, and bupropion) to increase the success of smokers who

FIGURE 1 **Identifying High 30-Year/Lifetime Risk Groups Among Young Adults 20-39 Years**



Identifying high 30-year/lifetime risk groups in young adults aged 20-39 years focuses on 6 groups that can be easily identified and for which there are specific actions for clinicians to pursue. If risk factors are persistently elevated and statin therapy contemplated, a CAC score may be useful (see Discussion). *Hypercholesterolemia defined as LDL-C ≥190 mg/dL or 160 mg/dL with risk factors. †Duration (type 1 >20 years, type 2 >10 years) and either 1 or more major risk factors or complications such as diabetic microangiopathy including albuminuria or an ankle brachial index <0.9. ‡No progress in 2-5 years depending on severity of risk factor burden. CAC = coronary artery calcium score; CHD = coronary heart disease; DM = diabetes mellitus; FH = familial hypercholesterolemia; HC = hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); RF = risk factor.

attempt to quit.[12] Counseling and pharmacotherapy are each effective alone, but combining the 2 produces greater success that either alone.[13] The routine delivery of tobacco cessation advice and offer of treatment is an essential component of high-quality health care.

The Expert Consensus Decision Pathway developed by the American College of Cardiology provides a framework for delivering tobacco cessation treatment in outpatient and inpatient clinical settings.[11] The pathway recommends regular monitoring of tobacco use, advice to quit, and repeated efforts to connect smokers to effective tobacco cessation resources.

IMPROVING TOBACCO CESSATION RATES. Clinicians need to couple their advice to quit with a brief intervention such as prescribing pharmacological smoking cessation aids and providing an active referral to evidence-based behavioral support in the health care system and/or the community.[11] This improves actual use of cessation treatment compared with passively providing information about behavioral support or recommending the purchase of nonprescription nicotine replacement products.[11]

TABLE 1 Ranges for Lipid/Lipoproteins and Risk Markers

	Desirable, Not a Target	Borderline High	Mild	Moderate	Severe
LDL cholesterol	<100 mg/dL[a]	100-129 mg/dL	130-159 mg/dL	160-189 mg/dL	190 mg/dL or higher
Non HDL cholesterol	<130 mg/dL[a]	130-159 mg/dL	160-189 mg/dL	190-219 mg/dL	220 mg/dL or higher
Triglycerides	<100 mg/dL	150-200 mg/dL	200-299 mg/dL	300-499 mg/dL	High[b] 500-999 mg/dL Very high[b] >1,000 mg/dL
Apolipoprotein B	<90[a]	90-110	110-129	130-154	≥155 mg/dL
Lp(a) mg/dL or nmol/L 2 caveats: 1) Percentiles are given for Caucasian Americans and differ by ethnicity/race 2) No effective proven treatment for Lp(a) exists, so risk factor, not a target	<30 mg/dL <75 nmol/L			≥50 mg/dL ≥100-125 nmol/L (serve as risk enhancing factors) 100 nmol/L is 80th[c] and 125 is 85th percentile	>180 mg/dL and 430 nmol/L (these values provide risk equivalent to that of heterozygous FH)

[a]In highest-risk patients, lower is better. [b]Risk is for hyperlipidemic pancreatitis. [c]Corresponding percentile for African Americans is 148 nmol/L.
HDL = high-density lipoprotein; LDL = low-density lipoprotein; Lp(a) = lipoprotein (a).

An important obstacle is infrequent physician contact, especially among young men, as many young women interact with the health care system for gynecologic and prenatal care. For young adults with children, well-child visits to a pediatrician or family practitioner may provide an opportunity for intervention. Therefore, primary care physicians, obstetricians, and child health care providers are crucial for preventive efforts. Smoking cessation is particularly critical after the development of disease; continued smoking after MI is associated with increased cardiovascular mortality over 2 years.[6] Reaching young adult smokers with cessation messages and treatment will be maximized if efforts expand beyond the health care system. Other channels for communicating both tobacco use prevention and cessation messages to the young adult population include schools and colleges, the workplace, the military, and social media.

HYPERTENSION

Addressing elevated blood pressure (BP) is crucial to implementing current guideline recommendations.[14] BP can be controlled with health behavior changes (diet, regular activity, weight management) as well as inexpensive, effective, and safe medication therapy. Despite this, hypertension control rates have worsened in Americans in recent years including among young adults aged 18-44 years (36.7%). This is seen in groups often over-represented by young adults including those without health insurance (24.2%); those without a regular health provider (26.5%); and those who have not had a health care visit in the previous year (8.0%).[15]

Though elevated BP is currently defined as a BP ≥130/80 mm Hg for stage I hypertension, risk occurs at a much lower level.[16] Long-term risk analyses demonstrate the biology of hypertension in industrialized societies.[17] BP tracks and rises with age, and end-organ damage occurs early and at relatively low BP levels.[17] Observational studies have shown a graded increase in coronary artery calcium (CAC) and incident ASCVD events with higher systolic BP beginning as low as 90 mm Hg.[16] Further clinical trials to "prove" benefit of keeping BP <120 mm Hg are not likely to be performed. However, observational evidence provides strong support for achieving lower BP with initial emphasis on behavioral change.[1]

IMPLEMENTATION CHALLENGES IN THOSE WITH ELEVATED BP UNDER AGE 40. ASCVD prevention in young adults requires better implementation of current guideline recommendations: lifestyle therapy for all and pharmacologic therapy for all adults with stage 2 hypertension (≥140/≥90 mm Hg) and those with stage 1 hypertension (≥130/≥80 mm Hg) and increased ASCVD risk.

IMPROVING BP CONTROL. A recent American Heart Association (AHA) scientific statement encourages use of medication in stage 1 patients at low 10-year risk unable to achieve BP control with lifestyle interventions alone.[17] For patients who were identified as having hypertension during adolescence/childhood and were prescribed antihypertensive drug therapy, consideration should be given to the original indications for starting drug treatment and the need to continue antihypertensive medication and lifestyle behaviors as young adults. In young adults with stage

1 hypertension not controlled with lifestyle behaviors, special consideration should be given to use of antihypertensive medication in individuals with a family history of premature ASCVD, history of hypertension during pregnancy, or personal history of premature birth because these increase lifetime ASCVD risk. Earlier implementation of needed medication can reduce risk in young adults, but further implementation science is needed to improve guideline adherence and decrease disparities in BP control.[16] Better management of hypertension can be achieved: no new tests are necessary, office/home BP measurements suffice, and adequate medications exist. BP should be measured annually in children and adolescents beginning at age 3 years and at least annually in all adults age 18 and older.[14]

TABLE 2 Estimated 10- and 30-Year Risk of ASCVD Among Younger Adults

Sex	Smoker	Horizon	Age 20 y	Age 25 y	Age 30 y	Age 35 y	Age 40 y
Female							
	No	10-y					1
	No	30-y	1	3	4	7	9
	Yes	10-y					4
	Yes	30-y	3	5	8	12	17
Male							
	No	10-y					2
	No	30-y	2	4	7	11	15
	Yes	10-y					5
	Yes	30-y	5	9	14	20	26

Values are %. Ten-year risk calculated using Pooled Cohorts Equations and 30-year risk calculated using 30-year Framingham risk score (ASCVD). We assumed systolic blood pressure = 130 mm Hg, total cholesterol = 220 mg/dL, high-density lipoprotein (HDL) cholesterol = 45 mg/dL (resulting in non-HDL cholesterol of 175 mg/dL) and no diabetes.

ASCVD = atherosclerotic cardiovascular disease.

HYPERCHOLESTEROLEMIA

PREVALENCE OF DYSLIPIDEMIA IS HIGH IN YOUNG ADULTS. Cholesterol levels measured early in life influence the development and progression of atherosclerosis and long-term ASCVD risk.[18-20] The first critical step to managing lipid-related risk is appropriate screening. Screening guidelines for children and adolescents are discussed in detail in the 2018 cholesterol guidelines.[19] Adults should have standard lipids and the traditional ASCVD risk factors assessed at least every 5 years starting at age 20.[19-21] Only one-half of youths aged 6-19 years have ideal levels for standard lipids and apoB, and about 25% of adolescents have at least 1 component of their lipid profile in an adverse range.[22] Those with the highest values (Table 1) require further evaluation and intensive risk factor control.

ASCVD RISK RELATES TO DURATION OF EXPOSURE. Research from multiple observational cohort studies has shown that risk of ASCVD increases with increased exposure to elevated low-density lipoprotein cholesterol (LDL-C), independent of other risk factors, in a dose-dependent fashion.[23] Similar to pack-years of smoking, increased duration of exposure to elevated LDL-C and non-HDL-C increased risk in young adults. In the CARDIA (Coronary Artery Risk Development in Young Adults) study, which enrolled adults aged 18-30 years with a median 16-year follow-up, incident CVD risk increased as accumulation of exposure to LDL-C increased, even after adjusting for other risk factors.[24] In the Framingham Offspring Cohort, researchers showed that for every 10-point increase in average non-HDL-C above 125 mg/dL between the ages of 35 and 55 years, future ASCVD risk increased by 33%.[25,26]

IMPROVING LIPID CONTROL IN YOUNG ADULTS. The impact of elevations in LDL-C and apoB appears to be stronger in younger individuals compared with older individuals. Both the Framingham risk scores and the pooled cohort equations (PCE) include interaction terms for age and lipids.[27] In the INTERHEART (Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction) case control study, the association between lipid levels and MI attenuated with increasing age.[25]

Although large cardiovascular outcomes trials of statins have not enrolled young adults, meta-analyses of individual patient data have failed to show a heterogeneity of effect by age or baseline risk.[28] Data from trials of children and adolescents with familial hypercholesterolemia (FH) further support the safety and efficacy of statins in younger age groups.[29] Finally, long-term follow-up data from trials such as WOSCOPS (West of Scotland Study) indicate that the benefit of early treatment with statin therapy persists even after therapy is discontinued, suggesting the potential of a legacy effect of early therapy.[30]

FAMILIAL HYPERCHOLESTEROLEMIA. Young adults with FH are at very high risk of cardiovascular disease and are recommended to initiate high-intensity statin therapy.[19] Based on the results of the 1999 to 2012 NHANES (National Health and Nutritional Examination Survey), the prevalence of probable/definite FH in the United States was estimated to 1 in 250 (95% CI: 1 in 311 to 1 in 209).[31] Although FH is rare, the prevalence of FH is higher in adults with premature ASCVD.[32-34] A systematic multinational review and meta-analysis of 42 studies from general populations and 20 from populations with ASCVD, found that the

TABLE 3 Advantages and Negatives for Different Risk Prediction Targets

Solutions for Predicting Longer-Term Risk	Advantage	Negatives
1. Use the existing 30-y risk algorithm.	• Reputable, well-characterized Framingham population used for model development with actual follow-up over 30 y. • Flexible modeling which allows estimation of treatment benefit under different scenarios and existence of programmed calculators.	The core limitations are • Small size and lack of diversity in the development cohort (whites only); • Use of older data; and • It is unclear whether 30-y follow-up is the optimal time horizon versus, for example, a full lifetime risk.
2. Develop a new lifetime risk calculator.	• Although the existing lifetime model does not directly apply to individuals aged 20-39 y and quantifies risk only for a set of categories, the idea of risk prediction until the age equal to average life expectancy is consistent with the desire to eradicate ASCVD.	• The challenge with building such a model would be in identifying cohorts with sufficient follow-up. • This could be partially overcome with modeling: considering age as a time scale and assuming that shorter risk estimates across different ages can be combined into 1 longer-term estimate.
3. Focus on estimating the risk of subclinical disease.	• Predicting the risk of nonzero coronary artery calcium in the next 10 y would give a more tangible focus for the younger age group.	• Reliance on surrogate outcomes has the usual limitations related to misclassification error.
4. Focus solely on predicting the risk of reaching adverse levels of key causal risk factors.	• Hypertension: Framingham risk score predicting near-term risk of hypertension in adults aged 20-39 y, only in whites and not validated. • Lipids: consider 2 elevated measurements of non-HDL-C >160 mg/dL a few years apart as a strong predictor of future cholesterol trajectory. • Diabetes: consider models predicting the risk of type 2 diabetes.	Although predicting the probability of adverse causal factors is practically aligned to treatment decisions, the absence of integrated estimates of risk and risk reduction may provide an incomplete picture of the overall cardiometabolic risk burden and potential benefit.

ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol.

overall prevalence of FH, primarily by clinical criteria, was 1 in 311 in the general population and was 18-fold higher in those with ASCVD, largely due to coronary artery disease.[35]

IMPROVING IDENTIFICATION AND EFFECTIVE THERAPY OF FH. Many adults with FH do not receive treatment with high-intensity statins, demonstrate suboptimal adherence to statin therapy,[36] and if they have had an MI, have persistent LDL-C levels >70 mg/dL 1 year post-event. We need to overcome clinician hesitancy to treat younger patients and failure to use guideline-endorsed therapy, and address appropriately patient concerns about statin-associated muscle symptoms or the development of statin-associated DM.[37]

Moreover, in young adults, several factors contribute to underdiagnosis, including the absence of symptoms of FH, low prevalence of physical findings characteristic of FH,[38] and absence of universally agreed-upon diagnostic criteria and cost including potential insurability and employability implications of the molecular confirmation of FH.[39,40] Once patients are diagnosed with FH, cascade screening of family members is critical to identify undiagnosed cases. Physicians need to emphasize to first-degree relatives of a patient with confirmed FH that the likelihood of having FH is 1 in 2—screening is high yield!

All adults with FH should initiate statin therapy with a goal to reduce LDL-C by 50% or more. PCSK9 inhibitors are clinically appropriate and cost-effective in those primary prevention FH patients taking maximally tolerated statins and ezetimibe with LDL-C >130 mg/dL, or ≥100 mg/dL in the presence of poorly controlled cardiometabolic risk factors or ≥70 mg/dL with established ASCVD.[41] New modes of treatment requiring less frequent dosing are also under investigation.[42]

OTHER TARGETS FOR ASSESSING AND LOWERING LIPID-RELATED RISK

APOLIPOPROTEIN B. A standard lipid panel measures total cholesterol, HDL-C, and triglycerides, and calculates LDL-C and non-HDL-C. ApoB is a measure of the number of non-HDL particles per volume, which is often, but not always, correlated with LDL-C measurements. ApoB is currently not part of a standard lipid panel in the United States. ApoB is better correlated with non-HDL-C than with LDL-C because although an apoB molecule is carried on each LDL, there is also an apoB molecule on each triglyceride-rich lipoprotein that may be present. In some persons, LDL-C and apoB are discordant. Discordant individuals have lower than average levels of LDL-C and higher than average apoB levels, and are at increased risk of ASCVD. For example, in the CARDIA study, individuals with high apoB or discordantly high apoB/low LDL-C (or non-HDL-C) had 1.5- to 2.3-fold higher risk of developing CAC 25 years later.[43]

Improving identification of risk using ApoB levels. ApoB testing is low-cost and widely available. Measuring apoB to identify discordant adults provides useful information, particularly in those with cardiometabolic risk factors such as elevated triglycerides with lower LDL-C, personal/family history of premature ASCVD or genetic dyslipoproteinemias.[19,43] ApoB is an enhancing factor that should be considered in the aforementioned situations. Early identification of younger individuals with elevated apoB offers an opportunity to initiate earlier and more intensive preventive therapies beginning with lifestyle.[19,21]

TRIGLYCERIDES. Elevated triglycerides are associated with increased risk of ASCVD, but it is less clear whether triglycerides are causally associated or whether triglycerides are a marker of another atherogenic moiety of the triglyceride-rich lipoproteins. Although some studies found independent associations for triglycerides with CVD risk, a meta-analysis of 68 prospective studies (>300,000 individuals) did not, after adjusting for non-HDL-C or apoB.[44] Genetic studies suggest that association between plasma triglycerides and ASCVD risk is causal, but many genetic variants are pleiotropic and are often associated with differences in very LDL/remnant cholesterol, apoB, or HDL-C, making it challenging to identify the causal atherogenic component. In a large meta-analysis of randomized trials, triglyceride lowering was associated with lower ASCVD risk, which was somewhat lower than seen for LDL-C. Importantly, this risk reduction was attenuated when the REDUCE-IT trial (Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial) was excluded.[45]

Whether or not triglycerides are causal for ASCVD, persistent hypertriglyceridemia serves as an important marker for young adults at higher risk of events.[46] Hypertriglyceridemia is multifactorial, arising from the interaction of genetic and nongenetic factors. Plasma triglycerides are usually mildly to moderately elevated in patients with insulin resistance, abdominal obesity, and poor health behaviors. Severe elevation in triglycerides is often due to the combination of unhealthful diet and inadequate physical activity on a background susceptibility of multiple genetic defects.[47] Persistent hypertriglyceridemia is a call to action for young adults to improve metabolic fitness.

In a global systematic review and meta-analysis of risk factors for premature MI, mild elevation in triglycerides (>150 mg/dL) was associated with 2- to 3-fold higher risk of premature MI, similar to the magnitude of risk noted for total cholesterol >200 mg/dL or HDL-C <60 mg/dL.[48] It is notable that these mild triglyceride elevations were associated with higher risk of premature events. In addition, prospective data from the Women's Health Study suggests that triglycerides are an important risk marker for premature CHD events in women, with a magnitude of risk stronger than that of LDL-C or non-HDL-C.[49] Severe elevations in triglycerides (>500 mg/dL) should be treated regardless of age to prevent hyperlipidemic pancreatitis and reduce ASCVD risk.[19,46] Although there are no available medication therapies to lower ASCVD risk in otherwise healthy individuals with less severely elevated triglycerides (150-499 mg/dL), those who do have triglycerides in this range should be considered at higher long-term risk and counseled on appropriate lifestyle interventions.

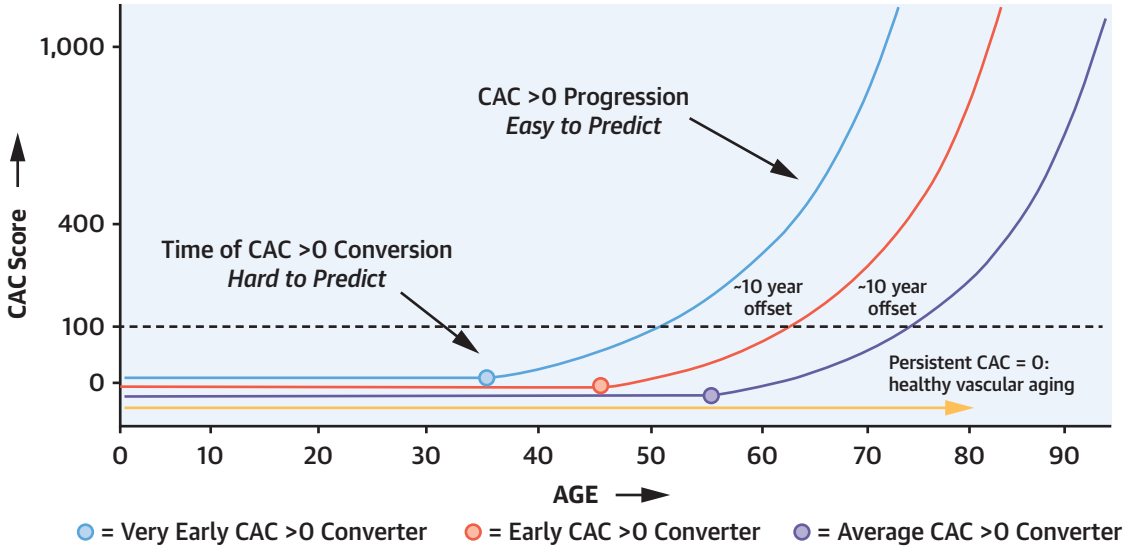
Improving evaluation and treatment of hypertriglyceridemia. The "2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients With Persistent Hypertriglyceridemia" provides indispensable algorithms for the clinician who sees young adults with hypertriglyceridemia.[46]

LIPOPROTEIN (a). Lipoprotein (a), or Lp(a), is a subtype of LDL distinct from LDL and carries a single molecule of apo(a). Apo(a) comes in different varieties (isoforms) that are genetically determined by the *LPA* gene. Similar to LDL, Lp(a) is produced in the liver, and carries 1 apoB per particle, free cholesterol, cholesterol esters, triglycerides, and phospholipids including oxidized phospholipids. Fasting is not required for Lp(a) testing.[50] Lp(a) levels are stable over long periods of time as seen in a large cohort study[51] as well as in JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin)[52] and ODYSSEY Outcomes (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab)[53] randomized controlled trials (RCTs). Nongenetic factors that affect Lp(a) levels include chronic kidney disease (especially nephrotic syndrome), liver disease, hypothyroidism, DM, postmenopausal state, acute inflammation, and some medications.[54]

Observational studies, genetic Mendelian randomization studies, and meta-analyses have found an approximately 10% to 20% relative risk increase in ASCVD risk per SD higher Lp(a).[52,54,55] In the Women's Health Study, Lp(a) levels measured in midlife were associated (per SD) with ~10% to 20% increased risk of future CHD events, which did not

FIGURE 2 Time Course of Conversion to CAC >0

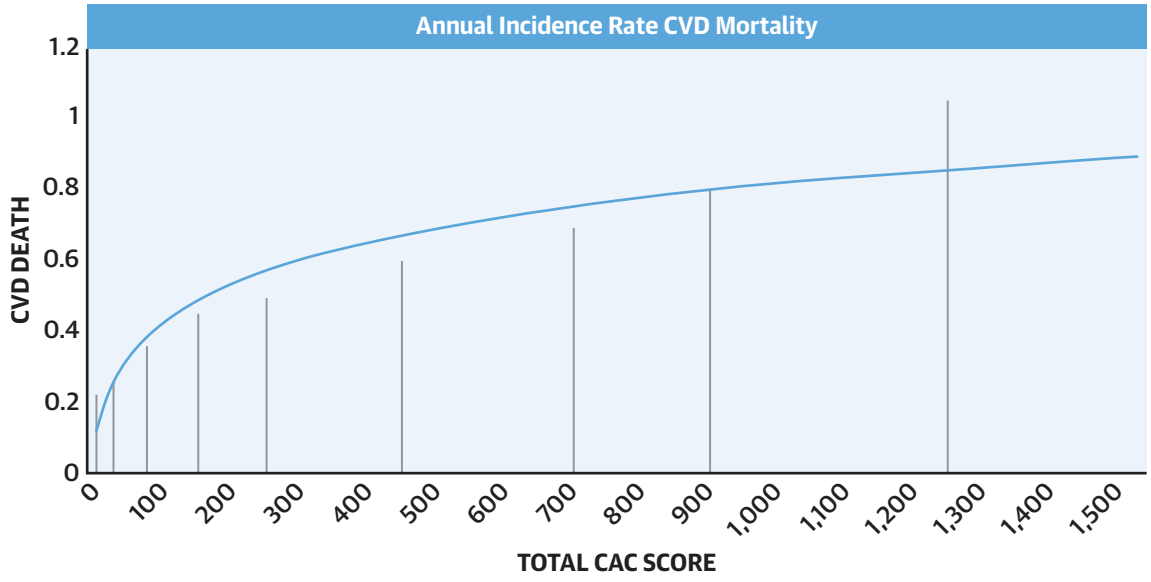
A



B

White Male Patient at the 90th Percentile			
Age 40	Age 50	Age 60	Age 70
10	110	452	1,345

C



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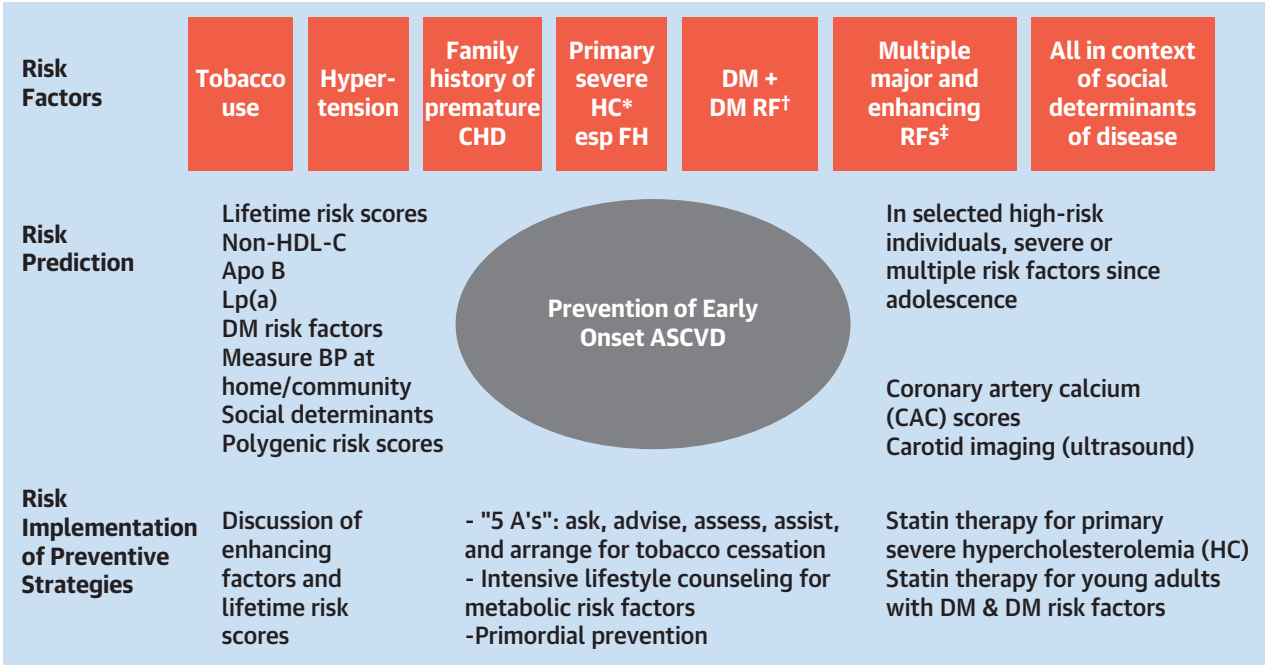
CENTRAL ILLUSTRATION **Approach to Atherosclerotic Cardiovascular Disease Prevention in Young Adults**



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An approach to prevention of early onset ASCVD requires identification of major groups of risk factors, singly or in combination. To further risk prediction, validated tools include lipid/lipoprotein risk factors and DM risk factors. Obtaining blood pressure measurements may require community outreach. Understanding social determinants of risk puts risk factor analysis in context. Imaging may be useful in a selected group of individuals as discussed in the text. Finally, risk reduction implementation requires extensive lifestyle counseling, perhaps available in multi-disciplinary metabolic clinics, and/or statin therapy is needed in those found to have primary severe hypercholesterolemia or DM with DM risk factors. *Hypercholesterolemia defined as LDL-C ≥190 mg/dL or 160 mg/dL with risk factors. †Duration (type 1 >20 years, type 2 >10 years) and either 1 or more major risk factors or complications such as diabetic microangiopathy including albuminuria or an ankle brachial index <0.9. ‡No progress in 2-5 years depending on severity of risk factor burden. apoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CAC = coronary artery calcium score; CHD = coronary heart disease; DM = diabetes mellitus; FH = familial hypercholesterolemia; HC = hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); RF = risk factors.

differ by age at CHD onset,[49] unlike other standard lipid and apoB associations that attenuated at older age of onset. Although evidence supports Lp(a) as a causal risk factor for ASCVD,[54] therapies to lower ASCVD risk via Lp(a) are still under investigation.

Improving evaluation and management of risk with Lp(a). Guidelines indicate that a high level of Lp(a) is a long-term risk factor that favors preventive therapies targeting other modifiable risk factors.[19,21,56] However, guidelines differ in who should get tested and the cutpoints used to classify those at higher risk. Lack of harmonization of Lp(a) measurements, differing percentiles for various population groups, and lack of a validated therapy for Lp(a) limit the ability to create uniform cutpoints. Notably, European[21] and Canadian[56] guidelines have endorsed screening of Lp(a) once in a lifetime to identify those at very high risk who merit intensive

FIGURE 2 Continued

(A) Coronary artery calcium score (CAC) score as a function of age. Many individuals retain a CAC score of zero for one-half of their life or longer before developing coronary calcification. However, others develop CAC decades earlier. This shows curves of very early, early, and average converters to CAC >0. Reproduced with permission from Blaha.[91] **(B)** Example of white male patient at 90th percentile over the life course. After the onset of coronary calcification, CAC scores slowly rise, commonly taking 10-15 years before CAC scores exceed 100 Agatston units; over the next 10-15 years CAC scores may grow to >1,000 Agatston units. **(C)** Annual incidence rate cardiovascular disease (CVD) mortality as a function of CAC score. Analyses show the greatest prognostic value of CAC is at its low range (CAC scores 0-100). CVD event rates vary widely between individuals with CAC = 0 vs CAC = 100, before leveling off at higher scores.[90-95]

TABLE 4 Addressing High-Risk Conditions in Young Adults 20-39 Years

	Key Points and Implications
Tobacco use	• Ask regarding smoking history at each medical encounter. • Employ regular monitoring of tobacco use, advice to quit, and repeated efforts to connect smokers to effective tobacco cessation resources (including medication or counseling).[11-13] • Primary care physicians, obstetricians, and child health care providers should be a focus for preventive efforts.
Hypertension and elevated BP	• Measure BP properly in office visit and give appropriate advice for BP home measurements. • Consider additional treatment in young adults with stage 1 hypertension (130-139 mm Hg) not controlled with a suitable period of lifestyle behavior change.[17] • Give special consideration for use of antihypertensive medication in individuals with a family history of premature ASCVD, history of hypertension during pregnancy, or a personal history of premature birth. • Continue antihypertensive medication and lifestyle behavior change if hypertension during adolescence (or childhood) requiring antihypertensive drug therapy.
Family history of premature ASCVD	• Update regularly. • Address risk factor burden, counsel regarding tobacco avoidance/cessation and utilize proven risk factor reduction strategies.
Lipids	• Measure lipids either fasting or non-fasting in all young adults seeking non-emergency medical care. • Advise all how to pursue healthy dietary behavior change, but particularly focus on those with additional ASCVD risk factors and/or a family history of premature ASCVD. • Consider for drug treatment those with severe abnormalities of lipids/lipoproteins per guidelines.[19,20]
Elevated LDL-C	• Rule out secondary causes of severe hypercholesterolemia such as severe restricted carbohydrate diets high in saturated fats, hypothyroidism, nephrotic syndrome, obstructive liver disease. • Identify and treat early those with severe hypercholesterolemia—for example, LDL-C ≥190 mg/dL, or ≥160 mg/dL, particularly in the presence of a personal or family history of premature ASCVD. Per guidelines, add statins to healthy life habits to reduce subsequent risk of heart attack and stroke.[19] • Perform cascade screening of first-degree relatives in those identified with FH to efficiently find cases (1 in 2).
Hypertriglyceridemia ApoB/non-HDL-C Lipoprotein (a)	• Treat persistent hypertriglyceridemia as a marker of increased cardiometabolic risk by an initial focus per guidelines on appropriate diet, physical activity and weight control.[19] • Understand how levels of non-HDL-C and apoB are especially useful in patients with hypertriglyceridemia to assess further ASCVD risk. • Understand how levels of Lp(a) serve as a risk factor in those with a personal or family history of premature ASCVD but understand that Lp(a) is not a target of therapy.
Diabetes	• Identify young adults with type 1 diabetes of ≥20 y duration, or type 2 diabetes of ≥10 y duration, and/or microvascular disease, or additional ASCVD risk factors, as those at enhanced risk for subsequent ASCVD. • Considering above qualifiers, these patients are candidates for statin therapy and aggressive non-lipid risk factor management per guidelines.[19]
Metabolic syndrome	• Understand how the presence of the metabolic syndrome, a marker for overnutrition and insufficient physical activity, identifies individuals at increased risk for development of fatty liver, type 2 diabetes, and ASCVD. • Choose as first-line treatment, lifestyle intervention characterized by gradual weight loss, adherence to heart healthy dietary patterns, and regular aerobic exercise. • This may require referral to preventive cardiology and/or multidisciplinary clinics that can increase chances for success.
Multiple major risk factors and enhancing factors	• Review all the factors that have an impact on the patient's subsequent ASCVD risk. • Because a 10-y risk score would not be available in the 20- to 39-y-old age group, longer-term or 30-y-old risk is important to present to the patient. • This personalizes the risk discussion. • It allows clinicians and patients to address reducing the trajectory of risk over this time (as noted above) and consider what additional testing may be required to help with therapeutic decision (based on available data).

LDL-C = low-density lipoprotein cholesterol; other abbreviations as in Tables 1, 2, and 3.

risk factor control. Once measurement issues are resolved and especially if current RCTs show significant, safe benefits for novel methods of reducing high Lp(a), this strategy has the promise of identifying and treating those with enhanced ASCVD risk.[21,56]

DIABETES

Although RCTs have proven the benefit of statin therapy for primary prevention of ASCVD in people with DM aged 40-75 years,[57] there have been no risk factor intervention trials in cohorts with DM aged <40 years except for the Diabetes Control and Complications Trial in type 1 DM. This study showed that 6.5 years of intensive control of hyperglycemia reduced ASCVD events after an average follow-up of 18 years.[58] Furthermore, there are few long-term prospective studies in patients with DM aged <40 years that provide guidance for outcomes-based ASCVD risk assessment. More definitive data are needed to guide preventive management strategies in this group, because the population incidence of DM diagnosed before 40 years of age has been increasing over the past 2 decades, especially for type 2 DM, and even among children and adolescents where it is especially prominent in minority race/ethnicity groups.[59] Aside from the fact that DM onset at <40 years of age carries with it a longer lifetime exposure to the disease and its complications compared with those with later onset, there is increasing evidence that earlier-onset type 2 DM is more rapidly progressive than it is in older adults[60] and is associated with a greater risk of

ASCVD compared with similarly aged individuals with type 1 DM.[61] This is likely related to the higher prevalence of cardiovascular risk factors and earlier development of microangiopathic complications such as retinopathy, neuropathy, and nephropathy,[62] all of which are known to enhance ASCVD risk in DM.[57]

Available evidence indicates that whereas rates of ASCVD are low in those aged <30 years, the risk increases with time, reaching intermediate levels by 30-39 years of age in a sizable subgroup of individuals, especially those with longer duration of DM, namely 10 years' duration of type 2 DM,[63] or 20 years' duration of type 1 DM.[64] In addition, about one-half of those with DM aged 40-49 years are already at intermediate levels of ASCVD risk.[65]

About 50% of adults with type 2 DM aged 30-39 years have coronary plaque using computed tomography (CT) angiography, and 25% are more likely to have CAC than non-diabetic control subjects after adjustment for known risk factors.[66] In type 1 DM, CAC was present in 29% of a cohort, with average age 40 years, where CAC presence was related to duration of DM and cardiovascular risk factors and was significantly associated with an increased risk of CVD events.[67]

IMPROVING EVALUATION AND MANAGEMENT OF DM IN YOUNG ADULTS. The 2018 cholesterol guidelines recommended that in adults aged 20-39 years with a duration of at least 10 years for type 2 DM or 20 years for type 1 DM, and a major risk factor and/or microvascular disease, or other risk-enhancing factors, it may be reasonable to initiate statin therapy.[19,57] The National Lipid Association proposed that CAC scoring may be reasonable to aid in ASCVD risk stratification and statin treatment decisions in young adults, adding that if a CAC score is >100, it may be reasonable to choose high-intensity statin therapy.[68] In summary, a significant proportion of young adults with DM, particularly those aged >30 years should be considered for initiation of statin treatment in addition to effective management of other CVD risk factors and enhancers that are prevalent in this age group, particularly in those with type 2 DM.

METABOLIC SYNDROME

The metabolic syndrome (MetS) is a multiplex risk factor for ASCVD and includes[69] dyslipidemia (elevated triglycerides and apoB, and reduced HDL-C), dysglycemia, elevated BP, prothrombotic state, and a proinflammatory state.[70] Clinical diagnosis of MetS requires 3 or more of 5 easily measured clinical criteria or thresholds for diagnosis. These include elevated waist circumference (>102 cm in men and women),[71] elevated blood pressure (≥130/85 mm Hg), elevated fasting triglycerides (≥150 mg/dL), low HDL-C (<40 mg/dL in men and <50 mg/dL in women), and elevated blood glucose (≥100 mg/dL).[69] In Asian populations, waist circumference >90 cm in men or >80 cm in women is abnormal.[69]

In aggregate, the MetS doubles the risk of future ASCVD events.[72,73] In the absence of categorical hyperglycemia, the presence of MetS carries a 5-fold risk of developing DM.[74] Thus, the 2018 guidelines[19] identified MetS as a risk-enhancing factor. The core abnormality of the MetS consists of an imbalance between intake and catabolism of nutrients (overnutrition).[75] This abnormality is characterized by an increased accumulation of lipid in muscle and liver.[76] Excess lipid in muscle is responsible for insulin resistance and elevated plasma glucose concentration. Overloading the liver with lipids promotes development of fatty liver. Mechanisms whereby overnutrition contribute to high BP, prothrombotic state, and proinflammatory state likely are multifactorial and not entirely understood. A simple indicator of overnutrition is the presence of upper body obesity. When nutrients are not fully catabolized in peripheral tissues, they are stored in upper body adipose tissue. An increased waist girth is the best clinical indicator of abdominal obesity and overnutrition.

The MetS can be reversed by caloric restriction and increased physical activity. The syndrome is rapidly reversed in patients undergoing bariatric surgery.[77] The reversal of metabolic risk factors occurs before significant weight reduction, indicating the key role of nutrient intake. The MetS can also be reversed by increased nutrient catabolism, occurring with increased physical activity.[78] Approximately one-third of U.S. adults develop MetS by middle-age (>40 years)[79] when obesity in the U.S. population peaks. Younger adults are less obese, and the prevalence of MetS is lower. This lower prevalence may result from greater metabolic rate (due to greater muscle mass) and more physical activity.

IMPROVING EVALUATION AND TREATMENT OF MetS. Because MetS emerges as a powerful risk factor by middle age, efforts should be made to retard its development in young adulthood. Clinicians should point out to patients the relationship between their lower abdominal obesity and metabolic abnormalities of lipids, glucose, and BP. Addressing this is best accomplished by combination of reduced caloric intake and increased physical activity. The AHA/American College of Cardiology and related societies provide educational materials concerning adjusting caloric intake and recommendations for regular

physical activity. Clinicians need to not only offer effective counseling for excess calorie and simple carbohydrate ingestion, but also couple that with a prescription for regular physical activity. Initiation of better eating habits and improved physical activity is more likely to be successful when introduced in young adulthood than later in life.

RISK ASSESSMENT TOOLS

IMPROVING RISK STRATIFICATION IN YOUNG ADULTS. The PCE are not designed for young adults under 40 years of age.[80] For young adults, 30-year or lifetime risk of a first ASCVD event can be useful for risk discussions with patients. A 30-year risk model[81] is based on Framingham Heart Study data and includes the same risk factors as the PCE, except for race because Framingham is almost entirely Caucasian. The lifetime risk calculation recommended by the 2018 cholesterol guideline is based on larger data, integrating several National Heart, Lung, and Blood Institute-funded and other cohorts.[82] However, unlike the 30-year model, it is based on risk factors assessed at ages 45 and older, so application to the 20-39 age group would require extrapolation. Furthermore, estimates provided are based on predefined risk categories based on numbers of risk factors rather than a continuous risk estimation for every combination of risk factors.

In Table 2, we display 10- and 30-year risks of ASCVD for 20-, 25-, 30-, 35-, and 40-year-old women and men, stratified by smoking, assuming a systolic BP of 130 mm Hg, total cholesterol = 220 mg/dL, HDL-C = 45 mg/dL (resulting in non-HDL-C of 175 mg/dL), and no DM. A few observations are striking. First, it emphasizes that for those aged 20-39 years, 10-year risks would be low. However, by contrast, 30-year risk can be substantial, especially among smokers, far exceeding simple tripling of a 10-year risk. The applicability of the 30-year risk calculator in younger adults is seen when applied to a nationally representative NHANES sample.[83]

Among adults aged 30-39 years, the average 30-year risk of ASCVD is 4.2% for those with non-HDL-C <130 mg/dL, 6.8% for those with non-HDL-C 130 to 160 mg/dL, and 11.0% when non-HDL-C >160 mg/dL. Using the additive feature of the calculator to model annualized and longer-term benefit of immediate versus delayed initiation of intensive lipid-lowering, the authors estimate that 25% to 50% of the 30-year risk could be avoided with immediate lipid-lowering.

Implications. Given the aforementioned considerations, options for risk assessment among young adults 20-39 years are outlined in Table 3. However, for simplicity, persistently elevated non-HDL-C, particularly in the presence of other major ASCVD risk factors, may help to identify those for whom earlier preventive therapies may be reasonable.[84] Clinicians are cautioned not to assess ASCVD risk by unproven adjustments to current short-term risk equations designed for those adults 40 to 75 years.

FAMILY HISTORY AND ETHNICITY. A large component of risk for ASCVD can be attributed to inherited risk and genetic susceptibility A. family history (FamHx) of premature ASCVD in first-degree relatives <55 years in men and <65 years in women is a risk-enhancing factor.[19] Like other risk-enhancing factors, it imparts a higher lifetime than short-term risk. Too often, family history of ASCVD is poorly assessed, documented, or not known. The 2018 AHA/American College of Cardiology/multisociety cholesterol guidelines identified ethnicity as a risk-enhancing factor. South Asian status results in higher rates of ASCVD for both immigrants and nonimmigrants but is currently ascribed to increased prevalence of known risk factors such as insulin resistance.[85]

Implications. The presence of a FamHx of premature ASCVD prompts careful assessment and treatment of treatable risk factors such as hypertension, dyslipidemia, and diabetes. FamHx should be updated often. Ethnicity, especially South Asian ancestry, may provide clues as to a greater risk factor burden for patients.

GENETIC RISK SCORES. Quantification of genetic risk for ASCVD could inform risk earlier in life. Many common genetic variants of small individual effects play a large relative role in the risk of ASCVD. Advances in array-based genotyping have led to efforts to derive and validate largescale, genome-wide PRS, which integrate millions of commonly occurring single nucleotide variants for a variety of common diseases.[86]

To date, no studies have examined the clinical utility of PRS in risk stratification for ASCVD in individuals aged <40 years.[87,88] However, an analysis of the CARDIA study showed that PRS was significantly associated with the presence of CAC >0, suggesting the potential for utility of PRS at younger ages before the onset of traditional risk factors.[89] However, comparison to long-term risk prediction, such as 30-year risk equations that have been derived in U.S. and UK adults and are recommended by current clinical guidelines was not performed.

Implications. Future studies examining the utility of PRS in younger adults need to consider targeting

those without evidence of traditional risk factors and compare PRS against long-term risk models for ASCVD or imaging of atherosclerosis.

SPECIFIC FACTORS IN YOUNG WOMEN. The 2018 cholesterol guidelines recommended that a comprehensive pregnancy history should be obtained for ACVD risk assessment of women, because pregnancy-related risk factors such as pre-eclampsia are early indicators of future cardiovascular risk.[19] This is particularly relevant for younger women in whom global risk scores are in a low-risk range. MetS variables serve to prompt the clinician to look for polycystic ovarian syndrome, hormone contraceptive use, and gestational DM.[73]

Implications. Per guidelines, premature menopause (<40 years old) and preeclampsia, especially recurrent preeclampsia, signal longer-term ASCVD risk. They are an essential part of a prevention checklist for women 20-39 years.

CAC TESTING. CAC scanning offers the ability to detect coronary atherosclerosis in its earliest stages. CAC is identified using noncontrast cardiac-gated CT of the heart. This is a rapid test using low radiation (~1 mSv) that can be performed at low cost on any modern multidetector CT scanner using a highly standardized protocol.

Although CAC has been widely used as a decision aid with the goal of detecting CAC in middle-aged adults, there are emerging data regarding detecting low CAC burden in young adults.[90] Many are not aware that the Agatston score, the unit of measurement, is on an exponential scale.[91] CAC scores grow as a function of the baseline score (typically 20%-25% per year). Many individuals retain a CAC score of zero (CAC = 0) for one-half of their life or longer before developing coronary calcification, whereas others develop CAC decades earlier (**Figure 2A**). After the onset of coronary calcification, CAC scores slowly rise, commonly taking 10 to 15 years before CAC scores reach ~100; over the next 10 to 15 years, CAC scores may grow to >1,000[92,93] (**Figure 2B**). Analyses show the greatest prognostic value of CAC is at its low range (CAC scores 0-100).[91] CVD event rates vary widely between individuals with CAC = 0 vs CAC = 100, before leveling off at higher scores (**Figure 2C**). Therefore, focus has shifted toward identifying high-risk individuals at an early age when CAC scores are low. This provides decades available for risk modification before the onset of clinical ASCVD. For example, it is likely that middle-aged adults with clinically important CAC scores (for example, CAC ~450 at age 60) would have been identified with non-zero CAC scores up to 20-25 years earlier.

There is a small, but selectively important, yield of CAC scoring at an early age. An early report from the CARDIA study of 443 men and women aged 28-40 years showed the mean CAC score was low, ranging from 1 to 12 across the sex and race/ethnic groups.[94] The strongest modifiable risk factors were body mass index, systolic BP, and LDL-C. The Walter Reed Cohort Study of 13,387 young adult low-risk individuals aged 30-49 years, found that the presence and severity of CAC >0 (increased for CAC >100) was significantly associated with higher risk of major cardiovascular events and MI over 11 years of follow-up.[95]

A later report from CARDIA studied prognostic significance of premature CAC among over 3,000 individuals (55% were women, mean age of 40 years) who were followed for 12.5 years. Notably, 10% had CAC >0 with mean CAC score of 22.[96] Although individuals with CAC = 0 had very low CHD event rates (1 per 100 persons), there was a graded increase in risk with increasing CAC (**Figures 2A and 2B**). Young individuals with CAC 1 to 19 had an HR of 2.6 for all CHD events, those with CAC 20-99 had an HR of 5.8, whereas those with CAC ≥100 had an HR of 9.8.

The CAC Consortium is a large observational study of 22,346 patients referred for CAC scanning between the ages of 30 and 50 years.[90] Overall ASCVD risk was low, and a strong FamHx and abnormal lipids were common. In this cohort, 34.4% had CAC (approximately 21% in those aged 30-40 years). CHD, CVD, and all-cause mortality increased in a graded fashion with increasing CAC (**Figure 2C**). The crude CHD mortality rate was 10 times higher among those with CAC >100 compared with CAC = 0, and remained significant after multivariable adjustment.

A further report from the CAC Consortium presented sex-specific equations derived from a multivariable logistic model designed to estimate the expected probability of CAC >0 according to age and the presence of ASCVD risk factors.[90] CAC prevalence reached >25% in young men with at least 1 risk factor by age 40, whereas women with at least 1 traditional risk factor had >25% prevalence of CAC by age 50.[90] The presence of multiple risk factors is most concerning; by 40 years of age, approximately 1 of every 4 men with hypertension, dyslipidemia, smoking, or a FamHx of CHD would have CAC >0.

Implications. Although the presence of CAC is not common in those under 40, men with risk factors comprise a higher-risk group in whom a CAC score

may convey prognostic information. Use of CAC scores should ideally occur after a clinician-patient risk discussion to put the information gained in perspective. Its worthy of repeat mention that men and women with FH do not require risk scores or CAC scores for statin initiation; they have a high enough lifetime risk to merit therapy at a young age.

OTHER VASCULAR IMAGING. Carotid and iliofemoral imaging are complementary modalities that can be used to show atherosclerotic plaque in middle-aged adults over 40 years. The PESA (Progression of Early Subclinical Atherosclerosis) study [97] has taught us that presence of atherosclerotic plaque determined by ultrasound of carotids, iliofemoral, and aorta or by CT in the coronary tree (CAC) in 63% of adults occurs in mid-life at an average age of 46. Of note, plaque may be present in the iliofemoral area when a CAC score = 0. PESA highlighted that lifestyle factors such as poor sleep, socioeconomic factors, and diet were harmful. It emphasized the deleterious effect of the "social business eating pattern" as contrasted with the "Mediterranean" eating pattern. The former is characterized by consumption of red and processed meat, pre-prepared meals, appetizers, snacks, and alcoholic and sugar-sweetened beverages, together with frequent eating out. Although the PESA study looked at individuals aged >40 years, its lessons, especially as concerning lifestyle, have strong implications for clinician-patient risk discussions in young adults.

The Cardiovascular Risk in Young Finns study[98] demonstrated that detection of carotid atherosclerotic plaque in young adulthood before age 40 is not frequent (about 3.3%) but, when present, depended on the presence of childhood risk factors of systolic BP, level of LDL-C, cigarette smoking, and body mass index in adolescence. Carotid plaque in young adults was not seen when no childhood risk factors were measured. This further underscores the importance of risk factor control early in life. As with CAC, if noninvasive carotid imaging is used in young adults, its usefulness will be seen in those with risk factor burden acquired in childhood and adolescence.

CLINICIAN–PATIENT RISK DISCUSSION. Patient understanding of their own ASCVD risk is foundational to a clinician-patient risk discussion, yet most patients are unable at baseline to estimate their own risk of ASCVD.[99] Lifetime risk estimates being numerically higher may lead to higher perceived 10-year risk, particularly in young adults at high lifetime, but numerically low 10-year, risk. A successful conversation about ASCVD prevention also involves identifying and addressing patient-reported barriers. For many patients, fear or unwillingness to take therapy may outweigh their perceived risk of heart disease. This is especially the case for statins, with fear of statin side effects being the leading patient-reported reason for declining therapy.[100]

Implications. Better tools, and research supporting their effectiveness, are needed for clinicians to both communicate the benefits and risks of preventive therapies and address any misinformation about treatments.

BARRIERS AND OPPORTUNITIES IN ADDRESSING RISK IN YOUNG ADULTS. Less than 5% of Americans report adhering to all of AHA's Life Simple 7 health behaviors to prevent ASCVD.[3] Pediatricians deliver both weight loss and smoking cessation interventions to parents in the context of well-child care. As the 2018 cholesterol guidelines indicated in their children and adolescents section, a focus on obesity is a high priority. This section provides useful insights that can be important to doctors seeing adult patients with children. By young adulthood, regular doctor visits may occur less often. To close the risk factor recognition gap in these patients, we endorse measuring BP outside the office, addressing tobacco or substance abuse in the workplace or community, and regularly eliciting in women a history of pregnancy complications such as preeclampsia and/or history of premature menopause. To overcome a barrier to measuring lipids, nonfasting lipids, as recommended by guidelines,[19] should occur routinely in young adults seen in afternoon or early evening clinics. Eliciting and updating the FamHx should occur in all young adults because it can lead to more intensive risk factor screening, including consideration of Lp(a) levels and apoB. Finally, a 30-year risk estimation with non-HDL-C or apoB as well as CAC scoring for use in decision-making in selected young adults should be considered to guide the risk discussion. Statin therapy should not be deferred until age 40 in those with primary severe hypercholesterolemia or those with diabetes with diabetes risk factors such as long duration and microangiopathic features.

SUMMARY

To reduce subsequent ASCVD in young adults 20-39 years, high-risk conditions can be identified and appropriately intervened upon (**Central Illustration**). Implications of our analysis are seen in **Table 4**. It is important to assess tobacco use at every young adult health care visit and provide effective intervention because the benefit of quitting before age 40 years is

substantial. Assessing and managing hypertension in young adults requires lifestyle changes including diet, activity, and weight control. Persistent elevations in BP require additional attention with pharmacotherapy. In young adults with LDL-C ≥160 mg/dL, presence of a FamHx of premature ASCVD should lead to more intensive evaluation and statin treatment. Once FH and/or very elevated levels of Lp(a) are diagnosed, statin treatment to reduce LDL-C levels as per guidelines[19] and implementation of cascade screening in family members can have a significant impact beyond the individual patient. Nonfasting lipids, including non-HDL-C and/or apoB, may provide more accurate risk assessment than LDL-C alone. They are especially useful in those with persistent hypertriglyceridemia in whom an above average apoB indicates heightened risk even though LDL-C levels may be below average. MetS, a marker of increased cardiometabolic risk, requires initiation of guideline-directed lifestyle interventions. Cardiometabolic clinics that can provide the additional services such as dietary and exercise counseling may be especially helpful to the clinician. Most important, a systematic appraisal as suggested by this review holds the promise to deliver increased clinical attention and appropriate therapy to those young adults at highest risk for premature MI in the subsequent years ahead.

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