ATHEROSCLEROSIS IN YOUNG ADULTS

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THIS EPISODE'S OVERVIEW

- Atherosclerosis in Young Adults
- Risk Factor Burden
- Evolution of Premature CAD
- CAD and Sudden Cardiac Death in Young Adults
- Managing CAD in Young Adults
- Risk Assessment Tools

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ATHEROSCLEROSIS BURDEN

- 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.
- 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 less than 40 years.
- They had similar risk profiles except for more substance abuse and spontaneous coronary artery dissection and less hypertension.

JACC VOL. 79, NO. 8, 2022 Stone et al MARCH 1, 2022:819 – 836 Addressing ASCVD Risk Factors in Young Adults 20-39 Years

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RISK FACTOR BURDEN AND LONG-TERM PROGNOSIS OF PATIENTS WITH PREMATURE CORONARY ARTERY DISEASE

Past or current smoking was the most frequent cardiovascular factor (60.8%), followed by hypertension (52.8%) and family history of CAD (39.8%). Within a 10-year follow-up, 52.9% of patients had at least 1 MACE, 18.6% had at least 2 recurrent MACEs, and 7.9% had at least 3 recurrent MACEs, with death occurring in 20.9% of patients. Across follow-up, 31.7% to 37.2% of patients continued smoking, 81.7% to 89.3% had low-density lipoprotein cholesterol levels beyond the goal of 70 mg/dL, and 16% had new-onset diabetes mellitus. Female sex, diabetes mellitus, chronic kidney disease, multivessel disease, and chronic inflammatory disease were factors associated with recurrent MACEs.

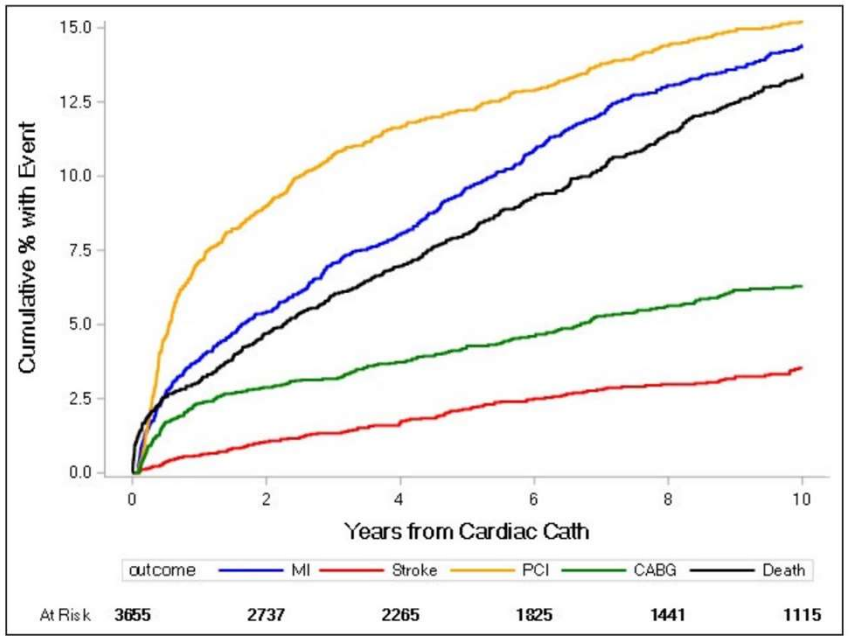

Figure 1. Time to first subsequent major adverse cardiovascular event within 10 years after premature coronary artery disease diagnosis.
CABG indicates coronary artery bypass grafting; Cath, catheterization; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

DOI : 10.1161/JAHA.120.017712

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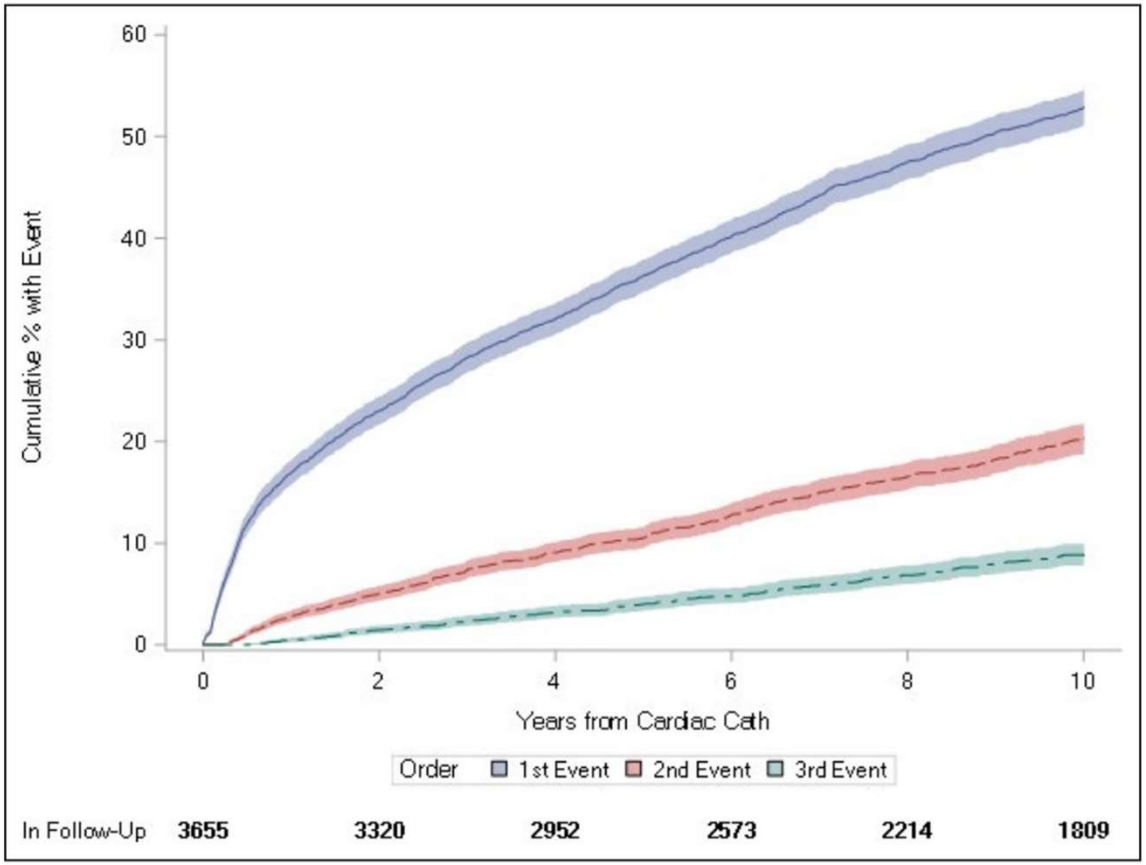

Figure 2. Time to first, second, or third major adverse cardiovascular event within 10 years after premature coronary artery disease diagnosis.
Cath indicates catheterization.

DOI : 10.1161/JAHA.120.017712

Table 2. Factors Associated With Time to First Ischemic Recurrence

Covariate	Univariable	Univariable *P* Value	Multivariable	Multivariable *P* Value
	Hazard Ratio (95% CI)		Hazard Ratio (95% CI)	
Age (per 10-y increase)	1.06 (0.96–1.16)	0.282	1.03 (0.93–1.14)	0.565
Sex (women vs men)	1.32 (1.20–1.47)	<0.001	1.15 (1.03–1.28)	0.010
BMI ≥27 kg/m^2 (per 5-kg/m^2 increase)	1.06 (1.02–1.10)	0.002	1.04 (1.00–1.09)	0.052
Racial/Ethnic group (White is the reference)		<0.001		0.054
Black	1.29 (1.16–1.44)		1.10 (0.98–1.23)	
Native American and other (eg, Hispanic, Pacific Islander)	1.16 (0.97–1.39)		1.16 (0.96–1.39)	
Chronic inflammation	1.69 (1.29–2.20)	<0.001	1.61 (1.23–2.11)	<0.001
Family history of coronary disease	1.04 (0.95–1.15)	0.364	1.06 (0.96–1.17)	0.213
Admission with ACS vs no ACS	0.83 (0.75–0.93)	<0.001	1.10 (0.99–1.23)	0.080
Current/former smoker	0.96 (0.87–1.06)	0.431	1.03 (0.93–1.13)	0.627
History of hypertension	1.27 (1.15–1.39)	<0.001	1.03 (0.93–1.14)	0.521
Diabetes mellitus	1.68 (1.52–1.86)	<0.001	1.35 (1.21–1.51)	<0.001
eGFR per 20 mL/min per 1.73 m^2 decrease	1.34 (1.28–1.40)	<0.001	1.19 (1.13–1.25)	<0.001
LDL-C ≥120 mg/dL per 20-mg/dL increase	0.97 (0.93–1.02)	0.280	1.02 (0.96–1.08)	0.523
Triglycerides per 50-mg/dL increase	1.01 (0.99–1.04)	0.237	1.00 (0.98–1.03)	0.909
Multivessel disease	1.39 (1.27–1.53)	<0.001	1.47 (1.33–1.63)	<0.001
Statin at discharge	0.80 (0.72–0.88)	<0.001	1.01 (0.91–1.13)	0.823
Subsequent treatment within 30 d		<0.001		<0.001
PCI vs medical treatment	0.41 (0.37–0.45)		0.45 (0.41–0.50)	
CABG vs medical treatment	0.29 (0.24–0.34)		0.25 (0.21–0.30)	

ACS indicates acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; and PCI, percutaneous coronary intervention.

DOI : 10.1161/JAHA.120.017712

Table 3. Factors Associated With Multiple Ischemic Recurrences

Covariate	Univariable	Univariable *P* Value	Multivariable	Multivariable *P* Value
	Rate Ratio (95% CI)		Rate Ratio (95% CI)	
Age (per 10-y increase)	0.95 (0.65–1.41)	0.817	0.88 (0.62–1.25)	0.470
Sex (women vs men)	1.45 (0.96–2.17)	0.075	1.13 (0.77–1.65)	0.535
BMI ≥27 kg/m^2 (per 5-kg/m^2 increase)	1.07 (0.91–1.25)	0.410	1.05 (0.90–1.22)	0.531
Racial/Ethnic group (White is the reference)		0.175		0.512
Black	1.51 (0.98–2.34)		1.27 (0.85–1.90)	
Native American and other (eg, Hispanic, Pacific Islander)	1.09 (0.52–2.30)		1.09 (0.56–2.11)	
Chronic inflammation	2.05 (0.59–7.10)	0.255	1.87 (0.63–5.52)	0.259
Family history of coronary disease	0.98 (0.67–1.43)	0.904	1.05 (0.74–1.48)	0.803
Admission with ACS vs no ACS	0.82 (0.53–1.26)	0.365	1.09 (0.73–1.62)	0.673
Current/former smoker	0.90 (0.62–1.33)	0.610	1.04 (0.72–1.49)	0.842
History of hypertension	1.47 (1.01–2.14)	0.044	1.11 (0.77–1.58)	0.581
Diabetes mellitus	1.99 (1.29–3.06)	0.002	1.47 (0.99–2.20)	0.058
eGFR per 20 mL/min per 1.73 m^2 decrease	1.48 (1.24–1.77)	<0.001	1.29 (1.06–1.55)	0.010
LDL-C ≥120 mg/dL per 20-mg/dL increase	0.92 (0.77–1.10)	0.375	0.96 (0.80–1.16)	0.677
Triglycerides per 50-mg/dL increase	1.01 (0.92–1.10)	0.875	1.00 (0.92–1.09)	0.969
Multivessel disease	1.50 (1.03–2.17)	0.034	1.44 (1.00–2.06)	0.049
Statin at discharge	0.84 (0.57–1.23)	0.365	1.01 (0.70–1.48)	0.943
Subsequent treatment within 30 d		<0.001		<0.001
PCI vs medical treatment	0.42 (0.28–0.61)		0.48 (0.33–0.69)	
CABG vs medical treatment	0.30 (0.14–0.61)		0.27 (0.14–0.52)	

ACS indicates acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; and PCI, percutaneous coronary intervention.

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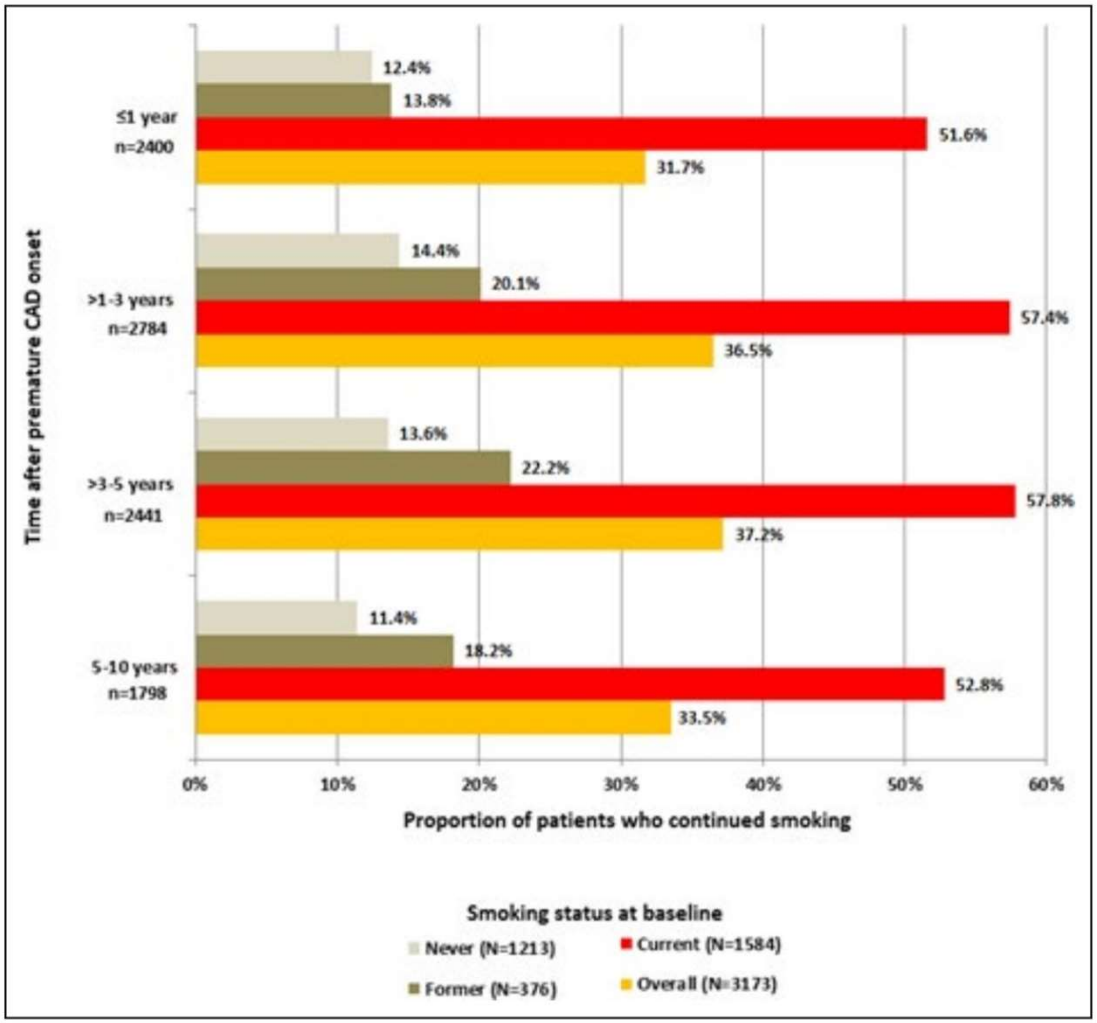

Figure 3. **Smoking continuation after premature coronary artery disease (CAD) onset, stratified by baseline smoking status.**

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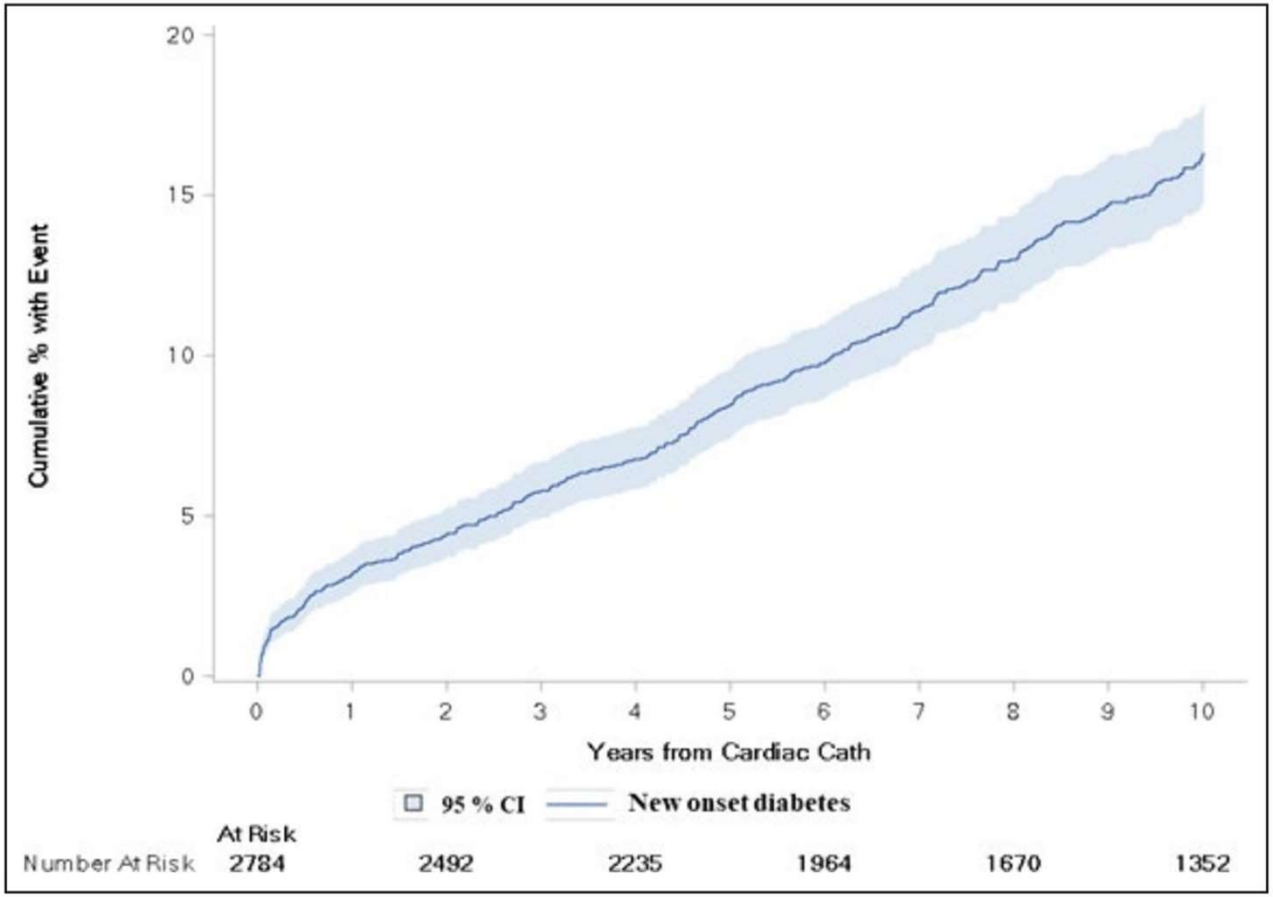

Figure 4. Cumulative rate of new-onset diabetes mellitus after premature coronary artery disease diagnosis.
Cath indicates catheterization.

DOI : 10.1161/JAHA.120.017712

EVOLUTION AND OUTCOMES OF PREMATURE CORONARY ARTERY DISEASE

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Table 1 Depiction of current frequently used societal guidelines in regard to screening recommendations for traditional risk factors

	ACC/AHA recommendations [9•]	USPSTF recommendations [10]—of note, update currently in progress [11]	Future directions
Lipid screening	• Age 20–40 years: screen every 4–6 years • Age 40–75 years: screen every year	• Ages 20–40: screen if risk factors for CHD present[a] • Men: Screen when >35 years • Women: when > 45 years	• Routine obstetric lipid screening for women • Consider universal screening between the ages of 18–20 • Updates in the USPTF guidelines are currently in progress
Statin initiation	• Age 20–75 years: high-intensity statin if LDL-C ≥190 • Age 40–75 years with T2DM: moderate-intensity statin (with risk estimate[b] to consider high-intensity statin) • Age 40–75 years and LDL-C ≥ 70mg/dl mg/dl without DM, and ASCVD ≥ 7.5%: start moderate-intensity statin • Age 40–75 years and LDL-C ≥ 70mg/dl and <190 mg/dl without DM, and ASCVD risk 7.5–19%, risk-enhancing factors favor initiation of statin therapy[b] • Age 40–75 years and LDL-C ≥ 70mg/dl and <190 mg/dl without DM, and ASCVD risk 7.5–19%, consider using CAC for stratification and initiating statin if CAC is ≥100 Agatston units or ≥75th percentile	• Age 40–75 with ASCVD ≥10%: If no CVD then initiate only if all criteria are met: (1) aged 40–75 years; (2) they have 1 or more CVD risk factors; and (3) they have a calculated 10-year risk of a cardiovascular event of 10% or greater • Age 40–75 with ASCVD 7.5–10%: Clinicians may choose to offer a low-to moderate dose statin to certain adults without a history of CVD when all of the following criteria are met: (1) aged 40–75 years; (2) they have 1 or more CVD risk factors and (3) they have a calculated 10-year ASCVD risk of 7.5–10%	• Sex- and age-targeted statin initiation including non-traditional risk factors for younger demographics • Ubiquitous use of non-statin medications to continue to lower risk in patients that are uncontrolled by statin alone • Machine learning to tailor statin initiation on individual risk profiles
CAC screening	• Ages 40–75 years without DM and LDL 70–189 mg/dl at ASCVD risk of ≥7.5–19% to inform statin therapy decision if uncertain [12•]	• Does not recommend at this time	• Consider screening young patients with high CAC risk scores as described by CARDIA study

https://doi.org/10.1007/s11886-021-01457-8

Hypertension screening	• Age 20 start screening at least every 2 years if BP <120/80 mm Hg	• Ages >40, have high-normal blood pressure, overweight or obese and African Americans, screen annually • Ages 18–39 with normal blood pressure who do not have other risk factors screen every 3–5 years
Hypertension management	• Normal BP (BP <120/80): promote optimal lifestyle habits • Elevated BP (BP 120–120/<80 mm Hg): non-pharmacological therapy • Stage 1 Hypertension (BP 130–139/80–89 mmHg): ° Estimated 10-year CVD risk ≥10%: non-pharmacological therapy and BP lowering medication ° Estimated 10-year CVD risk < 10%: non-pharmacological therapy • Stage 2 Hypertension (BP ≥140/90 mm Hg): non-pharmacological therapy and BP-lowering medication	• For nonblack patients, initial treatment consists of a thiazide diuretic, calcium-channel blocker, angiotensin-converting enzyme inhibitor, or angiotensin-receptor blocker. For black patients, initial treatment is thiazide or a calcium-channel blocker. Initial or add-on treatment for patients with chronic kidney disease consists of either an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker (not both)

Note the discrepancies in screening guidelines particularly in younger patients.

[a] Risk factors include diabetes, HTN, smoking, family history of CAD or HLD

[b] Risk-enhancers: in diabetics include ≥ 10 years for T2DM and 20 years for type 1 DM, ≥ 30 mcg albumin/mg creatinine, eGFR <60 ml/min/1.73m^2, retinopathy, neuropathy, ABI <0.9.

https://doi.org/10.1007/s11886-021-01457-8

BURDEN OF CORONARY ARTERY DISEASE AS A CAUSE OF SUDDEN CARDIAC ARREST IN THE YOUNG

TABLE 1 Characteristics of CAD-Related SCA in Young (Age <40 Years) Patients Compared With Young Non-CAD Cases and CAD-Related SCA in Older (Age ≥40 Years) Patients

	<40 Years Non-CAD (n = 84)	p Value	<40 Years CAD (n = 58) (Ref)	p Value	≥40 Years CAD (n = 1,177)
Age, yrs	30.9 ± 6.1	<0.001	35.2 ± 4.4	<0.001	62.4 ± 12.0
Sex	62 (73.8)	0.07	51 (87.9)	0.47	982 (83.4)
Prior known cardiac disease	34 (40.5)	<0.001	6 (10.9)	<0.001	414 (36.7)
CAD	0 (0.0)	0.15	2 (3.6)	<0.001	347 (30.9)
≥1 cardiovascular risk factor	42 (50.6)	<0.001	46 (82.1)	0.10	1,009 (89.9)
Hypertension	7 (8.4)	0.85	6 (10.9)	<0.001	469 (41.8)
Overweight (BMI >25 kg/m^2)	18 (21.7)	0.62	15 (26.8)	0.09	440 (38.9)
Current smoking	24 (28.9)	<0.001	33 (58.9)	0.02	477 (42.5)
Dyslipidemia	1 (1.2)	0.001	9 (16.4)	0.02	362 (32.2)
Diabetes mellitus	3 (3.6)	1.00	2 (3.6)	<0.001	235 (20.9)
Family history of CAD	7 (8.4)	0.40	8 (14.5)	0.36	110 (9.8)
ST-segment elevation on first ECG	12 (16.9)	<0.001	34 (64.2)	0.25	600 (55.1)
Discharged alive	60 (71.4)	0.003	26 (44.8)	0.82	499 (42.4)

Values are mean ± SD or n (%).

BMI = body mass index; CAD = coronary artery disease; ECG = electrocardiogram; SCA = sudden cardiac arrest.

JACC VOL. 73, NO. 16, 2019 Letters APRIL 30, 2019:2117 – 2 2

MANAGING ATHEROSCLEROTIC CARDIOVASCULAR RISK IN YOUNG ADULTS

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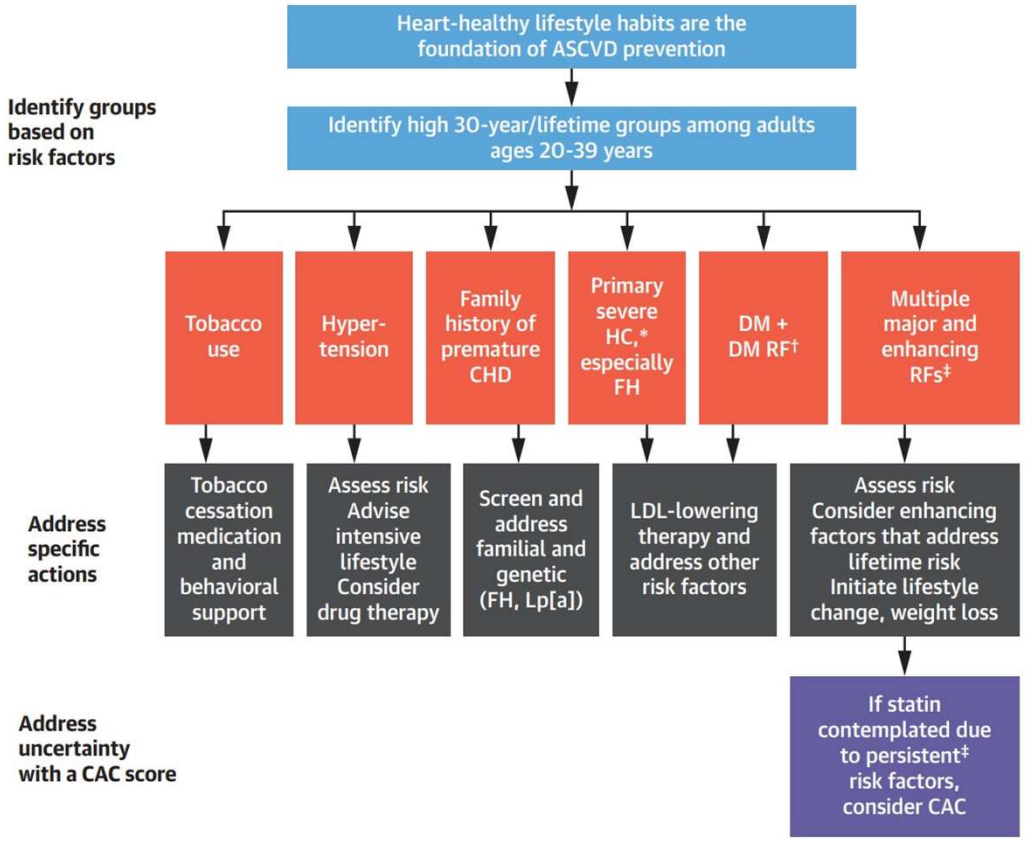
FIGURE 1 Identifying High 30-Year/Lifetime Risk Groups Among Young Adults 20-39 Years



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.

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TOBACCO USE

- CIGARETTE SMOKING INCREASES VIRTUALLY ALL CLINICAL MANIFESTATIONS OF ASCVD.
- Smoking acts synergistically with hypertension, DM, and hyperlipidemia to increase ASCVD risk.
- 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.
- 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.
- 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%).

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- Although e-cigarettes have lesser toxic material than cigarettes, there are some studies that document negative effects on ASCVD factors.
- THE BENEFITS OF SMOKING CESSATION ARE SUBSTANTIAL, ESPECIALLY EARLY IN LIFE. Smok ing decreases an individual's life expectancy by approximately 10 years.
- 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%.
- 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 attempt to quit.

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HYPERTENSION

- 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%).
- Though elevated BP is currently defined as a BP 130/80 mm Hg for stage I hypertension, risk occurs at a much lower level.
- BP tracks and rises with age, and end-organ damage occurs early and at relatively low BP levels.
- 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.

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- 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.
- 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.
- In young adults with stage1 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.
- 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.

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HYPERCHOLESTEROLEMIA

- Cholesterol levels measured early in life influence the development and progression of atherosclerosis and long-term ASCVD risk.
- Adults should have standard lipids and the traditional ASCVD risk factors assessed at least every 5 years starting at age 20.
- 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 require further evaluation and intensive risk factor control.
- 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. Similar to pack-years of smoking, increased duration of exposure to elevated LDL-C and non–HDL-C increased risk in young adults.

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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).

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- In the Framingham Offspring Cohort, researchers showed that for every 10-point increase in average non–HDL-C above 125 mg/dL be tween the ages of 35 and 55 years, future ASCVD risk increased by 33%.
- 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.
- Data from trials of children and adolescents with familial hypercholesterolemia (FH) further support the safety and efficacy of statins in younger age groups.
- Finally, long-term follow-up data from tri als 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.
- 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).
- Although FH is rare, the prevalence of FH is higher in adults with premature ASCVD.

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- 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 more than 100 mg/dL in the presence of poorly controlled cardiometabolic risk factors or more than 70 mg/dL with established ASCVD.

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.

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APOLIPOPROTEIN B

- 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 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.
- Measuring apoB to identify discordant adults pro vides useful information, particularly in those with cardiometabolic risk factors such as elevated tri glycerides with lower LDL-C, personal/family history of premature ASCVD or genetic dyslipoproteinemias.

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TRIGLYCERIDES

- 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.
- 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.
- See also episode 023- Hypertriglyceridemia; a Friend or Foe?

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Lipoprotein (a)

- 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.
- Lp(a) levels are stable over long periods of time as seen in a large cohort studies.
- Nongenetic factors that affect Lp(a) levels include chronic kidney disease (especially nephrotic syndrome), liver disease, hypothyroidism, DM, post-menopausal state, acute inflammation, and some medications.
- 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).
- Guidelines indicate that a high level of Lp(a) is a long-term risk factor that favors preventive therapies targeting other modifiable risk factors.
- 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 and Canadian guidelines have endorsed screening of Lp(a) once in a lifetime to identify those at very high risk who merit intensive risk factor control.

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DIABETES

- Aside from the fact that DM onset at earlier age than 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 adults60 and is associated with a greater risk of ASCVD compared with similarly aged individuals with type 1 DM.
- 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. 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.
- You can also listen episodes of 026 and 027 with diabetes mellitus wrap-up.

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METABOLIC SYNDROME

- Includes dyslipidemia (elevated triglycerides and apoB, and reduced HDL-C), dysglycemia, elevated BP, prothrombotic state, and a proinflammatory state.
- 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), elevated blood pressure (130/85 mm Hg), elevated fasting triglycerides (150 mg/dL), low HDL-C less than 40 mg/dl and elevated blood glucose more than 100 mg/dl.
- In aggregate, the MetS doubles the risk of future ASCVD events.
- In the absence of categorical hyperglycemia, the presence of MetS carries a 5-fold risk of developing DM.
- Mechanisms whereby overnutrition contribute to high BP, prothrombotic state, and proinflammatory state likely are multifac torial 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.

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- The MetS can be reversed by caloric restriction and increased physical activity. The syndrome is rapidly reversed in patients undergoing bariatric surgery.
- 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.
- 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.

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RISK ASSESSMENT TOOLS

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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.

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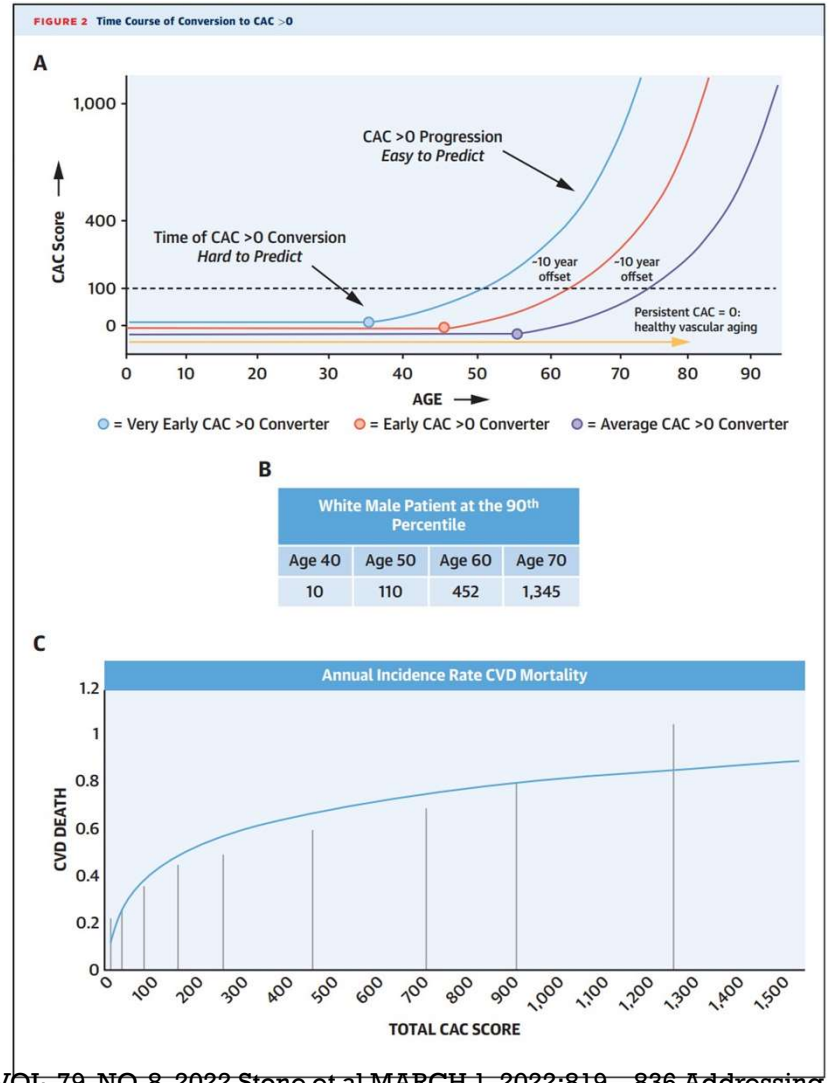

(A) Coronary artery calcium score (CAC) score as a function of age. Many individuals retain a CAC score of zero for one-half of their life or longer before developing coronary calcification. However, others develop CAC decades earlier. This shows curves of very early, early, and average converters to 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 calci fication, 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 ¼ 0 vs CAC ¼ 100, before leveling off at higher scores.

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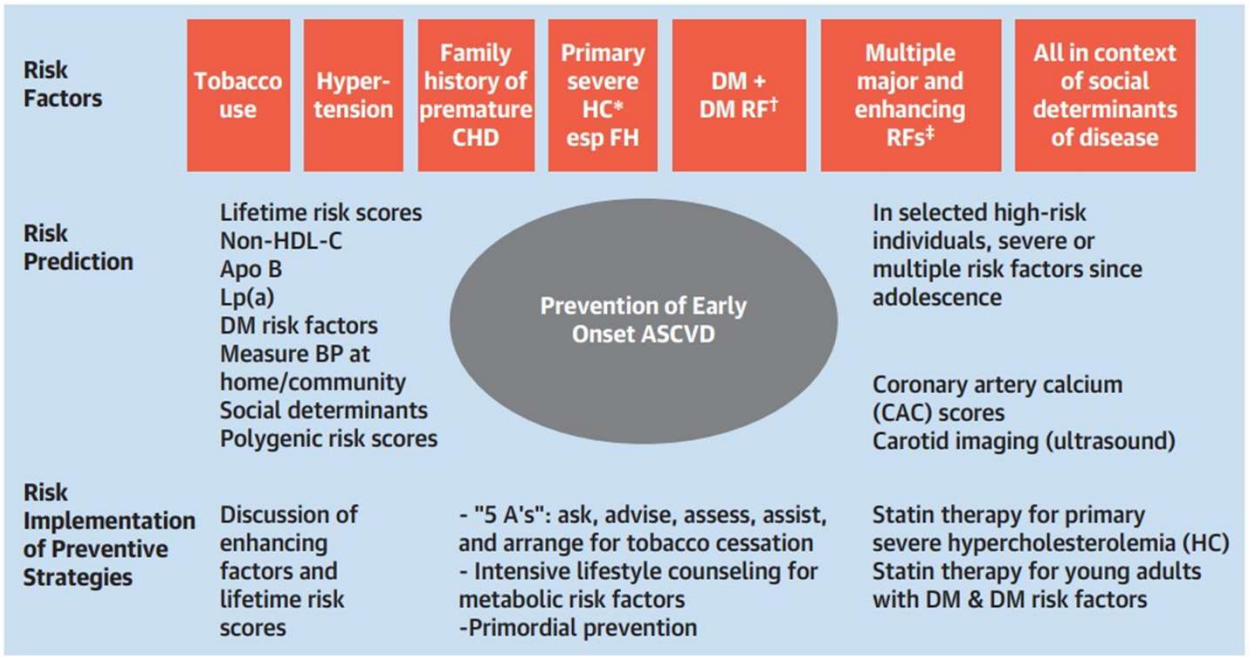
CENTRAL ILLUSTRATION Approach to Atherosclerotic Cardiovascular Disease Prevention in Young Adults



Stone, N.J. et al. J Am Coll Cardiol. 2022;79(8):819-836.

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.

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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.

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