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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

How Low to Go With Glucose, Cholesterol, and Blood Pressure in Primary Prevention of CVD

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ABSTRACT

Diabetes, hyperlipidemia, and hypertension are modifiable risk factors that predict cardiovascular disease events. The effect of these risk factors on incident cardiovascular disease increases with progressively higher levels of glucose, low-density lipoprotein cholesterol, and blood pressure. The thresholds for initiating treatment of these modifiable risk factors and the optimal goals of risk factor modification are a focus of primary prevention research. Although an aggressive approach is appealing, adverse events may occur, and potential physiological barriers may exist. This paper discusses primary prevention of coronary heart disease that may be achieved through modification of diabetes, hyperlipidemia, and hypertension by summarizing current guidelines and pertinent clinical trial data from intervention trials that included a primary prevention cohort. (J Am Coll Cardiol 2017;70:2171–85) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Deaths from atherosclerotic cardiovascular diseases (CVD) have declined in the past 3 decades; however, CVD remains the leading cause of death, accounting for nearly 1 in 3 deaths (1). The increasing incidences of obesity and type 2 diabetes mellitus (DM) contribute to this high rate (2,3). The INTERHEART (Effect of Potentially Modifiable Risk Factors Associated with Myocardial

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CRP = C-reactive protein

CVD = cardiovascular disease

DM = diabetes mellitus

HgA1c = hemoglobin A1c

HTN = hypertension

LDL-C = low density lipoprotein cholesterol

MI = myocardial infarction

PCSK9 = proprotein convertase subtilisin/kexin type 9

SBP = systolic blood pressure

Infarction in 52 Countries) study investigated risk factors associated with CVD death rates. INTERHEART measured 9 risk factors prior to a first myocardial infarction (MI) and found that they contributed to over 90% of the risk for a first MI. These 9 risk factors included DM, hypertension (HTN), and lipoprotein profile represented by varying apolipoprotein (Apo) B/A1 ratio strata (3,4). These data suggest that there is a significant opportunity for affecting public health by reducing CVD events through risk factor modification and prevention.

Prevention may be categorized as primordial, primary, secondary, and tertiary (**Central Illustration**). Primary prevention refers to the modification of risk factors associated with disease development, secondary prevention to the control of disease progression once present, and tertiary prevention to mitigating the consequences of advanced disease on functional status and quality of life. Primordial prevention refers to achieving a state of health that prevents risk factors for disease from developing. Although the opportunity for societal benefit is the greatest if this "time zero" before disease develops is preserved, this would require population-based strategies and systems-wide collaboration, which are difficult to achieve (2,5–7).

Epidemiological studies conducted in the past 4 to 5 decades have identified DM, hyperlipidemia, and HTN as predictors of CVD risk. The consistency of these data has resulted in CVD risk calculators that integrate multiple risk factors (2,3). In addition to there being significant pathophysiological interplay between these risk factors, another common denominator is their effect on the microvasculature. The microcirculation regulates blood flow and oxygen delivery via vasodilation and vasoconstriction of arterioles downstream of the macrovasculature. The coronary arteriolar bed increases coronary flow by modulating >55% of the total coronary vascular resistance. This is referred to as coronary flow reserve, which in the absence of epicardial (prearteriole) disease serves as a functional assessment of the coronary microcirculation (8,9). Impaired vasoreactivity of the microvasculature can affect the pressure and flow gradients that match perfusion to metabolic demand, causing myocardial ischemia (8). Resultantly, coronary microvascular disease was first used to explain anginal symptoms in patients without overt macrovascular disease (10,11). Postulated mechanisms for coronary microvascular disease that are shared between HTN, DM, and the metabolic syndrome include endothelial and smooth muscle dysfunction, dysregulation of nitric oxide synthesis, and the production of growth factors including angiotensin and endothelins (10,11). Microvascular disease in diabetic patients has been correlated with increased CVD events (12). In another observational study that included asymptomatic diabetic patients without coronary artery disease (CAD), a coronary flow reserve <2.5 was associated with a composite endpoint, which included mortality, acute coronary syndrome, or revascularization (13). This suggests a correlation between microvascular disease in diabetic patients and CVD. Furthermore, there are studies that have found lower coronary flow reserve in patients with HTN and hypercholesterolemia (9,14). A potential opportunity for averting the significant morbidity and mortality associated with CVD may be targeting prevention efforts at a stage before microvascular disease has developed.

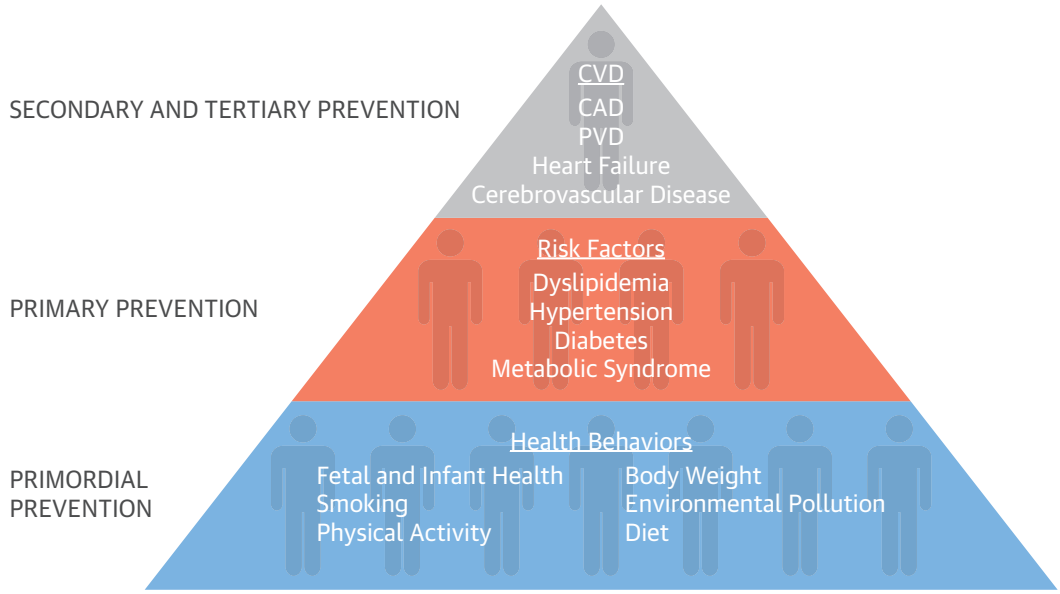
This paper discusses the primary prevention of CAD through the modification of 3 risk factors—DM, hyperlipidemia, and HTN—by summarizing the current guidelines and the varying perspectives and controversies regarding these guidelines that stem from an evolving evidence base.

CURRENT GUIDELINES

Prevention of CVD through glucose lowering in persons with DM and blood pressure in persons with HTN are target based. Specifically, in known diabetic patients, the target hemoglobin A1c (HgA1c) is 7%, with a lower threshold of 6.5% accepted when patient-specific characteristics, including length of disease and known CAD, are considered (15). In HTN, Eighth Joint National Committee recommendations suggested initiation of treatment at 140/90 mm Hg and have raised the target blood pressures for high-risk patients, including those with DM, cerebrovascular disease, chronic kidney disease, and CAD, from 130/80 to 140/90 mm Hg. There was also a change in blood pressure goal in individuals age >60 years to 150/90 mm Hg (16). This new upper threshold for treatment in this age group is particularly controversial, and the American Heart Association (AHA) and the American College of Cardiology (ACC) are expected to publish updated HTN guidelines soon (17).

The 2013 AHA/ACC cholesterol guidelines departed significantly from the paradigm of treating to a target low-density lipoprotein cholesterol (LDL-C) and instead shifted treatment toward differentiating between primary versus secondary CVD, and the overall risk of developing CVD. Specifically, 4 separate groups were defined based on presence or absence of

CENTRAL ILLUSTRATION **Cardiovascular Disease Prevention and Health Promotion**



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This figure depicts the tiered approach to preventing CVD. Primordial prevention makes up the base and optimizes health behaviors to reduce the development of CVD risk factors. The second tier is primary prevention, which targets CVD risk factors to prevent the development of CVD. Last, the apex is secondary and tertiary prevention, where CVD is targeted to prevent progression and development of additional CVD. Adapted with permission from Vaduganathan et al. (5). CAD = coronary artery disease; CVD = cardiovascular disease; PVD = peripheral vascular disease.

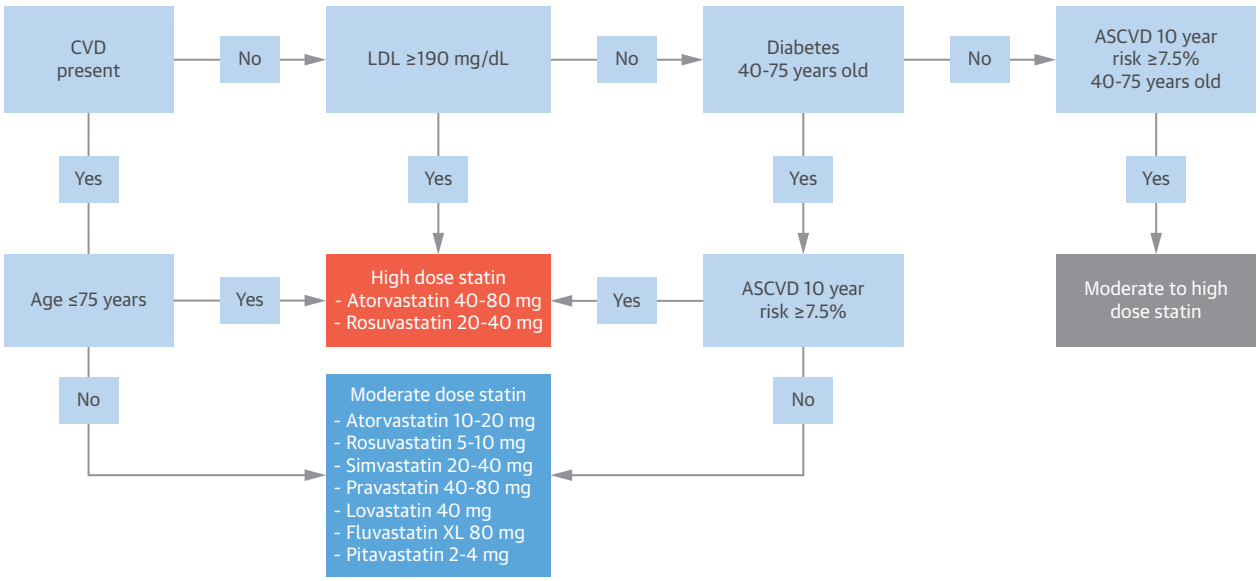
CVD, LDL-C levels ≥190 mg/dl, DM, and atherosclerotic cardiovascular disease (ASCVD) risk as determined by pooled risk equations, which are the basis for the AHA/ACC ASCVD risk calculator (**Figure 1**). In those who do not meet these criteria, other risk factors including genetic hyperlipidemias, family history, elevated high-sensitivity C-reactive protein (CRP), coronary artery calcium score, ankle-brachial index <0.9, and elevated life time risk for ASCVD can be used to refine treatment decisions (18,19).

Increasingly, clinical trials and guidelines are using CVD risk to guide treatment strategies (20,21). The AHA/ACC recommends using the pooled cohort ASCVD risk calculator. Assessment of risk is challenging because of limitations of contemporary data, including a delay in the acquisition of real-time clinical event data, and unexplained correlations resulting from unknown confounders or interactions with unmeasured variables. The most significant concern regarding this calculator is the overestimation of risk that has been attributed to the use of older National Heart, Lung, and Blood Institute data. Older data may not reflect current demographic changes, advances in disease modifying therapies, or population-based lifestyle changes that include trends in smoking and eating habits (19,21–23). One validation study that used a multiethnic cohort identified in 2008 and followed through 2013 overestimated ASCVD risk at 5 years in all risk groups (24). Another study that enrolled individuals from 2008 to 2009 found that ASCVD risk was overestimated by 167% in the total cohort (25). A separate study by Muntner et al. (26) compared observed with estimated rates of CVD using the ASCVD risk in individuals enrolled between 2003 and 2007. Although this study also showed an overestimation of risk in the overall cohort, the size of the overestimation decreased when higher-risk patients were excluded or when outcomes data were augmented with Medicare claims data (26).

DIABETES

Pre-DM is a recognized risk factor for the development of both DM and CVD (27,28). However, there are limited data to support pharmacological

FIGURE 1 2013 ACC/AHA Statin Therapy Recommendations



This figure depicts a flowchart of ACC/AHA's recommended algorithm for the initiation of statins. The first clinical variable affecting initiation of statin therapy is the presence of CVD. In the absence of CVD, LDL cholesterol, diabetes, and ASCVD risk make up the criteria for starting statins for the primary prevention of CVD. Adapted with permission from Stone et al. (18). ACC = American College of Cardiology; AHA = American Heart Association; ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; LDL = low density lipoprotein.

antihyperglycemic treatment in pre-diabetic patients. The Diabetes Prevention Program study randomized pre-diabetic individuals between 1996 and 1999 to intensive lifestyle modifications, metformin, or placebo (29). The lifestyle modification group had the highest reduction in incident DM compared with both metformin and placebo. Although metformin was also superior to placebo in this primary outcome, the effect size was smaller in the subset of patients with lower body mass index, and the gastrointestinal side effects were significantly greater (29). Interestingly, when the trial was extended to include 10-year follow-up data, with intensive lifestyle support offered to all trial participants, there was no difference in DM incidence rates during the follow-up period (30). This suggests that in patients exposed to intensive lifestyle modification, metformin may not have a sustained benefit in reducing progression to DM. The ORIGIN (Outcome Reduction with an Initial Glargine Intervention) study randomized high-risk CVD individuals (of whom 59% had prior CVD) with impaired glucose tolerance, impaired fasting glucose, or newly diagnosed type 2 DM to glargine versus a standard-of-care antihyperglycemic regimen. Of interest is that although this study did not test a more- versus less-intense glucose control regimen, pre-DM patients randomized to glargine had lower incident rates of DM at 3 months ($p < 0.05$), but at a cost of increased rates of severe hypoglycemia. However, even with delayed progression to DM, there was no difference in cardiovascular events between the 2 treatment groups after a median follow-up of 6.2 years (31). Similarly, 2 meta-analyses assessing the effect of insulin secretagogues (sulfonylureas), metformin, dipeptidyl-peptidase (DPP)-4 inhibitors, and glucagon-like peptide-1 analogues on the incidence of DM concluded that there were insufficient data to support initiation of these pharmacologic agents in pre-diabetic individuals (32,33). Pre-DM is associated with hyperlipidemia and obesity, and current evidence supports counseling these individuals based on their overall risk and on modification of concomitant risk factors (28).

DOES EARLY VERSUS LATE DISEASE COURSE AFFECT THE HgA1c TARGET IN DIABETIC PATIENTS?

The SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis In Myocardial Infarction 53) trial was a prospective, double-blinded, placebo-controlled trial that randomized individuals with type 2 DM to saxagliptin versus placebo in addition to usual care (34). This trial included individuals with known CVD (79%) and those at risk of developing

CVD (21%), defined as at least age 55 years with HTN, hyperlipidemia, or active smoking. The primary endpoint was a composite of CVD death, MI, or ischemic stroke at 2 years. In a risk-adjusted analysis that was stratified by baseline HgA1c, individuals with HgA1c <7% had the lowest risk of developing the primary endpoint at 2 years. These results suggest an association between HgA1c levels and macrovascular events.

Two trials that included newly diagnosed diabetic patients and assessed glycemic control on CVD were the UKPDS (United Kingdom Prospective Diabetes Study) and the DCC/EDIC (Diabetes Control and Complications/Epidemiology of Diabetes Interventions and Complications Trial) (35,36). Because patients were newly diagnosed, there was a higher likelihood that these individuals did not have end-organ complications at randomization. The outcomes of these trials suggest a benefit to earlier glucose control and that CVD risk accrues over time.

As a result of earlier interventions, the duration of health without CVD may be prolonged, and longer clinical follow-up may be required to assess the effect of these interventions. UKPDS was a prospective trial that randomized newly diagnosed individuals with type 2 DM to either intensive (fasting plasma glucose 106 mg/dl) or conventional glycemic control (fasting plasma glucose 270 mg/dl) (35). The primary endpoint in the trial was a composite that included death and evidence of end-organ disease (35). The mean age of the study population was 53 years, with a mean HgA1c of 7%. At baseline, 36% of patients had retinopathy and 2% had proteinuria. Both of these characteristics have been used to identify patients with microvascular involvement in a trial with a median 10-year follow-up. The mean HgA1c achieved was 7% in the intensive group and 7.9% in the nonintensive group. The statistically significant risk reduction of 12% in the DM-related complication endpoint was driven by a 25% reduction in renal and retinal microvascular complications. There was a trend toward reduced MIs ($p = 0.052$) (35), which became significant ($p = 0.02$) 10 years after the close of the original trial. Of note, by this time point, differences in glycemic control were no longer present (HgA1c was 8% in both groups) (15).

Time to event is another important factor to consider. As in the UKPDS trial, the DCC/EDIC trial did not find any differences in CVD outcomes until after trial completion. Analysis at the end of the original study, which included 6.5 years of treatment, showed a nonsignificant decrease in CVD outcomes including MI, stroke, or death (36). This trial randomized type 1 DM patients between 1983 and 1993. After the study closed, the surviving patient cohort (97% of the original) were enrolled in an epidemiological study to assess the long-term effects of glycemic control. The mean HgA1c was 7% in the intensive group and 9% in the standard control group during the active treatment study. During the subsequent follow-up study, which had a mean follow-up time of 17 years, the HgA1c for both groups was 8%. There was a 57% reduction in the composite CVD endpoint compared with the standard arm ($p = 0.02$) (15,36). Because this trial enrolled individuals with type 1 DM only, the mean baseline age was 27 years, with only 5% having microalbuminuria and no enrollees having HTN or hyperlipidemia. The younger age of this patient population and likely decreased time of exposure to hyperglycemia suggests that their vascular health was probably better at baseline than those in UKPDS.

The UKPDS and DCC/EDIC trials suggest that the maladaptive response to hyperglycemia is dose-dependent and that the benefit of intensive glycemic control may persist after treatment. This has been termed the legacy effect (37). Similarly, just as treatment benefits accrue with time, time is also required for the maladaptive vascular response to hyperglycemia to become irreversible and have CVD significance.

Unlike the 2 aforementioned trials, which included newly diagnosed diabetic patients, the enrollees in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation), VADT (Veterans Affairs Diabetes Trial), and ACCORD (Action to Control Cardiovascular Risk in Diabetes) trials had a higher risk profile. The enrollment criteria for these trials, outcomes, and baseline characteristics are shown in **Table 1**.

In ADVANCE, although there was a statistically significant difference in the primary composite outcome that combined both macrovascular and microvascular events (hazard ratio [HR]: 0.9; $p = 0.013$), this was driven by fewer microvascular events and particularly by a reduction in diabetic nephropathy (38). Although there were no differences in the secondary outcomes, there was an expected increase in severe hypoglycemia (HR: 1.86; $p < 0.001$) (38).

In VADT, there was no significant difference in the primary outcome between treatment groups. Secondary analyses, which stratified enrollees by duration of DM, found in the intensive arm that there was a mortality benefit in individuals with DM duration <12 years and an increased risk of mortality in those with DM duration >18 years (16,38,39). Similarly, analysis stratified by coronary artery calcium score showed that patients with scores <100 had reduced CVD events (39). Of note, severe hypoglycemia, which was seen in 20% of the intensive

TABLE 1 Summary of Higher Risk Diabetes Trials

	ADVANCE (38)	VADT (39,40)	ACCORD (39,41)
N	11,140	1,791	10,251
Baseline characteristics			
Age, mean/yr	66	60	62
Prior CVD, %	32.2	40.0	33.7
DM duration, mean/yr	8.0	11.5	10.0
HgA1c, %			
Intensive	6.5	6.9	6.7
Conventional	7.3	8.4	7.5
Follow-up time, median/yr	5.0	5.6	3.5
Trial design			
Inclusion criteria	Noninsulin dependent type 2 DM Age ≥55 yrs with 1 CVD risk factor	HgA1c >7.5% on insulin or maximum oral therapies Age >41 yrs	HgA1c 7.5%–9% Age 40–79 yrs with CVD Age 55–79 yrs without CVD but with atherosclerosis, albuminuria, LVH, or ≥2 CVD risk factors
Treatment groups	HgA1c ≤6.5% vs. standard treatment	HgA1c <6.0% vs. HgA1c <9.0%	HgA1c <6.0% vs. HgA1c 7.0%–7.9%
Primary outcome	Composite (MI, stroke, CVD death, retinopathy, nephropathy)	Composite (CVD death, MI, stroke, CHF, inoperable CAD, amputation, PCI, vascular intervention)	Composite (MI, stroke, CVD death)
BP component	Yes	No	Yes

ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; CVD = cardiovascular disease; DM = diabetes mellitus; HgA1c = hemoglobin A1c; LVH = left ventricular hypertrophy; MI = myocardial infarction; PCI = percutaneous coronary intervention; VADT = Veterans Affairs Diabetes Trial.

group compared with only 8% in the conventional group, was associated with a 4-fold increase in CVD death. A subsequent study followed enrollees who survived the active part of the VADT trial for a median time of 9.7 years. In this follow-up study, a statistically significant risk reduction in the primary outcome (0.83; p = 0.04) was eventually achieved. Of note, there was no change in CVD or all-cause mortality. Similar to the other studies, the HgA1c in the 2 groups narrowed to 7.8% and 8.3% (40).

ACCORD showed a 22% relative increase in mortality (1% absolute increase) over the 3.5-year treatment period in diabetic individuals who were treated to a target HgA1c <6%. Interestingly, 3 years after randomization, there was a decrease in the primary outcome that was driven by a significant reduction in nonfatal MIs. In the subgroup analysis, patients without prior CVD had a significantly lower primary outcome (a composite of MI, stroke, and CVD death) if their blood glucose target was <6.0 mg/dl versus 7 to 7.9 mg/dl (41). This again suggests that in a subgroup of patients who may not have overt CHD, there may be a benefit to more aggressive glucose control (41). One consideration when interpreting these data is that the target HgA1c occurred within 4 months of randomization. This is in contrast to VADT, where target HgA1c was achieved over 2 years (39).

RISKS OF INTENSIVE GLYCEMIC CONTROL. ACCORD was the only trial to show an increased risk of mortality. Otherwise, hypoglycemia is a consistent adverse effect of intensive glucose control. The VADT trial showed an increase in CVD events with severe hypoglycemia. The postulated mechanism for this is increased adrenergic activation and an associated increase in heart rate, systolic blood pressure (SBP), and cardiac output, which can exacerbate ischemia in at-risk vessels (15). This is further evidenced by the lack of association between CVD events and hypoglycemia in the lower-risk population included in the UKPDS study (15).

Microvascular disease is likely a precursor to macrovascular disease, and although it may be overly simplistic to suggest this, early prevention of hyperglycemia or even risk stratification of patients by retinal imaging and proteinuria may be necessary to determine the appropriate glycemic target. Furthermore, because vascular complications likely occur in a time-dependent spectrum that begins in the microvasculature and ends with macrovascular complications, the benefit of glycemic control may not be evident for several years. This should be considered in individuals who may have had DM for longer and in older individuals, in whom the risk of hypoglycemia as well as macrovascular complications may outweigh

the incremental benefit that accrues over time with tighter glycemic control.

LDL-CHOLESTEROL

Atherosclerosis begins with the deposition of lipids in the vascular wall and is mediated by disturbances in cholesterol homeostasis (42). Prior to the current AHA/ACC 2013 guidelines, treatments had focused on target cholesterol for determining the initiation of statins and other nonstatin lipid-modifying therapies (43). The new guidelines ushered in a paradigm shift that used CVD risk, instead of LDL-C levels, as a guide to treatment. Part of this was inspired by evidence that the atherosclerotic process began in infancy and possibly even earlier, with genetic factors influencing the development of CAD. For instance, 1 study that used intracoronary ultrasound on donor hearts found the presence of plaque in 17% of hearts between the ages of 13 to 19 years and in 60% of hearts between the ages of 30 to 39 years (2). This change in guidelines significantly expanded the indication for statins, with 1 study estimating an increase from 43 million individuals (37.5% of the U.S. adult population) to 56 million (48.6%). Appropriately, a majority of these newly eligible individuals met the primary prevention criteria (10 million) (44,45).

WHEN SHOULD STATIN THERAPY BE INITIATED?

The Cardiovascular Risk in Young Finns study followed individuals from age 3 to 18 years for 27 years and found that physical inactivity and reduced fruit intake correlated with accelerated carotid intima-media thickness. Furthermore, correction of these risk factors during childhood attenuated the risk for progression during adulthood (2). The Bogalusa Heart Study similarly followed individuals from childhood to adulthood (46,47). Autopsy data on study participants who died from non-CVD deaths found an increasing prevalence of coronary fatty streaks with age (50% of patients age 2 to 15 years and 85% of patients age 21 to 39 years). Antemortem body mass index, SBP, total cholesterol, and LDL-C were correlated with the presence of coronary fatty streaks (46). A follow-up survey conducted in 2000 to 2001 on nondeceased participants (mean age 31.9 years) included carotid intima-media thickness by ultrasound and found that higher childhood measurements of non-high-density lipoprotein cholesterol, LDL-C, and apoB were associated with increased carotid intima-media thickness (47). The CARDIA (Coronary Artery Risk Development in Young Adults Study), on the other hand, suggested a role for more aggressive lipid-lowering therapy. This was a longitudinal study that followed patients age 18 to 30 years for either 15 or 20 years until a coronary artery calcium scan after the age of 35 years. Interestingly, coronary artery calcium scores >0 were associated with LDL-C >100 mg/dl prior to the age of 35 years, even after risk adjustment (48). These studies suggest that in childhood to early adulthood, lifestyle changes should be implemented. However, cholesterol-lowering therapies can be considered if LDL-C levels remain elevated after institution of these interventions.

Although there have been pharmacological trials looking at the primary prevention population, the majority of them have focused on higher-risk populations. Two trials that included low-risk populations were the MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese) and JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) trials. MEGA compared incidence of CAD in individuals age 40 to 70 years with a total cholesterol between 220 and 270 mg/dl who were treated with diet alone versus diet plus pravastatin. Incidence of CAD was significantly lower in the statin treatment group (49). The JUPITER trial included men age ≥50 years and women age ≥60 years with an LDL-C <130 mg/dl and a high-sensitivity CRP ≥2.0 mg/dl, of whom 50% had a Framingham score ≤10% (50). These individuals were randomized to rosuvastatin versus placebo, with the primary endpoint being a composite of MI, stroke, arterial revascularization, hospitalization for unstable angina, or CVD death. Similar to MEGA, the JUPITER trial showed a reduction in the primary endpoint in the statin treatment group.

More recently, HOPE-3 (Heart Outcomes Prevention Evaluation-3) was a 2 × 2 factorial design trial that assessed treatment with a candesartan and hydrochlorothiazide combination pill and rosuvastatin 10 mg compared with placebo in individuals with intermediate CVD risk. Inclusion criteria for this trial were men age ≥55 years and women age ≥65 years with at least 1 of the following CVD risk factors: elevated waist-to-hip ratio, low high-density lipoprotein cholesterol, current or recent tobacco use, dysglycemia, and family history of premature CAD; women age ≥60 years with 2 of the aforementioned cardiovascular risk factors were also included. Prediabetic patients were included (51,52). Of note, the trial protocol only excluded "documented clinically manifest" CVD and did not require either invasive or noninvasive confirmation. To assess tolerability to treatment and avoid drop-outs and adherence issues, there was a 4-week run-in phase for the medications, and only those without significant side effects

TABLE 2 Cholesterol Lowering in Intermediate-Risk Persons Without Cardiovascular Disease (HOPE-3): Primary and Secondary Outcomes

	Rosuvastatin Group (n = 6,361)	Placebo Group (n = 6,344)	Hazard Ratio (95% CI)	p Value
Coprimary outcomes				
First coprimary outcome*	235 (3.7)	304 (4.8)	0.76 (0.64-0.91)	0.002
Second coprimary outcome†	277 (4.4)	363 (5.7)	0.75 (0.64-0.88)	<0.001
Secondary outcome‡	306 (4.8)	393 (6.2)	0.77 (0.66-0.89)	<0.001

Values are n (%) unless otherwise indicated. *Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. †Composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest, heart failure, or revascularization. ‡Composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest, heart failure, revascularization, or angina with evidence of ischemia. Data from Yusuf et al. (52).

CI = confidence interval; HOPE-3 = Heart Outcomes Prevention Evaluation-3.

underwent randomization. The primary outcomes were a composite that included CVD death, nonfatal MI, or nonfatal stroke, and the prior composite endpoint with the addition of resuscitated cardiac arrest, heart failure, or revascularization. Secondary outcomes included DM, cognitive function, and erectile dysfunction. Safety outcomes included cancer, myopathy, rhabdomyolysis, and hospitalization (52).

This trial randomized individuals between 2007 and 2010. Median follow-up was 5.6 years. At baseline, the mean age of the trial participants was 65.7 years, and 5.8% had uncomplicated DM. Drug adherence by the end of the trial was ~75%. The incidence of the primary outcome was reduced in the treatment group compared with the placebo group (**Table 2**). Secondary analyses, which included the individual components of the primary endpoint, revealed stroke to be a primary contributor to the effect size of treatment with rosuvastatin. There was also no change in treatment effect in subgroup analyses stratified by demographics, SBP, LDL-C, and CRP (52).

Notably, the incidence of new-onset DM was the same in both groups. In terms of safety outcomes, although the incidences of myalgias and muscle weakness were increased in the treatment group (5.8% vs. 4.7%; $p < 0.005$), there was no difference in liver enzyme elevation or permanent discontinuation of the study drug because of muscle complaints including rhabdomyolysis or myopathy (52).

Last, ECAD (Eliminate Coronary Artery Disease) is an ongoing trial designed to determine whether treatment with atorvastatin reduces CVD events in a lower-risk population than previously evaluated. The study population includes men age 35 to 50 years and women age 45 to 59 years who have no history of CVD, an LDL-C ≥70 mg/dl, and at least 1 of the following risk factors: current smoking, HTN, truncal obesity, family history of premature MI (before 60 years of age), or South Asian ethnic history (53).

As lower-risk populations are considered for statins, the adverse effect profile needs to be considered. It must be understood that the risk-benefit ratio favoring statins decreases as the patient population moves into a lower-risk group and as the intensity of the statin increases (54). The CTT (Cholesterol Treatment Trialists') Collaboration concludes that although there may be a slight increase in hemorrhagic strokes, myopathy and DM are the only significant adverse effects that can be reliably attributed to statin use. Furthermore, elevated transaminases, defined as ≥3× the normal limit, in isolation are not specific for significant hepatocellular injury. As a result, routine surveillance of transaminases is not recommended due to the inappropriate discontinuation of statins (55,56). Similarly, a recent review of statin trials showed no association between statins and objective measures of cognitive decline (57).

HOW MUCH CAN LDL-C LEVELS BE LOWERED? Another controversy in the 2013 ACC/AHA cholesterol guidelines is the removal of specific LDL-C goals as targets of therapy (43). There is no definitive evidence that there is a true lower threshold for LDL-C levels. Two trials evaluating the addition of nonstatins to statin therapy, IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) and FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk), found that incremental decreases in LDL-C were associated with fewer cardiovascular events and no increase in serious adverse events. IMPROVE-IT randomized patients following an acute coronary syndrome event to simvastatin with or without ezetimibe, and FOURIER randomized patients who were at high CVD risk (with 81% having had a prior MI) to atorvastatin with or without evolocumab (58,59). Although both trials targeted secondary CVD prevention cohorts, these results suggest a potential role for investigating nonstatins in primary CVD prevention in very high-risk patients. Longer-term follow-up from proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor trials, such as the FOURIER OLE, will provide more information concerning the safety of very low LDL-C levels (60,61). From a biological perspective, neonatal levels of LDL-C at birth range from 21 to 39 mg/dl and have been postulated as a physiological lower limit (22,62,63). Results from the PCSK9 trials, which found no difference in adverse events, including neurocognitive events, hemorrhagic strokes, or incidence of new-onset DM

between patients with an LDL-C <25 and ≥25 mg/dl, suggest that there is no clinically significant lower LDL-C limit (64–67). The main caveat to extrapolating these data is limited follow-up and differences in the patient populations. In particular, as mentioned earlier, the majority of patients enrolled in the PCSK9 inhibitor trials were secondary prevention patients who were older and who likely had reduced exposure time to low levels of LDL-C compared with a primary prevention cohort.

A meta-analysis carried out by the CTT Collaboration reported a 1% relative risk reduction for every 1.8 mg/dl of LDL-C lowered to a lower threshold of 50 mg/dl in individuals with a baseline cholesterol of >78 mg/dl (20,22,64,68). Efforts to lower LDL-C are driven by the concept of residual risk even after optimal risk factor modification. Part of this may be some unaccounted epiphenomenon or that lifetime exposure to LDL-C needs to be considered. This perspective was introduced in Mendelian studies examining people with PCSK9 loss of function who have a disproportionately lower lifetime risk for CAD compared with those enrolled in clinical trials. A meta-analysis of these studies showed that lifelong exposure to lower levels of LDL-C conferred a 3-fold greater risk reduction than treatment with statins started later in life (69). Current guidelines recommend a decrease in statin dose after 2 consecutive readings of LDL-C <40 mg/dl (18). However, data from PCSK9 inhibitor trials have not shown safety concerns at LDL-C levels <25 mg/dl (60,64–67).

HYPERTENSION

Although there is indisputable evidence that controlling blood pressure is associated with a reduction in CVD events, blood pressure targets, thresholds for beginning pharmacological treatment, and how different comorbidities factor into the management of an individual's blood pressure are controversial (70).

WHEN SHOULD ANTIHYPERTENSIVE TREATMENT BE INITIATED? With the most recent Eighth Joint National Committee recommendations, HTN treatment is initiated at an SBP >140 mm Hg. However, based on observational data, CVD risk begins to accrue at lower values. A meta-analysis of prospective observational studies found a direct correlation between CVD deaths and SBP down to a threshold of 115 mm Hg (71). As many as 39% of male and 23% of female patients have an SBP between 130 and 139 mm Hg and are at increased risk of developing HTN. An analysis using the Framingham cohort stratified individuals by their baseline blood pressure into the following groups: optimal (<120 mm Hg), normal (120 to 129 mm Hg), and high-normal (130 to 139 mm Hg). CVD risk, adjusted for diabetic status, cholesterol, age, sex, body mass index, and smoking status, was higher in patients with high-normal versus optimal blood pressures (72). Based on these data, 2 randomized trials, PHARAO (Prevention of Hypertension With the Angiotensin-Converting Enzyme Inhibitor Ramipril in Patients With High-Normal Blood Pressure) and TROPHY (TRial Of Preventing HYpertension), attempted to answer whether pharmacological intervention should be initiated at SBP >130 mm Hg (73,74). Both of these trials showed that initiation of pharmacological agents delayed the onset of HTN. However, because these trials were not powered to assess differences in CVD event rates, no reduction in CVD events was found (74,75). Furthermore, although treatment was not associated with increased adverse events, ramipril was associated with more cough (4.8% vs. 0.4%) (74,75). Thus, to date, there are minimal data to support treating pre-HTN.

In the HOPE-3 trial, the HTN arm received a fixed-dose combination pill of candesartan and hydrochlorothiazide (76). The design of this trial was novel, because rather than categorizing individuals by their risk factors, it evaluated the effectiveness of risk factor–modifying treatments on individuals who had an increased risk of developing CVD. Thus, strict inclusion criteria based on definitions for hyperlipidemia and HTN were not used. Furthermore, individuals with a baseline diagnosis of HTN could be included as long as they were not previously on a thiazide, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker.

At the end of the study, the mean decrease in blood pressure was 10 mm Hg in the treatment group versus 4 mm Hg in the control group ($p < 0.05$). There was no difference in primary or secondary endpoints. Importantly, a subgroup analysis that stratified baseline blood pressure into tertiles (≤131 mm Hg, 132 to 143 mm Hg, and >143 mm Hg) found a benefit in the primary outcome in the >143 mm Hg group. Of note, there was separation of the Kaplan-Meier curves for stroke, MI, and revascularization with time, which suggests that these differences may become significant with longer follow-up (76). Although there were no differences in the safety outcomes, there was an increased incidence of symptomatic hypotension, dizziness, and lightheadedness in the treatment group. This trial has important clinical implications because it supports current guidelines that individuals without HTN who are at intermediate CVD risk should not be pharmacologically treated (76). However, given the increased relative risk of CVD

TABLE 3 Definitions of Clinical and Subclinical Cardiovascular Disease (Excluding Stroke) in SPRINT

Clinical cardiovascular disease
Prior myocardial infarction, coronary revascularization, or carotid intervention
Prior peripheral artery intervention
Acute coronary syndrome, positive exercise stress test, or positive cardiac imaging study
≥50% stenosis of coronary, carotid, or peripheral artery
Abdominal aortic aneurysm ≥5 cm with or without repair
Subclinical cardiovascular disease within the past 2 yrs
Coronary artery calcium score ≥400 Agatston units
Ankle-brachial index ≤0.90
Left ventricular hypertrophy identified by electrocardiogram, echocardiogram, or other cardiac imaging

Data from Wright et al. (87).
SPRINT = Systolic Blood Pressure Intervention Trial.

events based on epidemiological studies, it is reasonable to encourage lifestyle changes that include exercise, sodium restriction, and nutritional counseling.

HOW LOW SHOULD WE GO? There is significant debate over what the SBP treatment target should be. Much of this arises from the J-curve phenomenon in CVD outcomes, excluding stroke, described in observational data and randomized controlled trials evaluating HTN therapies (77–80). The mechanisms for this relationship include the presence of atherosclerotic plaques and decreased perfusion pressures distally. These data are primarily from individuals with HTN, DM, or pre-existing CVD (81,82). Thus, the presence of this phenomenon in a primary prevention cohort is less clear. Prior to SPRINT (Systolic Blood Pressure Intervention Trial), few trials included a significant number of individuals without a prior history of CVD.

One of the first trials that was designed to assess the J-curve phenomenon was the HOT (Hypertension Optimal Treatment) trial, which randomized individuals with HTN to treatment groups of diastolic blood pressure ≤90, ≤85, or ≤80 mm Hg (83). The mean age of patients in this trial was 61 years, and 1.5% had pre-existing CVD. This trial found no increase in CVD events in the lower diastolic blood pressure group, but also did not find a difference in CVD risk reduction (83).

VALUE (Valsartan Antihypertensive Long-Term Use Evaluation) was a randomized controlled trial that included individuals age ≥50 years with a high CVD risk (determined by diabetes mellitus, current smoking, total cholesterol, left ventricular hypertrophy, proteinuria, or raised serum creatinine) or with coronary or peripheral artery disease. The treatment arms in the trial were valsartan and amlodipine with a target SBP <140 mm Hg. The mean age of the participants was 67 years, and 46% of them had pre-existing CAD (84). A post hoc analysis that stratified by baseline CAD showed no J-curve. However, although no increase in CVD risk was found, there was similarly no additional benefit conferred by obtaining an SBP <130 mm Hg (85).

In the ACCORD study, participants with type 2 DM were randomly assigned to intensive therapy (blood pressure target <120 mm Hg) versus standard therapy (blood pressure target <140 mm Hg). The primary composite outcome was nonfatal MI, nonfatal stroke, or death from CVD causes. At 1 year, the mean SBP in each group was 119.3 and 133.5 mm Hg, respectively. However, there was no difference in the primary outcome between groups (86). The authors comment that the event rate in the standard group was almost 50% lower than the expected rate, suggesting that the study was underpowered. Additionally, the diverging Kaplan-Meier curves suggest that the outcomes may have become significant if there had been more subjects or if the study had continued for a longer period (87).

SPRINT was a randomized controlled trial that also compared an intensive blood pressure treatment strategy (SBP <120 mm Hg) to a standard blood pressure treatment strategy (SBP <140 mm Hg). Inclusion criteria for the trial were age ≥50 years, an SBP between 130 and 180 mm Hg, and categorized as having an increased CVD risk defined as: clinical or subclinical CVD (**Table 3**), chronic kidney disease with an estimated glomerular filtration rate 20 to 60 ml/m/1.73 m^2, a 10-year CVD risk ≥15%, or age ≥75 years. Of note, individuals with prior stroke or DM were excluded (87).

The primary outcome was a composite outcome of MI, acute coronary syndrome, stroke, acute decompensated heart failure, or CVD death. Secondary outcomes included the individual components of the composite, as well as death from any cause and the composite of the primary outcome with death from any cause. Safety outcomes included worsening kidney function (87).

Study participants were randomized between 2010 and 2013. Median follow up was 3.26 years before the trial was ended early because of the primary outcome benefit seen in the intensive-treatment group. The mean age in the trial was 68 years; 17% of the trial participants had clinical CVD, which included peripheral artery disease; 10% were not on antihypertensive treatment at baseline, and 61% had a Framingham risk score ≥15%. The primary composite outcome rate was 1.65%/year in

the intensive-treatment group compared with 2.19%/year in the standard group, which translated to a relative risk reduction of 25% and an absolute risk reduction of 0.54%/year. The composite endpoint was driven by the heart failure outcome and CVD deaths. Interestingly, in terms of secondary endpoints, there were no significant differences in rates of MIs, acute coronary syndrome, or stroke. Some considerations that affect interpretation include the early termination of the trial and its effects on longer-term outcomes, as well as the high percentage of individuals already tolerating a multidrug regimen (mean number of antihypertensive agents at baseline was 1.8) (87).

Although there were no differences in the renal safety outcomes in those with chronic kidney disease at randomization, in those without chronic kidney disease, individuals in the intensive-treatment group compared with the standard-treatment group had a ≥30% reduction in GFR (HR: 3.49; 95% confidence interval: 2.44 to 5.10). As expected, there were more serious adverse events in the intensive- than standard-treatment group ($p < 0.001$), which included hypotension, syncope, electrolyte abnormalities, and acute kidney injury/failure (87).

The aforementioned trials suggest that in appropriately selected individuals, lower SBP will reduce CVD events and mortality without increasing MIs. A recent meta-analysis that stratified groups by baseline SBP found a similar decrease in CVD events, CAD, stroke, heart failure, and all-cause mortality across all SBP groups, including the lowest (<130 mm Hg). Analysis stratified by presence of baseline CAD did not change these findings (70).

Even with this evidence, it is important to consider the potential adverse effects of tight blood pressure control such as syncope, dizziness, and renal injury on patient adherence. An interesting meta-analysis calculated a risk-benefit ratio of antihypertensive treatment that used permanent discontinuation of antihypertensive treatment as a proxy for a significant adverse event (88). This meta-analysis found that for incremental reductions in SBP below 130 mm Hg, the relative risk of permanent discontinuations increased disproportionately to any additional benefit gained from a CVD risk-reduction perspective. This suggests that although there may still be an overall benefit to lower SBP, the cost of doing so in terms of medication discontinuation may not be worth it. With respect to SPRINT, it is important to note that the method used for SBP measurement, an average of three automatic blood pressure readings taken in a quiet room after being seated alone, was unlike that used in other trials and is different from real world practice. Thus, the SBP readings reported in SPRINT could have been ~5 to 10 mm Hg higher if measured by a manual device, while talking, or in a public nonquiet room (89). Viewed in that light, the SBP targets in SPRINT are only slightly lower than what guidelines currently recommend.

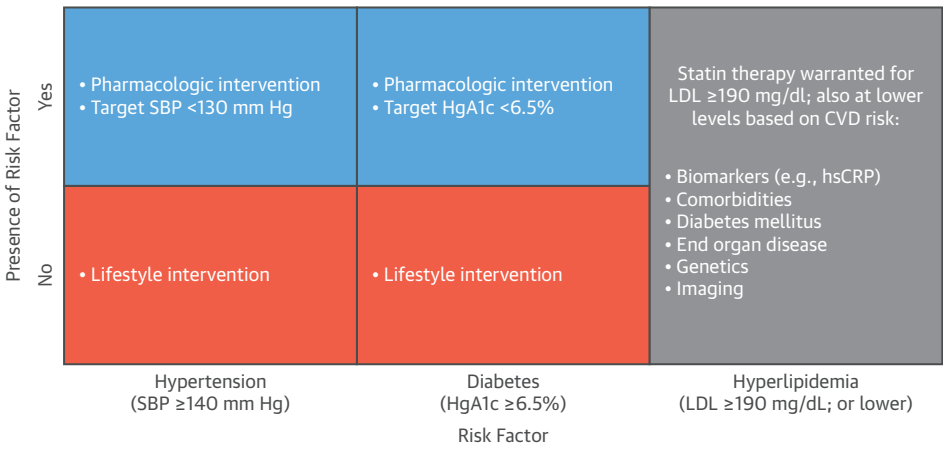
RECOMMENDATIONS AND FUTURE DIRECTIONS

The continuum of health before the overt development of CAD can be classified into 2 groups: those who do not yet have the risk factors that confer an increased risk for developing CVD, and those who already have them. From a primordial prevention perspective, preserving a state of health before the onset of DM, hypercholesterolemia, or HTN has the greatest potential for decreasing CVD morbidity and mortality. However, strategies to achieve this are resource intensive.

With regard to primary prevention of CVD, it is clear that for DM and HTN, there is no role for pharmacological interventions in individuals without overt disease, and rather, changes in lifestyle should be encouraged. Aggressive glycemic control (HgA1c <6.5%) should be considered in diabetic patients without CAD and especially in those without evidence of microvascular disease. Importantly, extrapolating the experience from ACCORD, although glycemic control is important, targets should be achieved slowly. Similarly, in individuals without CVD or DM, once individuals become hypertensive by current guidelines (SBP ≥140 mm Hg), pharmacological interventions should be initiated with a target SBP of <130 mm Hg (**Figure 2**).

Interestingly, unlike DM and HTN, even in the absence of overt hyperlipidemia, there appears to be an opportunity to reduce CVD events by initiating statin therapy in individuals who are at intermediate CVD risk. Accurate identification of individuals with subclinical disease allows not only earlier lifestyle interventions or risk factor modifications but also the reclassification of patients and discontinuation of a therapy where the risk-benefit ratio may not have been favorable. Developing a model that correctly discriminates between a nonmodifiable versus a modifiable disease state is challenging. As a result, identifying new methods and variables that improve our estimation of risk should be a priority.

FIGURE 2 Recommendations for Modulating Risk Factors for the Primary Prevention of Cardiovascular Disease



This figure summarizes the treatment recommendations for HTN, DM, and hyperlipidemia in the primary prevention of CVD before and after development of the risk factor. Pharmacological intervention should only be initiated in HTN and DM after the risk factor has developed. This is in contrast to hyperlipidemia, where risk stratification will determine whether statin therapy is warranted. DM = diabetes mellitus; HgA1c = hemoglobin A1c; hsCRP = high-sensitivity C-reactive protein; HTN = hypertension; SBP = systolic blood pressure; other abbreviations as in **Figure 1**.

Furthermore, given the evidence that the atherosclerotic process begins early in infancy, current risk calculators may not completely identify who would benefit from lipid-lowering therapy (2,90). As a result, starting treatment earlier than indicated by conventional risk calculators must be considered. Different calculators could possibly be developed that are based on genetics, additional markers of disease (proteinuria, glucosuria, ankle-brachial index, or left ventricular hypertrophy), data from bioimaging (coronary artery calcium and the presence of carotid and peripheral plaques), or biomarkers (CRP, troponin, brain natriuretic peptide, and lipoprotein [a]). Regarding bioimaging, coronary artery calcium and carotid plaque quantification have been shown to improve discrimination of risk using the ASCVD Pooled Cohort equation (91-93). Additionally, 1 study that measured carotid, aortic, and iliofemoral disease by ultrasound and coronary artery calcification in individuals without a prior history CVD found that disease in the iliofemoral region was strongly correlated with coronary artery calcification and aortic disease (94). Given the high prevalence of iliofemoral disease, if incident CVD events can be correlated with its presence, iliofemoral disease may help with future risk stratification (94). A recent CVD risk prediction model, which combined variables derived from multiple modalities (left ventricular hypertrophy determined by ECG, coronary artery calcification, N-terminal prohormone of B-type natriuretic peptide, high-sensitivity cardiac troponin T, and high-sensitivity CRP) into a base risk calculator that included the ASCVD risk variables and statin use, significantly improved model discrimination (C-statistic: 0.79) (95). Although this model has not been validated, it suggests that there are opportunities to improve our current risk prediction models.

The idea of primordial prevention is what drives the efforts to target lower levels of risk and disease-specific targets in the primary prevention of CVD. The genetic risk of an individual is essentially a primordial CVD risk score or a baseline lifetime CVD risk that may be mitigated or amplified by environmental factors. Two studies have derived different genetic CVD risk scores (96,97). The first study examined the effect of lifestyle on CVD and found that within the highest genetic-risk group, a favorable lifestyle decreased CVD events compared with an unfavorable lifestyle (96). The second study compared the effect size of statin therapy on CVD events by genetic risk group and found a relative risk reduction of 46% in the highest-risk group compared with 26% in all others ($p = 0.05$) (97). Genetic risk scores that characterize an individual's genetic CVD risk would identify individuals who would benefit from risk reduction therapies at the earliest time point.

Although it is attractive to consider pharmacological therapies in lower-risk patients, adverse effects and physiological barriers may make the risk-benefit ratio unfavorable, particularly if adherence to medications is affected. Appropriate selection of individuals who will benefit from more aggressive pharmacological therapies will hinge on the accuracy of CVD risk calculators. Lifestyle and behavioral interventions, although difficult to implement and adopt, do not have this lower limit and should be the intervention for the lowest-risk groups.

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