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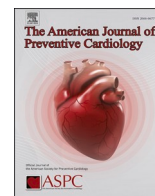
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State-of-the-Art Review

Earlier treatment in adults with high lifetime risk of cardiovascular diseases: What prevention trials are feasible and could change clinical practice? Report of a National Heart, Lung, and Blood Institute (NHLBI) Workshop

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ABSTRACT

More than half of U.S. young adults have low ten-year but high lifetime risk of cardiovascular disease (CVD). Improving primary prevention in young adulthood may help reduce persistent CVD disparities and overall CVD morbidity and mortality. The National Heart, Lung, and Blood Institute (NHLBI) convened a workshop in 2021 to identify potential trial opportunities in CVD prevention in young adults. The workshop identified promising interventions that could be tested, including interventions that focus on a single cardiovascular risk factor (e.g., lipids or inflammation) to multiple risk factor interventions (e.g., multicomponent lifestyle interventions or fixed-low dose combination of medications). Given the sample size and duration for a trial with hard endpoints, more research is needed on the utility of intermediate endpoints identified noninvasively such as subclinical coronary atherosclerosis as a surrogate endpoint. For now, clinical outcomes trials with hard endpoints will more likely change clinical practice. Trial efficiency depends on accurate identification of high-risk young adults, which can potentially be done using traditional risk equations, coronary artery calcium screening, computerized tomography coronary angiography, and polygenic risk scores. Trials in young adults should include enhanced recruitment strategies with intense community engagement to enroll a trial population that is racially, ethnically, geographically, and socially diverse. Despite the challenges in conducting large prevention trials in young adults, recent advances including innovation in clinical trial conduct, new therapies and successful interventions in

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older populations, and an increasing recognition of a lifespan approach to risk assessment have made such trials more feasible than ever.

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1. Introduction

Despite reductions in cardiovascular disease (CVD) mortality through the early 21st century, progress has slowed, in large part due to increasing incidence and prevalence of CVD risk factors such as obesity, type 2 diabetes mellitus, and hypertension [1]. Promoting cardiovascular health and preventing CVD across the lifespan are areas of focus in the National Heart, Lung, and Blood Institute's (NHLBI) Strategic Vision [2]. Greater success in primary prevention in young adulthood may help mitigate persistent CVD disparities and reduce CVD mortality. Accordingly, the NHLBI convened a multidisciplinary workshop on February 19 and 26, 2021 to identify potential research opportunities for young adults with low short-term (e.g. ten-year) CVD risk but high lifetime risk [3]. In addition, workshop participants reviewed the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines on Hypertension (2017) [4], Blood Cholesterol (2018) [5], and Primary Prevention of CVD (2019) [6] and evaluated key considerations for designing feasible and potentially practice-changing trials of primary prevention interventions in early adulthood. This manuscript summarizes clinical trial opportunities related to cardiovascular prevention in young adults, including key design considerations such as the potential interventions to be tested, how to identify trial participants, the need to ensure representation in trials, and optimal trial endpoints.

2. Cardiovascular disease risk accumulates over time, but evidence on early intervention is scant

CVD remains the leading cause of death in the United States. A substantial body of evidence exists to demonstrate the cumulative effect of exposure to CVD risk factors in childhood and in young adulthood. Early, prolonged exposure to elevated blood pressure (BP) in adults age 18–45 is associated with future CVD risk in a graded relationship, such that an estimated 23.8% of CVD in young adults can be attributed to high blood pressure [7]. Similarly, cumulative exposure to elevated low density lipoprotein cholesterol (LDL-C), even at levels that are below guideline-recommended treatment thresholds, is also associated with an increase in long-term risk of cardiovascular events [8,9]. Lifestyle factors in young adults including diet, exercise, and smoking also impact CVD risk both directly and indirectly.

Unfortunately, the prevalence of CVD risk factors continues to rise, including in younger adults, along with rates of myocardial infarction and heart failure [8,10]. It seems reasonable that risk factors should be addressed in all ages. Yet evidence is lacking for how, when, and in whom should more aggressive primary prevention therapy begin in early adulthood. While BP management guidelines recommend pharmacologic therapy for all individuals with systolic BP (SBP) ≥ 140 or diastolic BP (DBP) ≥ 90 (with lower treatment thresholds for those at higher risk), the guideline acknowledges that this recommendation for treatment in younger adults is based on models, not trials: “modeling studies support the effectiveness and cost-effectiveness of treatment of younger, lower-risk patients over the course of their life spans.” [4] Adult cholesterol guidelines primarily focus on treatment of adults age 40 and above. Among younger adults, there are only very limited recommendations for cholesterol treatment, e.g. those with **severely elevated LDL-C hypercholesterolemia** (≥ 190 mg/dL) [5]. While healthy lifestyle is recommended throughout the lifespan, guidelines for hypertension [4], lipid management [5], and primary prevention [6] all note lack of randomized trial evidence available to guide initiation of

preventive drug therapy in young adults. Furthermore, while the primary prevention guidelines emphasize the importance of lifelong healthy diet, exercise, prevention of obesity, and smoking cessation or abstinence, scalable, durable, and effective strategies to improve adherence to a healthy lifestyle remain elusive.

3. Selection of participants: disparities in CVD start early and should be a key consideration in any prevention trial

Future cardiovascular prevention trials should be designed with the recognition that the social determinants of health substantially contribute to high risk for CVD, and trial strategies need to be implemented to ensure a representative trial sample. Disparities in CVD burden are well-documented, and emerge in young subpopulations. For example, Black Americans have a 30–45% increase in mortality from CVD compared with other groups [11–13]. Place is also important. The rate of decline in premature acute myocardial infarction mortality has slowed since 2011, especially in rural settings, while heart failure and hypertensive mortality rates have increased [14–16]. Multiple social risk factors contribute to disparities in cardiovascular disease, including neighborhood factors such as access to healthy food and walkability [17]. In a recent study, counties with more social vulnerabilities had higher premature CVD mortality [18]. Multi-level, place-based and community engaged research on interventions to address the modifiable social determinants of health will be critical to address cardiovascular disparities [19–21].

Given the variability in prevalence of cardiovascular risk factors over the lifespan, studies that seek to evaluate preventive strategies in early adulthood should include representative samples of Black, Hispanic/Latinx, and other racial/ethnic groups that have been historically underrepresented in clinical research as well as other high-risk groups including those at low socioeconomic status and rural populations [22]. Recently the National Academy of Science report recommended actions ranging from individual researchers to the federal government. Enrolling these participants will require early engagement during protocol development and active engagement of community representatives in the study design and development of clinical trial materials. Key principles in engagement of community and stakeholder representatives include establishing shared goals to create partnership, understanding community norms and values, respect for stakeholder autonomy, and leveraging community assets and strengths [23]. These approaches have been associated with significantly higher recruitment and retention of minority participants in research [24,25]. Diversity should start with the study leadership and staff, which should include individuals from various racial and ethnic backgrounds [23]. Finally, a long-term commitment to the community should also be part of any engagement effort, including a plan to disseminate and implement research findings in the communities where interventions have been tested.

Given the differential access to the healthcare system, effort and resources should be committed to recruit participants outside of traditional health care settings, and where possible, to deliver interventions at accessible, community-based settings. The barbershop hypertension intervention study can serve as a model for this type of inclusive research [26]. Other important venues to consider include safety net institutions such as public hospitals and federally-qualified health centers, community centers and libraries, and faith institutions. In addition, the complexity of the intervention and the study procedures should take into consideration other competing priorities and barriers to

participation that may differentially affect underserved populations, including transportation, scheduling of study visits, and alignment with clinical priorities. Study designs may also consider alternatives to patient-level randomization to preserve equity and maximize benefit to study participants, including comparative effectiveness analyses and stepped-wedge designs to allow all participants to receive the intervention.

Importantly, while the panel focused on prevention trials to lower CVD risk through addressing more proximal individual risk factors such as blood pressure, lipid levels, and lifestyle, the panel recognized the importance of research to better understand and address structural factors that drive disparities in CVD outcomes, including structural racism [14].

4. Selection of participants: young adults at the highest long-term risk for primary prevention trials

4.1. Risk scores

Given the size of the young adult population, strategies are needed to identify those at highest risk who may benefit the most from earlier prevention. Current lipid guidelines recommend using a combination of 10-year ASCVD risk score and “risk enhancing factors” to identify adults over 40 years of age at increased risk of CVD who may benefit from statin therapy, including pregnancy history (i.e., premature menopause and preeclampsia), elevated Lipoprotein a [Lp(a)] or apolipoprotein B (apoB), metabolic syndrome, chronic kidney disease, chronic inflammatory disease, elevated high sensitivity C-reactive protein (hsCRP), primary hypercholesterolemia (LDL-C \geq 160 mmHg), persistently elevated triglycerides (\geq 175 mg/dL non-fasting on 3 occasions), low ankle brachial index, a family history of premature CVD, and South Asian ancestry. Used alone, risk equations fare poorly in identifying young adults, particularly women, for treatment prior to the onset of ASCVD [27,28]. However, even with the addition of risk enhancers, most young adults with premature ASCVD would not have been recommended for statin therapy prior to their first event [27–29]. One key challenge both clinically and in potentially using risk enhancers to identify trial candidates is that many risk enhancers are not routinely measured or documented in young adults, and even traditional risk factors (blood pressure, lipid levels) are under-measured in young adults who may not obtain routine preventive care.

An alternate strategy to identify young adults for earlier prevention interventions is to use longer-term risk models such as lifetime CVD risk or 30-year risk [30,31]. Lifetime risk is easily calculated using common clinically measured factors and are easy to implement. Crossing the threshold into the high risk category reflects the effect of aging itself in addition to the effect of prolonged exposure to potentially modifiable risk factor levels. More than 50% of U.S. adults have low short-term and high long-term risk of cardiovascular events [31,32]. These adults often have clinically significant coronary artery calcium (CAC), show more progression of CAC, and have higher carotid intima-media thickness. Another score that may be useful to identify adults at high long-term risk, is the AHA’s Life’s Simple 7 score, which summarizes seven modifiable health and behavioral factors used to characterize ideal cardiovascular health: smoking, physical activity, diet, weight, glucose control, cholesterol and BP. The AHA’s Life Simple 7 score was recently updated to include sleep and is now called the Essential 8 score [33]. Young adults (age 18 to 24 years old) with elevated cardiovascular health scores are at lower risk of premature cardiovascular events [34, 35]. For any of these scores, what threshold should be used to identify a sufficiently “high-risk” young adult for a clinical trial remains unclear, and likely depends on the predicted strength of the intervention, duration of follow-up, and feasible sample size. In addition, efforts to mitigate misclassification should be explored such as measuring risk factors on more than one occasion, this will avoid enrolling people who would be less likely to benefit, while being exposed to treatments with

potential side effects

4.2. CAC scoring

CAC scoring has also emerged as a tool to help identify high-risk adults by identifying individuals with subclinical atherosclerotic disease. CAC testing is currently established for middle aged and older individuals to guide risk assessment and management decisions. CAC scoring may also be useful to identify high-risk young adults: in the presence of multiple risk factors nearly 1 in 4 young men and 1 in 6 young women have detectable CAC, which is associated with higher rates of all-cause and coronary-specific mortality [36–39]. Furthermore, CAC may also be helpful if used in combination with existing risk scores, as it was shown to improve reclassification of young adults beyond the 10-year risk score [40].

CAC scoring has been proposed as a way to identify those at highest risk of cardiovascular events for inclusion in primary prevention trials. In a modeling exercise, researchers showed that using CAC in addition to other risk-based criteria can be cost-effective for trial design, as the increasing event rate could potentially offset the increased cost of screening. However, using CAC may pose significant operational challenges as CAC measurement is still not widely used in clinical practice, and is often not covered by insurance, limiting the availability of CAC testing to those who can afford to pay for it. Thus, in order to prevent a significant selection bias and to obtain sufficiently large numbers of patients, trials that used CAC would need to ensure that all participants could easily obtain a scan. Furthermore, whether and how CAC scoring would impact patient motivation to participate or dropout rates is unknown, though it is possible that the presence of CAC could increase a patient’s motivation to participate in a study. Another challenge to using CAC for screening for a primary prevention trial is the impact on trial equipoise: if a person is found to have an extremely elevated CAC score, it may no longer be ethical to withhold certain treatments (e.g. lipid lowering). CAC scoring may also influence participant behavior and treatments in both the control and intervention arm – which has the potential to effect the overall event rate – if knowledge about the CAC score leads to changes in preventive treatment by outside clinicians or changes in participant behavior. Blinding those screened to test results may help mitigate this problem, but the ethics of withholding CAC results from participants deserve scrutiny.

Given the potential for CAC scoring to lead to changes in cardiovascular prevention therapies, CAC scoring itself was discussed as a possible intervention to be tested to reduce CVD events in young adult by leading to changes in therapy or participant behavior. These studies were discussed extensively in a two prior NHLBI workshops [41,42].

While the epidemiologic data regarding CAC in young adults are robust, some important data gaps remain. CAC is predictive of future events in men and women across all races/ethnicities; however, the distribution of CAC and the degree of risk elevation conferred by the presence of CAC varies by race and sex, remains unclear [41]. Furthermore, many adults with atherosclerosis can still have a CAC of zero due to the presence of only non-calcified plaques, a finding that is more common in both younger adults and in women [43]. Thus, caution needs to be taken in using CAC scores to identify high-risk young adults to avoid under-detection of high-risk women. One alternative or possible addition to CAC scoring to help identify high-risk young adults with subclinical atherosclerosis is coronary CT angiography (CCTA). CCTA can identify non-calcified plaque that is missed by CAC score, and may be helpful to augment CAC scoring in certain populations. However, feasibility limits widespread use of CCTA for large clinical trial population identification.

Another approach to identify high risk individuals that has been proposed is the use of non-invasive imaging of several vascular beds in addition to the heart, such as femoral arteries where subclinical atherosclerosis may be the most common [44]. Given the increasing using of CAC clinically, including in clinical practice guidelines, the

panel focused on CAC over imaging other vascular beds or alternative imaging techniques.

5. Genetic risk scores

In contrast to imaging studies which can only detect disease once prevalent, genetic studies may identify individuals – as early as birth – with very high lifetime risk of clinical CVD. Advances in whole-genome sequencing and ‘polygenic’ scoring have allowed for integration of information from many sites of common DNA variation into a single measure of inherited susceptibility for CVD. These scores can now identify up to 8% of the population with more than triple the normal prevalence of CVD [45–47]. These scores are largely independent of risk estimators such as the Pooled Cohort Equations, highlighting high-risk individuals who are not readily detected by family history or clinical factors [48,49]. To date, studies of genetic risk scores in middle-aged or older individuals have shown limited clinical utility, though it is possible that genetic risk may be more useful in younger populations. Although genetic scores are not modifiable, the risk they confer can be offset through primary prevention interventions: both cholesterol lowering and healthy lifestyle have been shown to lower cardiovascular risk among those with high polygenic scores.,

Although conceptually attractive, additional research into polygenic scores is needed. First, current scores have higher predictive capacity in those of European ancestry – not because genetics are less important in other groups, but because of relative lack of diverse population data to train machine learning algorithms [50,51]. Second, tools that integrate polygenic risk with clinical risk factors or scores, particularly in young adults, have not yet been well-validated. Third, although in principle the scores can be calculated using data from a genotyping array at a cost of less than \$50 US dollars, in practice the scores are not widely clinically available. As more data emerge regarding the optimal use of polygenic risk scores in younger adults, and access to testing improves, polygenic scores may become a useful tool to enrich a primary prevention trial in young adults.

Using genetics or CAC scoring may provide an evidence-based way to identify young adults at highest risk for cardiovascular events who may benefit from early preventive interventions, enriching trial event rates and avoiding treatment in those at lower risk. However, the feasibility of these approaches remains untested in intervention trials in younger adults. The utility and acceptability of these approaches in diverse populations, and the impact of knowledge of these risk factors on future participant behavior, are possible future research opportunities that can help guide the design and implementation of primary prevention trials.

6. Which interventions should be tested?

A wide range of interventions have potential to reduce CVD in high-risk younger adults, ranging from strategies that are predominantly behavioral to pharmacological, to strategies which principally target one risk factor, to strategies which combine behavioral with pharmacological components. Most interventions considered have already demonstrated efficacy in older populations, but have yet to be proven effective in younger populations.

6.1. Lifestyle and behavior

Healthy diet, regular physical activity, weight control, and smoking cessation are critical for preventing both CVD and cardiovascular risk factors such as hypertension and diabetes. A systematic review of 94 RCTs for patients with elevated BP or lipid levels has shown that behavioral counseling to promote healthy diet and physical activity can improve cardiovascular risk factors and hard cardiovascular outcomes, with higher intensity studies leading to greater benefits [52,53]. Obesity is an important modifiable cardiovascular risk factor in early adulthood. In one review of 122 wt loss trials, most trials demonstrated weight loss

and reduction in waist circumference, though the amount of weight loss was modest (5%), and results on other risk factors were mixed. Results from the EARLY Consortium of Studies (Early Adult Reduction of Weight through Lifestyle Intervention) showed that young adults are motivated to join and stay in lifestyle intervention studies, with over 80% retention at 2 years.

Despite these studies demonstrating feasibility of lifestyle to improve risk factor control in the clinical trial setting, widespread dissemination of behavioral interventions to promote healthier diet, physical activity, and healthy weight has not occurred. Real-world implementation studies are needed to determine the best way to deliver the most effective interventions to a broad population in a cost-effective way. Trial designs may also consider single vs multiple behavior interventions, long-term maintenance, and implementation in clinical practice or community settings. In addition, populations under-represented in studies, such as those with limited English proficiency, low literacy, lower access to healthy foods, and who are economically distressed, remain understudied [19,21]. Evaluating which behavioral interventions are best suited for these populations will be an important research opportunity in the next phase of clinical research.

Future prevention trials with lifestyle and behavioral interventions may also test the impact of new technologies to deliver behavioral interventions. This includes digital app-based behavioral interventions, novel meal delivery mechanisms, and wearables and sensors to improve adherence to self-monitoring and improve data capture. Importantly, trials using digital interventions should consider how to include populations who do not have the same degree of access to the technologies used, including smartphones and wireless internet.

Dietary approaches may be helpful beyond the prevention or treatment of obesity. Dietary approaches to reduce sodium and increase dietary potassium can improve blood pressure control in persons with hypertension, though the impact of a DASH diet on preventing hypertension in young adults has not been studied [54]. Other areas for research include the long-term cardiometabolic impact of dietary interventions that aim to lower intake of ultra-processed foods, excess dietary sugar, or other saturated and trans fats. Dietary strategies may also be implemented at a population level, rather than an individual level. In a large cluster-randomized trial in China, salt substitution with 25% potassium chloride led to a 14% reduction in the risk of stroke and a 12% reduction in all-cause mortality. The impact of this on young adults remains to be seen, but the trial provides a potential blueprint for community-level interventions focused on reduction in sodium and increases in dietary potassium.

Smoking remains a major contributor to CVD, and young adults who smoke are at very high lifetime risk of events. Tobacco cessation trials have also shown success for both pharmacologic and behavioral interventions, though most trials have included older populations. Few large prevention trials have successfully tested strategies that have behavioral and pharmacological components either in sequence or in combination, or other simple and sufficiently potent strategies that may be implemented in communities. As there is more information about the use of chronic vaping and marijuana in young adults and the causal role of these lifestyle habits in cardiovascular disorders, they may become possible targets for CVD prevention trials.

6.2. Pharmacologic treatments

There are several possible pharmacological approaches that might be considered in a prevention trial in younger adults at high lifetime risk, including established therapies such as statins and blood pressure lowering and new therapies including long-acting proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and newer antidiabetic agents. These agents may be tested alone or in combination with other pharmacologic or behavioral interventions.

6.3. LDL-C lowering

Genetic studies suggest that adults with exposure to very low levels of LDL-C and BP from birth are at low lifetime risk of CVD [55,56]. Moreover, multiple studies have shown that cumulative exposure to even small elevations in LDL-C increases long term risk of CHD [57,58]. Modest reductions in the level of LDL if initiated at an early age and sustained for a long time might have a larger impact than larger reductions in exposure initiated substantially later in adulthood. Biological plausibility exists to support the hypothesis that LDL-C lowering early in life can prevent a large proportion of CVD events by preventing the initiation of atherosclerotic plaque and stabilizing existing plaque. [30,]While extensively studied and shown effective and safe in older adults, no clinical trial has shown the efficacy of statins on lifetime CVD risk in a broad population of young adults. Statins have already shown potential to lower long-term CVD risk – in long-term follow up of clinical trials of statins, a legacy effect has been shown, with benefits of therapy continuing demonstrated well after the end of the trial [59,60] More direct support for initiation of LDL-C lowering earlier in life comes from studies of early treatment of persons with familial hypercholesterolemia (FH), in whom early statin initiation substantially reduces CVD risk in adulthood. One ongoing randomized trial is beginning to explore the potential of earlier statin treatment. The ECAD (Eliminate Coronary Artery Disease Trial NCT02245087) aims to enroll 10,000 participants (men age 35–50 and women age 45–59) who are free of CVD and randomizing them to atorvastatin 20 mg compared with placebo to evaluate the impact on cardiovascular events [58].

Some have proposed that early, aggressive lowering of LDL-C to very low levels could have the potential to completely prevent the development of later life clinical ASCVD events by arresting the development of subclinical atherosclerosis. This hypothesis is based on epidemiologic studies showing that lifetime exposure to low LDL-C levels is associated with low rates of clinical CVD events later in life, and that adults with loss of function mutations of PCSK9 which result in lower LDL-C levels from birth have very low rates of ASCVD [61]. Animal models further reveal that regression of early atherosclerotic plaques occurs when LDL-C levels are lowered to <30 mg/dL. A possible prevention trial would be an early, aggressive lowering of LDL-C to levels of 20–40 mg/dl in young adults, which might recapitulate the phenotype of genetically predicted lifetime lower LDL-C levels. After an initial intensive “induction” phase, long term moderate LDL-C lowering therapy and lifestyle may be sufficient to prevent resumption of atherosclerotic progression. Periodic intensive treatment every decade or so could be reserved for those who experience significant progression.

One barrier to long-term prevention with statins is the need to take a daily pill. New therapies such as inclisiran, a long-acting PCSK9 inhibitor, currently approved for use via twice annual injections (after an initial induction with three injections in the first year), may provide novel therapeutic approaches to risk reduction in young adults [62]. At present, however, inclisiran is priced too high to be useful in primary prevention. However, were the price to fall substantially, it may be a useful alternative to daily pills in primary prevention. In the future one-shot therapies such as gene editing of PCSK9 offers considerable promise [70]. Regardless of the treatment used, evaluation of the acceptability of various LDL-C lowering therapies and strategies to improve long-term adherence and persistence in young adults (and across all populations, including secondary prevention populations) are needed.

7. Prevention of hypertension and blood pressure lowering

Given the long-term risks and global burden of hypertension, prevention of hypertension has potential for significant public health impact. Among people with hypertension, lowering BP later in life does not completely restore the low-risk state, suggesting that hypertension causes some degree of incompletely reversible cardiac and vascular

damage, and reinforcing the need for earlier prevention of hypertension [55,63,64].

Pharmacologic treatments may also be effective in preventing hypertension, though data on their effectiveness are limited. The TROPHY study showed that treatment of adults at risk for hypertension with candesartan could not only delay the onset of hypertension but potentially decrease the risk of hypertension even after therapy is discontinued. Future research opportunities include evaluating the optimal duration of treatment of young adults, whether dietary interventions can lower the incidence of hypertension, and whether there is heterogeneity in the effect of pharmacologic therapy to prevent hypertension by race, sex, or age.

Among young adults with hypertension, the ideal treatment target and at what BP level to initiate treatment remains unclear. While current guidelines recommend treating young adults without other risk factors when blood pressure exceeds the threshold of <140 mmHg/<90 mmHg, whether treatment should be initiated at a lower BP remains uncertain. The SPRINT trial showed that lower systolic blood pressure treatment targets in older adults improves cardiovascular outcomes compared to a goal of <140 mmHg, but did not include young adults. The HOPE-3 trial failed to show benefit of blood pressure lowering in intermediate-risk adults, though the mean baseline blood pressure was 138/92 mmHg and the absolute decrease in BP was small across the trial, raising the question of whether the achieved reduction in BP was sufficient to lead to a benefit [65].

Other questions related to blood pressure in young persons also remain. First, what is the optimal way to assess of hypertension-related risk in young adults? Home BP or ambulatory BP measurements may be more correlated with long-term risk than single clinical measures [66]. Second, can long-term adherence to therapy and lifestyle interventions be sustained? New technologies provide opportunities for research across some of these questions, including wearable sensors and novel BP measurement devices, apps and other digital programs that support self-management, and decision support embedded in the electronic health record (EHR). Finally, population level interventions and health policy interventions offer the potential to lower blood pressure at the population level, but have yet to be studied at scale in the United States [67].

7.1. Polypill approach

In addition to prevention strategies that primarily focus on single risk factors, strategies that simultaneously address multiple risk factors have been evaluated. The polypill approach to cardiovascular prevention focuses on lowering both BP and cholesterol in a broadly-selected population based primarily on age and sex rather than risk factor level. By treating a large group of middle-aged individuals, a polypill strategy seeks to maximize the public health benefit of low-cost, low-risk therapy. A polypill study evaluating the impact of a polypill on cardiovascular risk factors that included both a statin and antihypertensive agents was successfully tested on intermediate outcomes (e.g., BP and LDL-C lowering) in a socioeconomically vulnerable, largely Black population at a federally qualified community health center in Alabama. Large polypill trials, such as TIPS-3 with CVD events as a primary outcome in older adults, have been conducted outside of the United States, but larger polypill studies in broader clinical settings in the United States have not been conducted. This strategy has potential to lead to broader population-level lowering of BP and lipids, with a single-pill strategy that may have better adherence than multiple therapies given simultaneously. Although the potentially higher rate of adherence is an attractive aspect of the polypill strategy, whether the reduction in either BP or lipids is sufficient to lead to a large reduction of events in a prevention trial in higher risk younger adults is uncertain. Finally, some have questioned whether all components of the polypill are needed or if a high-intensity statin is the “ultimate polypill” [65,68]. Of note, Bitencourt et al. suggested that even among middle aged individuals, the

benefit of polypill strategy may not have a uniform effect given the heterogeneity of underlying ASCVD risk in those treated [69]. Future prevention trials of a polypill based approach may also consider how to best implement the strategy in broader clinical practice.

7.2. Inflammation

Another potential pharmacologic target for prevention in young adults could be inflammation, which may be increased by obesity, metabolic syndrome, insulin resistance, and other elevated risk factor levels. Treatment of inflammation in adults with CVD with colchicine, a low-cost generic medication, demonstrated 23–31% reductions in rates of cardiovascular events among adults with established ASCVD [70,71]. Given the benefits seen in secondary prevention, it is possible that targeting inflammation in addition to LDL-C may yield similar benefits in terms of risk reduction in primary prevention. A study of colchicine in a high-risk, younger primary prevention population may consider a 2 × 2 factorial design with LDL-C lowering to allow quantification of the benefit of either therapy alone or in combination as part of a multi-component intervention.

7.3. Other pharmacologic agents

Two classes of medications, sodium glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-RA), have been shown to prevent cardiovascular disease across a broad range of populations including those with type 2 diabetes and those with chronic kidney disease. Some of GLP1-RA have also shown efficacy for weight loss in individuals without diabetes [72]. These agents, alone or in combination with others approaches, might be powerful therapies to lower the risk of atherosclerotic disease events. However, they have not been tested in younger adults with or without diabetes.

SGLT-2 inhibition is of particular interest since in addition to prevention of atherosclerotic cardiovascular events, this class of medications has also been shown to protect against renal dysfunction and improve outcomes in persons with heart failure. One avenue for research is whether use of SGLT-2 inhibitors can prevent heart failure in high-risk populations. While most risk prediction in young adults has focused on prediction of atherosclerotic disease, heart failure risk can also be assessed based on routinely collected clinical information [9]. Heart failure prevention is of particular importance to help mitigate cardiovascular disparities, as heart failure disproportionately impacts Black Americans.

8. Are hard endpoints required for primary prevention trials?

By design, any clinical trial of adults at low short-term but high lifetime risk will also have a low short-term event rate. While using a surrogate endpoint for such a trial is an intriguing opportunity, it is not clear what surrogate, if any, would be acceptable. For a surrogate to be valid, it must be in the causal pathway of the disease such that modification of the surrogate can clearly be shown to lower cardiovascular event rates. High density lipoprotein cholesterol (HDL-C) is an example of a surrogate that is correlated with cardiovascular events, but changing HDL-C with niacin or CETP inhibitors did not impact cardiovascular events [73,74]. To date, the only accepted surrogates from a regulatory perspective for cardiovascular disease are LDL-C and blood pressure.

Several potential imaging-based surrogate endpoints merit further consideration in primary prevention of ASCVD, including incidence of CAC, progression of coronary stenosis, atheroma volume, and prevalence of high-risk plaque or other specific plaque features such as low-attenuation, non-calcified plaque, or plaque neovascularization. CAC progression has been shown to be associated with cardiovascular events, but may not be an ideal endpoint in a study of therapies that may have benefit but may also increase CAC score. Studies of statin users show that statins may increase the calcification/stabilization of existing

coronary atheroma, while reducing the overall progression of plaque, decrease atheroma volume, and decrease high-risk plaque [75], which may in part explain part of their effect on lowering CVD events [76].

Total plaque volume and plaque characteristics can be evaluated using coronary CT angiography, and may be a better surrogate endpoint than CAC [77]. Which plaque features on coronary CT are best correlated with events, and more importantly, which correlates most strongly with benefit of prevention therapies, remains unknown. In order for a ASCVD prevention trial in young adults to utilize an imaging-based surrogate based on the burden or characteristics of coronary plaque, more research is needed to determine the prevalence of these intermediate endpoints in young adults and the correlation between these intermediate endpoints and clinical ASCVD outcomes. The latter is of particular importance as changes in surrogate endpoints may not lead to changes in event rates. Future studies might investigate the impact of specific treatments on imaging-based measures of coronary atheroma, which measure is most reliable, and which of these is best correlated with ultimate atherosclerotic cardiovascular events.

For studies where interventions are likely to lower blood pressure or heart failure, other imaging endpoints such as left ventricular mass may also be reasonable surrogates. Left ventricular mass tends to increase over time, and as a function of exposure to cumulative BP levels even within the clinically normal range [72]. LV mass can also be easily quantified both through computed tomography (CT) imaging and echocardiography. Once present, left ventricular hypertrophy (LVH) can regress with BP-lowering therapy and is associated with reduction in CVD events [63,66,78]. However, in order for LV mass to be a reliable surrogate, research demonstrating that LV mass changes on therapy correlate with outcomes is necessary.

For now, given the uncertainty in the ideal surrogate endpoint, a trial designed to test an intervention's impact on hard clinical outcomes would likely have the greatest impact on guidelines, payors, and clinical practice. If a large primary prevention trial were designed based on hard clinical events, the addition of imaging data such as CAC or coronary CT angiography would help address a number of the limitations of intermediate imaging-based endpoints. Any such trial based on hard outcomes must address the need for very long term adherence and compliance, as well as avoidance of drop-in over time.

The Central Illustration summarizes some of the key considerations for designing a clinical trial to lower long-term risk in young adults at high lifetime risk of CVD. Inclusion criteria considerations should be designed to identify high-risk adults to ensure sufficient power while balancing the need for external generalizability and feasibility of using the chosen inclusion criteria in general practice. Options for the intervention itself range from pharmacologic treatments to diet, lifestyle, and exercise interventions. While the most compelling clinical trial would be powered based on clinical events such as myocardial infarctions, acute coronary syndrome, heart failure, or strokes, other intermediate endpoints including imaging-based measures of atherosclerosis or left ventricular remodeling could also be considered. Study designs could range from traditional head-to-head placebo-controlled RCTs to more pragmatic studies comparing to usual care or with open-label designs. Research opportunities and gaps are summarized in Table 1.

9. Limitations

The panel was designed with a major focus to evaluate the impact of preventive strategies on ASCVD risk. While heart failure was discussed, particularly relative to the potential for studying SGLT2 inhibitors, the panel did not comprehensively review all potential strategies for prevention of heart failure. Similarly, while there is overlap in risk factors and potential interventions between ASCVD and other CVD, such as atrial fibrillation and non-atherosclerotic stroke, these were not discussed in detail, but are both important areas for prevention. The pace of innovation in CVD interventions means that research opportunities discussed in this paper will need to be further considered as new data

Table 1
Research opportunities in prevention intervention research in young adults with high lifetime CVD risk.

Addressing Disparities in Prevention and Clinical Trial Participation
<ul style="list-style-type: none"> • Interventions on the modifiable structural contributors to disparities in CVD events • Strategies for prevention trials to successfully recruit historically underrepresented and high risk groups
Identifying Young Adults at High Lifetime Risk
<ul style="list-style-type: none"> • Pilot testing the feasibility of CAC testing and polygenic risk scores for participant identification: impact on participant willingness to participate, study diversity, timeline, and resources • Assessment of potential role for CT coronary angiography in addition to CAC scoring • Potential impact of return of results from pre-screening activities on participant behaviors which may impact event rates
Potential Interventions in High-Risk Young Adults
<ul style="list-style-type: none"> • Behavioral interventions ■ Nutrition and physical activity interventions for weight loss, obesity treatment, and obesity prevention ○ May include innovative approaches including food delivery services, community interventions ■ Nutrition interventions to prevent cardiovascular disease ■ Smoking cessation programs (including behavioral interventions in combination with pharmacological therapies) ■ Sodium reduction and increased potassium diets for prevention of hypertension ○ May include individual or population level interventions ○ Pharmacological strategies: May be tested individually or in combination ■ LDL Lowering ○ Statins ○ Novel LDL lowering therapies: long-acting PCSK9 inhibitors (Inclisiran) ■ Blood pressure ○ Lower blood pressure targets for younger adults (e.g. extending SPRINT to younger groups) ○ Pharmacotherapy to prevent hypertension ○ Precision medicine approaches to hypertension to address heterogeneous responses to therapy ■ Polypill strategies: combination antihypertensive and lipid lowering ■ Targeting inflammation (colchicine) ■ Sodium glucose cotransporter-2 (SGLT-2) inhibitors ○ To prevent kidney disease or heart failure in at-risk populations without diabetes ○ To reduce CV events or prevent diabetes in young persons without diabetes ■ Glucagon-like peptide-1 receptor agonists (GLP-1RA) for prevention of atherosclerotic events, treatment of obesity, or prevention of diabetes ○ Strategies for long term adherence for behavioral, LDL-C, and blood pressure interventions including consideration of new technologies ○ Community level interventions (e.g. salt substitution): these were not a workshop focus but are important research opportunities
Potential Endpoints to Evaluate
<ul style="list-style-type: none"> • Hard outcomes: stroke, myocardial infarction, acute coronary syndromes, cardiovascular death • Imaging-based surrogate outcomes: <ul style="list-style-type: none"> ■ Incident coronary calcification (CAC >0) ■ coronary atherosclerosis measured with CT angiography ■ LV Mass (potentially for blood pressure treatment trials) • Research needs for surrogate outcomes include: <ul style="list-style-type: none"> ○ Correlation of coronary plaque imaging measures with future CVD events ○ Magnitude of change from prevention interventions in these endpoints ○ Correlation between the magnitude of expected change in endpoints with subsequent reduction of CVD events ○ Reliability and consistency over time ○ Feasibility and cost in a multi-center trial.

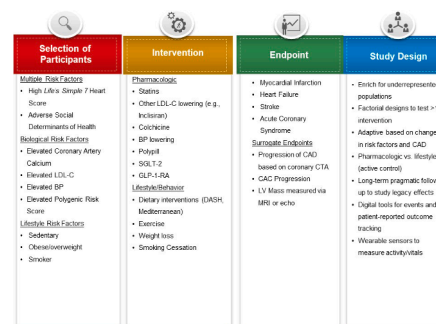
emerges. The panel focused on primary prevention of CVD in young adults with a high lifetime risk, and with the exception of prevention of hypertension, not on the very important potential of primordial prevention to prevent the development of cardiovascular risk factors in the first place. Next, the trial concepts presented are preliminary and are illustrative of the large number of possible interventions that could be considered as single or combination interventions. The panel did not discuss whether the proposed pharmacological interventions are safe in pregnancy. The panel did not consider interventions related to psychological or psychosocial risk factors such as depressive symptoms or occupational stress. Finally, the workshop focused largely on individual-level interventions, and not community-level or policy interventions for cardiovascular prevention.

10. Summary

More than half of the young adult population in the US has low short-term but high lifetime risk based on contemporary risk equations. New ways to identify high risk young adults including CAC, CT angiography, and genetics, may be useful to further risk-stratify the young adult population. While hard outcomes will be most effective in motivating patients, payers, and clinicians to use these therapies, intermediate endpoints such as coronary atherosclerosis identified noninvasively may be shown to be adequate surrogates and could be considered in the future. Several interventions appear to be promising, ranging from focusing on large reductions in a single cardiovascular risk factor to multiple risk factor interventions. Trials in primary prevention in young adults should include enhanced recruitment strategies involving more intense community engagement to obtain a trial population that is racially, ethnically, geographically, and socially diverse. Interventions studied should attempt to improve outcomes for all to help reduce disparities in cardiovascular care. Trial design should also consider the potential implementation of the intervention in clinical practice to maximize impact. As expected, there are multiple research opportunities to consider for future intervention studies in pursuit of the goal of greatly reducing or eliminating the high lifetime CVD risk in younger adults. The opportunities are wide-ranging but the identification of a successful strategy or strategies appears closer today because of the past successful intervention studies in older adults, the deepening knowledge of the lifespan approach to risk assessment, and the ongoing innovation occurring in so many aspects of CVD prevention research.

Central illustration legend

- BP: Blood Pressure
 - CAC: Coronary Artery Calcium
 - CAD: Coronary Artery Disease
 - CTA: Cardiac computed tomography angiography
 - DASH: Dietary Approach to Stop Hypertension
 - Echo: echocardiogram
 - GLP-1-RA: Glucagon-like peptide-1 receptor agonists
 - HCS: Health Care Systems
 - LDL-C: Low-Density Lipoprotein
 - LV: Left Ventricular
 - MRI: Magnetic Resonance Imaging
 - SGLT-2: Sodium-glucose Cotransporter-2
- Summary of Considerations for Primary Prevention Trial Designs for Young Adults at High Lifetime Risk
Central Illustration: Considerations for Primary Prevention Trial Designs for Young Adults at High Lifetime Risk



Central figure legend

The Figure summarizes various aspects of potential trial(s) for primary prevention of ASCVD in young adults at high long-term risk of ASCVD.

- BP: Blood Pressure
- CAC: Coronary Artery Calcium

CAD: Coronary Artery Disease
 CTA: Cardiac computed tomography angiography
 DASH: Dietary Approach to Stop Hypertension
 Echo: echocardiogram
 GLP-1-RA: Glucagon-like peptide-1 receptor agonists
 HCS: Health Care Systems
 LDL-C: Low-Density Lipoprotein
 LV: Left Ventricular
 MRI: Magnetic Resonance Imaging
 SGLT-2: Sodium-glucose Cotransporter-2

Declaration of Competing Interests

Ann Marie Navar has received funding for research to her institution from BMS, Esperion, and Janssen, and honoraria and consulting fees from Astra Zeneca, BI, Bayer, Janssen, Lilly, Novo Nordisk, Novartis, New Amsterdam, Cerner, and Pfizer.

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Amit V. Khera is an employee and holds equity in Verve Therapeutics; has served as a scientific advisor to Amgen, Maze Therapeutics, Navitor Pharmaceuticals, Sarepta Therapeutics, Novartis, Silence Therapeutics, Korro Bio, Veritas International, Color Health, Third Rock Ventures, Illumina, Foresite Labs, and Columbia University (NIH); received speaking fees from Illumina, MedGenome, Amgen, and the Novartis Institute for Biomedical Research; received a sponsored research agreement from IBM Research, and is listed as a co-inventor on a patent application for use of imaging data in assessing body fat distribution and associated cardiometabolic risk.

Donald Lloyd-Jones is an unpaid fiduciary officer of the American Heart Association."

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