

CONTEMPORARY REVIEW

Highlights in ASCVD Primary Prevention for 2021

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ABSTRACT: This review examines key studies published in 2021 that are related to primary prevention of atherosclerotic cardiovascular disease (ASCVD). Major randomized clinical trials (RCTs) concerning traditional risk factors or ASCVD events, meta-analyses, and key observational studies related to primary prevention of ASCVD were considered. The review includes interventions for weight loss, cardiometabolic and renal disease, blood pressure control, diet, and the occurrence of cardiovascular disease events. A few studies considered both primary and secondary prevention populations. The review is not exhaustive. We did not include studies that focused on heart failure or clinical presentations that may be difficult to classify, such as acute or chronic ischemic cardiovascular disease without myocardial infarction. Our purpose was to highlight recent research that will help the reader stay abreast of the changing field of cardiovascular prevention.

Key Words: diabetes ■ hypertension ■ obesity ■ primary prevention ■ risk factors

This review examines key studies published in 2021 that related to primary prevention of atherosclerotic cardiovascular disease (ASCVD). Major randomized clinical trials (RCTs) concerning traditional risk factors or ASCVD events, meta-analyses, and key observational studies related to primary prevention of ASCVD were considered. The review includes interventions for weight loss, cardiometabolic and renal disease, blood pressure control, diet, and the occurrence of cardiovascular disease events. A few studies considered both primary and secondary prevention populations. The review is not exhaustive. We did not include studies that focused on heart failure or clinical presentations that may be difficult to classify, such as acute or chronic ischemic cardiovascular disease without myocardial infarction. Our purpose was to highlight recent research that will help the reader stay abreast of the changing field of cardiovascular prevention.

bariatric surgery, and injectable semaglutide are key examples.¹⁻⁵ Overall, the degree of weight loss with behavior therapy was modest. Bariatric surgery was associated with significant long-term reductions in ASCVD risk, and injectable semaglutide also led to substantial weight loss.

Medicare currently covers behavioral therapy for obesity with up to 22 individual 15-minute in-clinic visits over 12 months. A cluster randomized trial compared 3 weight loss programs for 1407 adults with a BMI 30–45 kg/m² in rural Midwestern clinics.¹ Clinics were randomized to perform either in-clinic individual visits, in-clinic group visits, or telephone-based group visits. Weight change after 2 years of follow up was –4.4 kg for the in-clinic group visits, –3.9 kg for the telephone group and –2.6 kg for the in-person individual visits. The difference in weight loss between in-person group versus in-person individual visits was statistically significant (–1.9 kg, $P=0.01$), but unlikely to change clinical practice.¹ The authors suggested that programs with a combination of in-person and remote visits warrant further study, as they may allow for more contact with patients, and thus be more effective.

OBESITY

In 2021 several studies examined the effect of different strategies for weight loss—behavior modification,

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Nonstandard Abbreviations and Acronyms

BLPTTC	Blood Pressure Lowering Treatment Trialists Collaboration
CLICK	Chlorthalidone in Chronic Kidney Disease
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
FIGARO-DKD	Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease
FOS	Framingham Offspring Study
ILI	intensive lifestyle intervention
PESA	Progression of Early Subclinical Atherosclerosis
PROPEL	Promoting Successful Weight Loss in Primary Care in Louisiana
PURE	Prospective Urban Rural Epidemiology
QUARTET	Quadruple Ultra-Low-Dose Treatment for Hypertension
RADIANCE-HTN TRIO	Ultrasound renal denervation for hypertension resistant to a triple medication pill
REDUCE-IT	Reduction of Cardiovascular Events with Icosapent Ethyl—Intervention Trial
SCORED	Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk
SPRINT	Systolic Blood Pressure Intervention Trial
SSaSS	Salt Substitute and Stroke Study

STEP	Semaglutide Treatment Effect in People with Obesity
STEP	Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients
TIPS	The International Polycap Study 3
WAHA	Walnuts in Healthy Aging

A meta-analysis of 174 772 adults from 16 cohort studies and one clinical trial, reported that bariatric surgery was associated with a large reduction in mortality over 30 years of follow up (hazard ratio [HR]=0.51, $P<0.0001$). The authors reported a median increase in life expectancy of 6.1 years compared with non-surgical care.² The gain in median life expectancy among patients with type 2 diabetes (T2DM) was 9.3 years versus 5.1 years in the adults without diabetes.

A series of clinical trials reported the weight loss effects in non-diabetic adults with 68 weeks of injectable, glucose-lowering semaglutide, a glucagon-like peptide 1 receptor agonist (GLP-1 RA). This medication has been approved at doses up to 1 mg/week to help control glycemia in patients with T2DM. The randomized double-blind STEP1 (Semaglutide Treatment Effect in People with Obesity) trial investigated the effects of 2.4 mg/week semaglutide injections for 1961 adults with BMI ≥ 30 kg/m² or with BMI ≥ 27 kg/m² plus one or more comorbid diagnoses.³ At 68 weeks the authors reported a mean weight change of -14.9% in the intervention group versus -2.4% in the placebo ($P<0.001$); a mean weight loss $>5\%$ occurred in 86.4% with active therapy versus 31.5% with placebo, and weight loss $>10\%$ occurred in 69.1% with active therapy, 12.0% with placebo.

Companion STEP trials assessed adding the medication to a low-calorie diet, the impact of counseling visits, and the persistence of weight loss, all demonstrating substantial weight loss with the addition of semaglutide.^{4,5} In STEP 3, both treatment arms included a low-calorie diet for the first 8 weeks and counseling visits were provided for the duration of the trial. The study reported much greater weight loss in the semaglutide with counseling group compared with counseling alone.⁴ In STEP 4, semaglutide was administered to all 902 participants during the first 20 weeks of the trial (mean weight loss -10.6%), and subjects were subsequently randomly assigned to continued therapy or placebo for weeks 20 to 68.⁵ The investigation demonstrated additional weight loss

for the semaglutide treatment group from week 20 to week 68 (−7.9%), whereas participants randomized to placebo had mean weight gain +6.9% during weeks 20 to 68. On the basis of the STEP trials, the semaglutide 2.4 mg/weekly dose was approved by the US Food and Drug Administration as a weight loss agent in 2021.

CARDIOMETABOLIC AND CHRONIC KIDNEY DISEASE

Rossello et al examined the association between hemoglobin A1c (HgbA1c) and subclinical atherosclerosis (SA) using data from the observational PESA (Progression of Early Subclinical Atherosclerosis) study in Spain.⁶ Two-dimensional ultrasound and non-contrast cardiac CT were used to detect SA in the carotid and femoral/iliac arteries, the infrarenal aorta and coronary arteries in 3973 adults without diabetes, ages 40 to 54 years. Not surprisingly, adults with prediabetes were more likely than euglycemic adults to have SA in multiple vascular beds. However, the association of HgbA1c with multi-territorial SA was graded, and statistically significant even in adults with HgbA1c 5.5% to 5.6% (HR, 1.36 [95% CI 1.03–1.80]). When participants were stratified by 10-year estimated ASCVD risk, the association of HgbA1c with SA was significant for low-risk, but not moderate risk individuals. The findings of this study imply that preventive intervention is indicated even at levels of what we now regard as normoglycemia.

The PROPEL (Promoting Successful Weight Loss in Primary Care in Louisiana) cluster randomized trial studied whether an intensive lifestyle intervention (ILI) program delivered by health coaches embedded in 18 primary care clinics serving low-income patients would improve control of cardiometabolic risk factors versus usual care.⁷ Prior publication had shown that adults in the ILI lost more weight than those in usual care (mean difference −4.51% [95% CI, −5.93 to −3.10], $P<0.01$).⁸ ILI participants attending weekly sessions with health coaches (16 in-person sessions and 6 via phone) during the first 6 months, and monthly sessions (either in-person or phone) for 18 months. Health coaches helped participants develop a plan to achieve 10% weight loss by diet and exercise and tracked their progress remotely. Fasting blood glucose (FBG) decreased from baseline to 12 months (−4.5 mg/dL, $P=0.04$) but not at 24 months in the ILI arm. HDL-C increased by 4.7 mg/dL at 12-months and 4.3 mg/dL at 24 months in the ILI arm. FBG and HDL-C did not change with usual care. There was no difference between groups for blood pressure, total or LDL-C, or triglycerides, although BP and cholesterol levels were already well-controlled at baseline. While it is encouraging that

some gains were made in important cardiometabolic risk factors, whether those gains would continue after cessation of the program is unknown.

Several large RCTs evaluated whether the use of medications that target metabolic pathways reduce ASCVD risk in high-risk patients, such as those with chronic kidney disease. The trials showed that aggressive care to prevent ASCVD events and heart failure in patients with T2DM patients and chronic kidney disease continues to expand to include sodium-glucose cotransporter 2 inhibitor (SGLT2i), GLP1-RA, and a mineralocorticoid antagonist. The SCORED (Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk) trial evaluated the role of the oral SGLT2i, sotagliflozin, versus placebo to reduce composite ASCVD and heart failure events in 10584 adults with T2DM with estimated glomerular filtration rate (eGFR) 25 to 60 mL/min per 1.73 m².⁹ Over a median follow up of 16 months, the primary end point (ASCVD death, heart failure hospitalization, or urgent heart failure visit) event rate was 5.6 per 100 patient-years with sotagliflozin versus 7.5 events per 100 patient-years with placebo (HR=0.74, $P<0.001$).⁹ Adverse side effects of sotagliflozin included diarrhea, genital fungal infections, volume depletion, and diabetic ketoacidosis.

The cardiovascular effects of finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist, were studied prospectively in the FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease) trial.¹⁰ In FIGARO-DKD 7437 participants with either stage 2 to 4 chronic kidney disease (CKD) and moderately elevated albuminuria or stage 1 or 2 CKD and severely increased albuminuria were randomized to finerenone versus placebo, and all received maximally tolerated renin-angiotensin blockade before randomization. Adults with symptomatic heart failure with reduced ejection fraction were excluded. Over a median follow-up of 3.4 years, the primary outcome (composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for heart failure) occurred in 12.4% with finerenone versus 14.2% with placebo (HR=0.87, $P=0.03$). The outcome was primarily driven by a reduction in heart failure hospitalization (3.2% versus 4.4%). The incidence of serious adverse event rates was similar between groups, but hyperkalemia was more common with finerenone (10.8% versus 5.3%). Importantly, 60% of the participants had albuminuria in the setting of an eGFR >60 mL/min per 1.73 m², highlighting the complementary nature of both creatinine and urinary albumin-creatinine ratio. At baseline only 7.5% were taking a GLP1-RA and 8.5% were taking an SGLT2i.

HYPERTENSION

In 2021, RCT data provided insight into various strategies regarding blood pressure management, including salt substitution, lifestyle interventions, higher versus lower blood pressure targets, renal denervation, and chlorthalidone in patients with low eGFR. Two large meta-analyses addressed the risk of diabetes with blood pressure lowering, and whether the benefits of blood pressure lowering differed by age or baseline pressure.

The SSaSS (Salt Substitute and Stroke Study) was an open label cluster randomized trial in 600 rural Chinese villages.¹¹ Eligible participants included adults with poorly controlled blood pressure (≥ 140 mm Hg with or 160 mm Hg without medication) and age >60 years (27.4%) or prior stroke (72.6%). Intervention village participants were provided reduced sodium salt substitute (75% sodium chloride and 25% potassium chloride) free of charge. Control village participants continued to use regular salt (100% sodium chloride). The primary outcome was fatal and nonfatal stroke.

Among 20995 participants, the mean difference in SBP between the intervention and control arms was -3.34 mm Hg (95% CI, -4.51 to -2.18). Over a median follow-up of 5.1 years there was a significant reduction in stroke with the salt substitute (29.14 versus 33.65/1000 person-years, $P=0.006$) and MACE (49.1 versus 56.3/1000 person-years, $P<0.001$) (see [Table 1](#)). There was no significant difference in the incidence of definite hyperkalemia or sudden death. While the absolute risk reduction in events was modest, this magnitude of benefit could potentially prevent $>300\,000$ strokes and $>1\,000\,000$ vascular events when applied to the whole Chinese population. It is unclear whether the results can be generalized to more Westernized populations, in which salt intake is often from processed or restaurant food and where the relative incidence of stroke is lower. In addition, the increase in potassium intake may have contributed to some of the benefit with the salt substitute, given that raising potassium intake has also been shown to lower blood pressure.¹²

The RADIANCE-HTN TRIO trial evaluated ultrasound renal denervation therapy in patients with resistant hypertension, defined as blood pressure $>140/90$ mm Hg with at least 3 antihypertensive medications, including a diuretic.¹³ At enrollment participants were all treated with a combination pill (amlodipine 10 mg, valsartan 160 mg, hydrochlorothiazide 25 mg). If the blood pressure remained $>135/85$ mm Hg on ambulatory testing after 4 weeks of treatment then participants were randomized to renal denervation ($n=69$) versus sham procedure ($n=67$). With the fixed-dose combination pill the mean daytime ambulatory SBP decreased from 161.9 mm Hg to 150 mm Hg. With renal denervation

the additional reduction in systolic blood pressure was -4.5 mm Hg (95% CI -8.5 to -0.3 , $P=0.022$) greater than with the sham procedure at 2 months. Additionally, at 2 months 35% of the renal denervation group and 21% of the sham group had controlled blood pressure ($<135/85$ mm Hg). Complications were rare and longer-term efficacy and safety data are being collected.

Two large event-driven trials compared cardiovascular outcomes among higher risk adults randomized to higher versus lower SBP targets. Both trials were stopped early after ≈ 3.3 years because of a reduction in cardiovascular events with lower SBP. The final report of the SPRINT (Systolic Blood Pressure Intervention Trial) included data from additional adjudicated events, since it was first published in 2015, and 1 year of postintervention follow-up.¹⁴ In SPRINT, 9361 patients (mean age 67.9) with hypertension and ≥ 1 marker of cardiovascular risk were randomized to SBP targets of <120 mm Hg versus <140 mm Hg. After the trial was stopped early, patients were followed for a 1-year postintervention period, during which they were free to continue or change treatment targets. During the intervention the mean SBP in the intensive and standard-treatment groups were 120 and 133.9 mm Hg, respectively; in the postintervention period the mean SBP increased to 126.9 and 136.5 mm Hg, respectively. With the additional adjudicated events a significant reduction in the primary composite outcome persisted with intensive treatment (see [Table 1](#) for details, 1.77% per year versus 2.4% per year, $P<0.001$). Slightly higher incidence of hypotension (2.1% versus 1.2%, $P=0.001$) and electrolyte abnormalities (2.9% versus 2.2%, $P=0.03$) was noted with intensive treatment.

In the Chinese trial, STEP (Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients), 8511 adults with hypertension (mean age 66.2 years) were randomized to SBP targets 110 to <130 or 130 to <150 mm Hg.¹⁵ Almost 20% of the participants had diabetes, whereas patients with diabetes were excluded from SPRINT. Throughout follow-up, the mean SBP was 126.7 mm Hg in the intensive-treatment group and 135.9 mm Hg with standard treatment, almost identical to the SBPs achieved in the post-intervention phase of SPRINT. The total incidence of the composite primary outcome ([Table 1](#)) was significantly lower in the intensive versus standard-treatment group (3.5% versus 4.6%, $P=0.007$). However, there was no decrease in cardiovascular or all-cause mortality with intensive treatment. Incidence of dizziness, syncope, fracture, or adverse renal outcomes did not differ between treatment groups, but hypotension occurred more frequently in the intensive versus standard-treatment group (3.4% versus 2.6%, $P=0.03$).

Taken together, SPRINT and STEP blood pressure trials confirm the efficacy and safety of lowering SBP

Table 1. Summary of Randomized Controlled Trials Published in 2021 for Primary Prevention of ASCVD Events or Levels of ASCVD Risk Factors

Study	Study population	Intervention/study setting	Primary outcome	Secondary outcomes	Adverse outcomes
Obesity REPOWER (Rural Engagement in Primary Care for Optimizing Weight Reduction) ¹	1407 adults age 20–75 y and body mass index of 30–45 kg/m ²	Cluster randomized trial among 36 clinics in rural Midwestern US; Clinics randomized to perform either in-clinic individual visits, in-clinic group visits, or telephone-based group visits	Weight change at 24 mo A minimum clinically important difference was defined as 2.75 kg Mean weight loss at 24 mo was -4.4 kg (95% CI, -5.5 to -3.4 kg) in the in-clinic group intervention, -3.9 kg (95% CI, -5.0 to -2.9 kg) in the telephone group intervention, and -2.6 kg (95% CI, -3.6 to -1.5 kg) in the in-clinic individual intervention	At 6-mo follow-up, mean weight loss was -8.3 kg (95% CI, -9.2 to -7.4 kg) for in-clinic group visits, -7.7 kg (95% CI, -8.6 to -6.8 kg) for telephone group visits, and -5.7 kg (95% CI, -6.7 to -4.8 kg) for in-clinic individual visits At 24 mo, there was no significant difference between groups in the proportion of participants who achieved clinically meaningful weight loss >5%	Only 3 events were determined to be possibly study related (2 joint replacements and 1 cholecystectomy), and 1 probably related (recurrent syncope)
Obesity STEP (Semaglutide Treatment Effect in People with Obesity) ^{1,3}	1961 adults with BMI ≥30 kg/m ² (or ≥27 kg/m ² with ≥1 weight-related comorbidity) and without diabetes	68 wk of treatment with once-weekly subcutaneous semaglutide 2.4 mg or placebo, plus lifestyle intervention	Mean change in body weight from baseline to week 68 -14.9% with semaglutide and -2.4% with placebo, treatment difference -12.4 percentage points (95% CI -13.4 to -11.5); P<0.001	<ul style="list-style-type: none"> Weight loss of >5%, >10% and >15%, and >20% occurred in 86.4%, 69.1%, 50.5%, and 32.0%, respectively, with semaglutide vs 31.5%, 12.0%, 4.9%, and 1.7% with placebo Change in body weight from baseline to week 68 was -15.3 kg with semaglutide vs -2.6 kg with placebo group Change in SBP -6.16mm Hg with semaglutide vs -1.06mm Hg with placebo (P<0.001) Change in glycated hgb -0.45 percentage points with semaglutide vs -0.15 with placebo 	<ul style="list-style-type: none"> Gastrointestinal disorders (typically nausea, diarrhea, vomiting, and constipation) were the most frequently reported events and occurred more often with semaglutide than placebo (74.2% vs 47.9%) Discontinuation of study drug more common with semaglutide, mainly from GI events (7.0% vs 3.1%) Serious adverse events 9.8% semaglutide and 6.4% of placebo
Obesity STEP (Semaglutide Treatment Effect in People with Obesity) ^{3,4}	611 adults with BMI ≥30 kg/m ² (or ≥27 kg/m ² with ≥1 weight-related comorbidity) and without diabetes	Once-weekly subcutaneous semaglutide, 2.4 mg vs placebo combined with a low-calorie diet for the first 8 wk and intensive behavioral therapy (ie, 30 counseling visits) during 68 wk	Mean body weight change from baseline to week 68 -16.0% for semaglutide vs -5.7% for placebo Treatment difference, -10.3 percentage points (95% CI, -12.0 to -8.6); P<0.001	<ul style="list-style-type: none"> A higher proportion of participants in the semaglutide vs placebo group achieved weight losses of ≥10% or 15% (75.3% vs 27.0% and 55.8% vs 13.2%, respectively; P<0.001) 	<ul style="list-style-type: none"> Gastrointestinal adverse events were more frequent with semaglutide (82.8% vs placebo (63.2%)) Treatment was discontinued owing to these events in 3.4% with semaglutide vs 0% placebo

(Continued)

Table 1. Continued

Study	Study population	Intervention/study setting	Primary outcome	Secondary outcomes	Adverse outcomes
STEP (Semaglutide Treatment Effect in People with Obesity) 4 ^b	902 adults with BMI ≥30 kg/m ² (or ≥27 kg/m ² with ≥1 weight-related comorbidity) and without diabetes	Once-weekly subcutaneous semaglutide, 2.4 mg for 20 wk, then randomized to placebo or continued semaglutide for weeks 20–68 (both with lifestyle intervention)	<ul style="list-style-type: none"> Mean weight loss for all participants during 1st 20 wk 10.6% With continued semaglutide, mean body weight change from week 20 to week 68 was -7.9% vs +6.9% with the switch to placebo (difference, -14.8 percentage points [95% CI, -16.0 to -13.5]; <i>P</i><0.001) 	<p>Several parameters improved with continued s.c. semaglutide vs placebo (all <i>P</i><0.001)</p> <ul style="list-style-type: none"> Waist circumference (-9.7 cm [95% CI, -10.9 to -8.5 cm]), SBP (-3.9 mm Hg [95% CI, -5.8 to -2.0 mm Hg]), and SF-36 physical functioning score (2.5 [95% CI, 1.6–3.3]) 	<ul style="list-style-type: none"> Gastrointestinal events were reported in 49.1% participants who continued subcutaneous semaglutide vs 26.1% with placebo; similar proportions discontinued treatment because of adverse events with continued semaglutide (2.4%) and placebo (2.2%)
Cardiometabolic and chronic kidney disease					
PROPEL (Promoting Successful Weight Loss in Primary Care in Louisiana) ⁷	Health coaches embedded in 18 primary care clinics serving low-income patients (803 patients total)	Usual care received their normal primary care; Intensive lifestyle intervention (ILI) group received a 24-mo high-intensity lifestyle-based obesity treatment program, embedded in clinics, delivered by health coaches in weekly sessions	<p>Secondary analysis of previously published trial in which % weight loss at 24 mo was significantly greater with ILI (change in body weight, -4.99%; 95% CI, -6.02 to -3.96) than usual-care (-0.48%; 95% CI, -1.57 to 0.61)</p> <ul style="list-style-type: none"> In current analyses no change in fasting glucose, total and HDL cholesterol or SBP at 24 mo Increases in HDL-C greater with ILI than usual care (mean difference at 24 mo, 4.6 mg/dL [95% CI, 2.9–6.3]; <i>P</i><0.01) 	NA	None
SCORED (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk) trial ⁹	10584 patients with T2DM (glycated hemoglobin level, ≥7%), chronic kidney disease (estimated glomerular filtration rate, 25–60 mL/min per 1.73 m ²)	Sotagliflozin (200 mg once daily, increase to 400 mg as tolerated) vs placebo	<p>Composite of the total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure</p> <ul style="list-style-type: none"> 5.6 events per 100 patient-years in the sotagliflozin group and 7.5 events per 100 patient-years in the placebo group (hazard ratio, 0.74; 95% CI, 0.63–0.88; <i>P</i><0.001) 	<p>First occurrence of death from cardiovascular causes, nonfatal MI, or nonfatal stroke, the HR was 0.84 (95% CI, 0.72–0.99)</p>	<ul style="list-style-type: none"> Side effects more common with sotagliflozin than placebo Diarrhea 8.5% vs 6.0% Genital mycotic infections (2.4% vs 0.9%) DKA (0.6% vs 0.3%)

(Continued)

Table 1. Continued

Study	Study population	Intervention/study setting	Primary outcome	Secondary outcomes	Adverse outcomes
FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease) ¹⁰	7437 participants with either stage 2–4 CKD and moderately elevated albuminuria or stage 1 or 2 CKD and severely increased albuminuria	Finerenone 10–20 mg vs placebo	Composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for heart failure occurred in 12.4% with finerenone vs 14.2% with placebo (HR=0.87, P=0.03), median follow up 3.4 y	Composite of kidney failure, a sustained decrease from baseline of at least 40% in the eGFR, or death from renal causes (9.5% in the finerenone group and in 395 (10.8% in the placebo group (hazard ratio, 0.87; 95% CI, 0.76–1.01)	Hyperkalemia-related discontinuation of the trial regimen was higher with finerenone (1.2%) than with placebo (0.4%)
Hypertension					
SSaSS (Salt Substitute and Stroke Study) ¹¹	600 rural Chinese villages; Eligible participants (n=20995) included adults with poorly controlled blood pressure (≥ 140 mm Hg with or 160 mm Hg without medication) and age >60 y (27.4%) or prior stroke (72.6%)	Salt substitute (75% sodium chloride and 25% potassium chloride) free of charge vs sodium chloride 100%	Over a median follow-up of 5.1 y there was a significant reduction in stroke with the salt substitute (29.14 vs 33.65/1000 person-years, P=0.006)	Reduction in MACE with salt substitute (49.1 vs 56.3/1000 person-years, P<0.001)	No significant difference in the incidence of definite hyperkalemia
RADIANCE-HTN TRIO ¹³	136 patients with resistant hypertension, defined as blood pressure $\geq 140/90$ mm Hg with at least 3 antihypertensive medications, including a diuretic	Renal denervation vs sham procedure	Additional reduction in systolic blood pressure was -4.5 mm Hg (95% CI -8.5 to -0.3 , P=0.002) greater than with the sham procedure at 2 mo	At 2 mo 35% of renal denervation group and 21% of sham group had controlled blood pressure (<135/85 mm Hg)	None
SPRINT (final report) ¹⁴	9351 with hypertension and ≥ 1 marker of cardiovascular risk	SBP targets of <120 mm Hg vs <140 mm Hg	Significant reduction in composite of MI, other ACS, stroke, acute decompensated heart failure, or death from cardiovascular causes persisted with intensive treatment (1.77% per year vs 2.4% per year, P<0.001)	All-cause mortality decreased with intensive treatment, 1.06% per year vs 1.41% per year; hazard ratio, 0.75; 95% CI, 0.61–0.92	<ul style="list-style-type: none"> Higher incidence of hypotension (2.1% vs 1.2%, P=0.001) and electrolyte abnormalities (2.9% vs 2.2%, P=0.03) with intensive treatment
STEP (Chinese the Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients) ¹⁵	8511 adults with hypertension	SBP targets 110 to <130 or 130 to <150 mm Hg	Composite of stroke, ACS, ADHF, coronary revascularization, AF, or death from cardiovascular causes was significantly lower in the intensive vs standard-treatment group (3.5% vs 4.6%, P=0.007) over 3.3 y	Individual components of primary outcome favored intensive treatment: HR stroke 0.67 (95% CI, 0.47–0.97), ACS 0.67 (0.47–0.94), ADHF 0.27 (0.08–0.98), coronary revascularization 0.69 (0.40–1.18), AF 0.96 (0.55–1.68), and death from cardiovascular causes 0.72 (0.39–1.32)	Hypotension greater with intensive treatment (3.4% vs 2.6%, P=0.03) No difference in syncope, reduction in eGFR

(Continued)

Table 1. Continued

Study	Study population	Intervention/study setting	Primary outcome	Secondary outcomes	Adverse outcomes
CLICK (Chlorthalidone in Chronic Kidney Disease) trial ¹⁸	160 Adults with stage 4 kidney disease, poorly controlled HTN	Chlorthalidone vs placebo	Change in 24-h ambulatory systolic blood pressure from baseline to 12 wk; between-group difference -10.5 mm Hg (95% CI, -14.6 to -6.4) (P<0.001) with chlorthalidone	Percent change in urinary albumin-to-creatinine ratio from baseline to 12 wk -52% with chlorthalidone and -4% with placebo. (between-group difference, -50 percentage points; 95% CI, -60 to -37)	Increases in serum creatinine >25% from baseline 45% with chlorthalidone and 13% with placebo; OR for an increase in creatinine >25% with chlorthalidone 1.9 (95% CI, 0.4-10.3) among patients who were not on loop diuretics at baseline and 9.2 (95% CI, 3.0-31.3) among those who were
TRIUMPH study ¹⁷	140 adults with resistant hypertension	4-mo program of lifestyle modification (C-LIFE [Center-Based Lifestyle Intervention]) including dietary counseling, behavioral weight management, and exercise, or a single counseling session providing SEPA (Standardized Education and Physician Advice)	Reduction in clinic systolic BP was greater in C-LIFE (-12.5 [95% CI, -14.9 to -10.2] mm Hg) compared with SEPA (-7.1 [-95% CI, 10.4 to -3.7] mm Hg) (P=0.005)	24-h ambulatory systolic BP also was reduced in C-LIFE (-7.0 [95% CI, -8.5 to -4.0] mm Hg), with no change in SEPA (-0.3 [95% CI, -4.0 to 3.4] mm Hg) (P=0.001)	N/A
Polypill and fixed dose combination treatments					
TIPS-3 ¹⁸	5713 men ≥50, women ≥55 y with an INTERHEART risk score ≥10, or men and women ≥65 y with an INTERHEART risk score of ≥5; no prior ASCVD	4.6 y study, 2x2 factorial design of polypill (40 mg of simvastatin, 100 mg of atenolol, 25 mg of hydrochlorothiazide, and 10 mg of ramipril or placebo; ASA 81 mg or placebo)	Polypill: death from cardiovascular causes, myocardial infarction, stroke, resuscitated cardiac arrest, heart failure, or revascularization 4.4% polypill vs 5.5% placebo (HR 0.79 [0.63-1.00]). ASA: death from cardiovascular causes, myocardial infarction, or stroke 4.1% ASA vs 4.7% placebo (HR 0.86 [0.67-1.10]). Combined treatment 4.1% combined vs 5.8% placebo (HR 0.69 [0.50-0.97]).	Polypill: Death from cardiovascular causes, MI, stroke 3.9% vs 4.9% (HR 0.79 [0.61-1.01]). ASA: death from cardiovascular causes, MI, stroke, cancer 5.3% vs 6.2% (HR 0.86 [0.69-1.07])	Dizziness or hypotension 2.7% polypill vs 1.1% placebo; Major bleeding 0.7% ASA vs 0.7% placebo
QUARTET trial ¹⁹	591 Australian adults untreated or receiving monotherapy and elevated blood pressure (ie, systolic ≥140 or ≥130 mm Hg, respectively, or other comparable criteria)	Phase 3 trial, quadpill (irbesartan at 37.5 mg, amlodipine 1.25 mg, indapamide 0.625 mg, and bisoprolol 2.5 mg) vs irbesartan 150 mg indistinguishable monotherapy control, 12 wk follow-up and 12 mo extended follow-up subgroup	Difference in unattended office systolic blood pressure at 12 wk 6.9 mm Hg lower in quadpill vs control (95% CI 4.9-8.9; P<0.0001). At 52 wk 7.7 mm Hg lower quadpill group (95% CI 5.2-10.3)	Blood pressure control <140/90 mm Hg at 12 wk quadpill 76% vs control 58%; relative risk (RR) 1.30, (95% CI 1.15-1.47; P<0.0001). 52 wk 81% quadpill vs 62% control	Dizziness 31% quadpill vs 25.4% control (P=0.07). No difference in rates of serious events

(Continued)

Table 1. Continued

Study	Study population	Intervention/study setting	Primary outcome	Secondary outcomes	Adverse outcomes
Omega 3 fatty acids OMEMI (Omega-3 Fatty acids in Elderly with Myocardial Infarction) Trial ²⁰	1014 older men and women who had suffered an MI in the past 2–8 wk	Omega 3 fatty acids (1.8 g daily–930 mg EPA/660 mg DHA) vs a placebo (corn oil)	Recurrent non-fatal MI, unscheduled revascularization, heart failure hospitalization, stroke, and all-cause death. Over 2 y of follow-up there were 210 total primary events with no reduction in those randomized to omega 3 fatty acid supplementation vs placebo (HR 1.08 [95% CI, 0.82–1.41])	Atrial fibrillation occurred in 28 (7.2%) patients on n-3 PUFA vs 15 (4.0%) on placebo (1.84 [0.98–3.45]; <i>P</i> =0.06)	Major bleeding occurred in 54 (10.7%) and 56 (11.0%) in the n-3 PUFA and placebo groups, respectively (<i>P</i> =0.87)
STRENGTH (Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia) trial ⁴¹	10382 adults with established ASCVD, T1DM or T2DM with additional risk factors, or age >50 for men and 60 for women with additional risk factors. Lipid criteria for all were LDL <100 mg/dL on a maximally tolerated dose of a statin, HDL <42 mg/dL, TG 180–500 mg/dL	4 g daily of ω-3 carboxylic acid (CA) vs corn oil placebo	Secondary analysis of previously published trial to determine whether achieved plasma levels of EPA and DHA were associated with a composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization. Compared with corn oil, adjusted HR for the highest tertile of achieved plasma levels were 0.98 (95% CI, 0.83–1.16; <i>P</i> =0.81) for EPA, and 1.02 (95% CI, 0.86–1.20; <i>P</i> =0.85) for DHA		N/A
Diet WAHA (Walnuts and Healthy Aging) ²²	708 cognitively healthy adults ages 63–79 y, without major comorbidities; trial performed in Barcelona, Spain and California	Walnut-free (control) or walnut-supplemented diet (≈15% of energy, 30–60 g/d)	Secondary analysis from a study whose primary outcome was cognitive decline. Walnut diet significantly decreased (mg/dL) total cholesterol (mean –8.5 [95% CI, –11.2 to –5.4]), LDL-C (mean –4.3 [–6.6 to –1.6])	Total LDL particles and small LDL particle number decreased by 4.3% and 6.1%	None

AF indicates atrial fibrillation; ASA, aspirin; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; HDL, high density lipoprotein cholesterol; ILI, intensive lifestyle intervention; LDL, low density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MI, myocardial infarction; SBP, systolic blood pressure; T1DM, type 1 diabetes; T2DM, type 2 diabetes; and TG, triglycerides.

below 130 mm Hg in older adults at higher risk for CVD. Both trials reduced the risk of a composite outcome that included ASCVD events, heart failure, and CVD death. Both showed similar efficacy across multiple subgroups, including adults over age 70 to 75. In STEP the achieved SBP in the intensive treatment group was a few mm Hg higher than in SPRINT, perhaps helping to account for the lower incidence of adverse effects with intensive treatment in STEP, but also the failure to improve all-cause and cardiovascular mortality. A meta-analysis of 51 trials from the BPLTTC (Blood Pressure Lowering Treatment Trialists Collaboration) affirmed the results of SPRINT and STEP, showing a consistent reduction in CVD events with a 5 mm Hg reduction in SBP across a wide range of baseline pressures, down to 120 mm Hg.²³ As with SPRINT and STEP, the meta-analysis also showed benefit with blood pressure lowering among older adults.

In the CLICK (Chlorthalidone in Chronic Kidney Disease) trial 160 adults with poorly controlled hypertension and stage 4 CKD (eGFR 15 to <30 mL/min per 1.73 m²) were randomized to chlorthalidone versus placebo.¹⁶ The primary outcome was the change in 24-hour ambulatory SBP from baseline to 12 weeks. The starting dose of chlorthalidone was 12.5 mg daily, and the dose was doubled every 4 weeks to a maximum of 50 mg if the SBP remained \geq 135 mm Hg or for DBP \geq 85 mm Hg. By week 12 the mean SBP in the chlorthalidone group had decreased from 142.6 mm Hg to 131.6 mm Hg. The majority of the blood pressure change (–11 mm Hg) occurred with the initial 12.5 mg dose. Acute kidney injury (AKI) occurred more frequently with chlorthalidone than placebo (41% versus 13%), but the reduction in eGFR improved within 2 weeks of stopping the drug. Participants who were also taking a loop diuretic had 9.2-fold higher odds of experiencing an AKI with chlorthalidone versus placebo; the OR was 1.9 for those not taking a loop diuretic. Longer and larger trials are needed to evaluate safety and the potential impact on cardiovascular events, but the results support judicious use of chlorthalidone as an antihypertensive agent in adults with advanced CKD.

A second study from the BPLTTC addressed 2 additional questions related to blood pressure management—whether blood pressure lowering per se reduces the risk of developing diabetes, and whether specific medication modified the risk of incident diabetes.²⁴ Using individual participant data, the investigators performed a meta-analysis of 22 trials that compared a specific class of antihypertensive medication to placebo or a second class. After a median follow-up of 4.5 years, lowering SBP by 5 mm Hg was associated with diminished risk of type 2 diabetes across all trials by 11% (HR, 0.89 [95% CI 0.84–0.95]). There was no heterogeneity of effect based on BMI.

The authors reported that diabetes risk was reduced with ACEI and ARBs by 11%, calcium channel blockers did not affect diabetes risk, and thiazide diuretics and beta-blockers increased diabetes risk (thiazides RR, 1.20 [95% CI 1.07–1.35]) and beta-blockers (RR, 1.48 [95% CI 1.27–1.72]). An important limitation is that it is unknown whether the risk of diabetes differed among those with prediabetes or normoglycemia. In addition, the risk of diabetes associated with combination pills that included drugs with opposing effects—for example an ACEI with a diuretic—was also not assessed.

One trial evaluated the efficacy of addressing multiple behaviors to improve control of blood pressure in those with resistant hypertension. Blumenthal et al randomized 140 adults with resistant hypertension (mean age 63, 31% with diabetes, 21% with CKD) to a center-based 4-month program of dietary counseling, behavioral weight management, and exercise or a single counseling session.¹⁷ The primary end point was clinic systolic BP. The center-based program included education from a nutritionist about sodium and calorie reduction, plus weekly 45-minute group counseling sessions from a psychologist about behavior change. Participants also exercised at cardiac rehabilitation 30 to 45 minutes 3 times a week. Participants in the control arm met for an hour with a health educator to discuss BP management, and received a workbook with an individualized diet and exercise program that was similar to the intervention arm. Office BP decreased –12.5 mm Hg (95% CI –14.9 to –10.2) in the lifestyle program and –7.1 mm Hg (95% CI, –10.4 to –3.7) in the usual care arm ($P=0.005$).

POLYPILL AND FIXED DOSE COMBINATION TREATMENTS

A polypill strategy to prevent ASCVD has theoretical advantage over traditional approaches. With a polypill, fixed low dose combinations of multiple drugs classes, generally including agents to lower cholesterol and blood pressure, are provided to populations with average to increased risk.²⁵ Initially proposed from a modeling exercise and subsequently tested for risk factor reduction, studies are finally emerging to evaluate effects of polypills on ASCVD outcomes.^{26,27}

TIPS-3 Trial

The International Polycap Study 3 (TIPS-3) included 5713 individuals without cardiovascular disease (CVD) but at increased risk of CVD events based on an elevated INTERHEART score.¹⁸ A daily polypill comprised of 40 mg of simvastatin, 100 mg of atenolol, 25 mg of hydrochlorothiazide, and 10 mg of ramipril was evaluated. Participants were randomized in a 2×2 factorial trial to the polypill or matching placebo, and to aspirin

75 mg daily or matching placebo, allowing for separate analysis of the risks and benefits of the aspirin component.

The trial, comprising participants only from Asia, included a 3- to 4-week half dose polypill and aspirin run in period, and 24% of the initial cohort dropped out. After a mean follow up of 4.6 years, participants receiving the polypill had a lower risk of composite CVD events (death from cardiovascular causes, myocardial infarction, stroke, resuscitated cardiac arrest, heart failure, or revascularization) (4.4% versus 5.5%, HR, 0.79 [95% CI 0.63–1.00]), that was of marginal statistical significance. The greatest effect was observed in the combined polypill/aspirin group compared with double placebo (4.1% versus 5.8%, HR, 0.69 [95% CI 0.50–0.97]).

Serious adverse events were infrequent, but dizziness, hypotension and cough were more common among those assigned to the polypill; there was no excess of muscle symptoms. Interestingly, there was no increase in major or minor bleeding for those assigned to aspirin compared with placebo.

The TIPS-3 study adds to the growing evidence base advancing the polypill approach for CVD prevention from concept to a potentially viable strategy. However, the results have raised some concerns. First, overall adherence was suboptimal, achieving only \approx 68% at 48 months, and there was a high proportion of polypill discontinuation (\approx 40%). Second, the large proportion of dropouts during the run-in phase raises questions regarding the acceptability, tolerability, and adherence for an unselected population. Finally, whether aspirin should be included as part of the polypill remains uncertain, and it is still unclear why no excess in bleeding was observed in the aspirin treatment arm.

A subsequent individual participant level meta-analysis of 3 large primary prevention trial cohorts ($n=18\,162$), including TIPS-3, confirmed that the polypill interventions resulted in a lower risk of CVD events relative to the comparator group (3.0% versus 4.9%, HR, 0.62 [95% CI 0.53–0.73], $P<0.0001$), with a 5-year number needed to treat of 52.²⁸ The effect estimates were greatest for the fixed dosed combination containing aspirin, (HR, 0.53 [95% CI 0.41–0.67]) compared with the combination without aspirin, (HR, 0.68 [95% CI 0.57–0.81]), although aspirin as a separate component was only evaluable in the TIPS-3 trial.

Small, shorter-term studies that were previously published have demonstrated the feasibility and efficacy of an initial hypertension treatment strategy involving a single combination pill that contained quarter doses of 4 different blood pressure-lowering medications.²⁹ The theoretical advantage of such an approach is that using such low doses achieves a substantial proportion of blood pressure efficacy while minimizing adverse effects of each agent.

The QUARTET (Quadruple Ultra-Low-Dose Treatment for Hypertension) trial sought to assess the effects of a quad pill versus initial monotherapy on short- and longer-term treatment of hypertension.¹⁹ These 591 individuals were randomly assigned to a daily quad pill consisting of irbesartan 37.5 mg, amlodipine 1.25 mg, indapamide 0.625 mg, and bisoprolol 2.5 mg or an identical capsule containing 150 mg of irbesartan. Additional antihypertensive treatments could be added as needed, starting with amlodipine. At 12 weeks, SBP was 6.9 mm Hg lower ($P<0.001$) in the quad pill arm and hypertension control rates ($<140/90$) were significantly greater (76% versus 58%, $P<0.001$). Further, in the 417 individuals completing the 12-month follow-up, SBP was 7.7 mm Hg lower in the quad pill arm and hypertension control rates remained higher (81% versus 62%, $P<0.001$). Serious adverse events were infrequent and not statistically different in the quad pill versus control arms ($n=7$ versus 3).

The QUARTET study confirms the short-term findings and extends to 1 year the superiority of the quad pill over single agent therapy. Despite a greater proportion of additional blood pressure lowering agents added in the irbesartan arm (42.7% versus 24.3%), the quad pill arm still had persistently lower blood pressure goal achievement. Limitations include a predominantly White or Asian sample with a low prevalence of ASCVD or T2DM and a high rate of drug discontinuation in the intervention arm. However, given that hypertension affects \approx 40% of the worldwide adult population with persistently poor treatment rates using standard approaches, innovations such as the quad pill concept should be advanced.³⁰

OMEGA-3 FATTY ACIDS

Recent randomized trials have not supported routine fish oil supplementation to improve cardiovascular health, but the REDUCE-IT trial reported a few years ago that intake of high dose purified EPA without DHA significantly lowered ASCVD risk.³¹ Over the past year, 2 additional studies provided insight into the relationship between omega-3 fatty acids and ASCVD risk. While these reports included patients with established ASCVD, they were included in this review given that adults commonly use over-the-counter fish oil for cardiovascular prevention.³²

The OMEMI (Omega-3 Fatty acids in Elderly with Myocardial Infarction) trial was a multi-center, randomized trial of 1014 elderly men and women who had suffered an MI in the past 2 to 8 weeks.²⁰ Participants were randomized to omega 3 fatty acids (1.8 g daily–930 mg EPA/660 mg DHA) versus a placebo (corn oil). The primary outcome was recurrent non-fatal MI, unscheduled revascularization, heart failure hospitalization, stroke, and all-cause death. Over 2 years of

follow-up there were 210 total primary events with no reduction in those randomized to omega 3 fatty acid supplementation versus placebo (HR 1.08 [95% CI, 0.82–1.41]; *P*-value 0.60). As seen in other studies in this area, there was a trend toward an increase in the secondary outcome of new atrial fibrillation (*P*-value 0.06) with omega 3 supplementation. The results of this study provide further support to the lack of benefit of routine supplementation of omega 3 fatty acids for the primary or secondary prevention of ASCVD.

The Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH) trial reported no cardiovascular benefit to supplementation of 4 g/d of EPA/DHA in a high-risk cohort.³³ These results were in direct contrast to REDUCE-IT, which reported a 25% reduction in major ASCVD outcomes with supplementation of high dose purified EPA compared with a mineral oil placebo in a similar high-risk cohort.³¹

A secondary analysis from STRENGTH sought to provide insight into possible mechanisms behind the benefit seen in REDUCE-IT compared with the null effect in STRENGTH.²¹ The study analyzed incident ASCVD events according to tertiles of achieved plasma levels of EPA and DHA in the intervention group. The authors found no evidence of harm or benefit in individuals in the top tertile of achieved EPA as well as DHA plasma levels. These findings suggest that achieving high levels of plasma EPA is not associated with a reduction in ASCVD events, at least not in the presence of concomitant DHA supplementation. Reconciling the significant cardiovascular benefit seen in REDUCE-IT with the null results seen in the multiple trials of combinations of EPA/DHA remains unresolved.

DIET

Fruit and Vegetable Intake and Mortality

Multiple prior studies support the intake of fruits and vegetables for improved cardiovascular and overall health while suboptimal intake of fruits and vegetables is a significant contributor to morbidity and premature mortality in the US.³⁴ Recent data from the Nurses' Health Study and the Health Professionals Follow-up Study lend further support to this concept. Wang et al studied over 110 000 participants from these 2 cohorts and also conducted a meta-analysis, combining these 2 cohorts with 24 additional cohort studies evaluating the association between fruit and vegetable intake and mortality.³⁵ The authors found a non-linear inverse relationship between fruit and vegetable intake and total mortality, with a maximal benefit at 5 servings/day of fruits and vegetables, and with no additional benefit seen with higher intake. A similar relationship was seen

for cause-specific mortality including deaths from cancer, CVD, and respiratory causes. Analysis of the 2 cohorts as well as the meta-analysis demonstrated a ≈13% reduction in mortality with 5 servings of fruits and vegetables/day compared with 2 or fewer servings per day. While higher intake of most subgroups of fruits and vegetables was associated with lower mortality, intake of fruit juice and potatoes were not associated with lower mortality.

Vegetarians, Fish, Poultry, and Meat Eaters and Incident CVD

While there is general agreement that a *mostly* plant-based diet is optimal for CVD health, the degree to which consumption of animal-based proteins like fish, poultry, and red-meat should be encouraged, limited, or significantly restricted remains unclear. A recent publication from the UK Biobank sought to analyze different dietary approaches (vegetarians, fish eaters, fish and poultry eaters, and meat eaters) with incident CVD.³⁶ The study prospectively analyzed more than 422 000 (55% women) participants followed for 8.5 years. Compared with meat-eaters, fish eaters had a lower risk of incident CVD (HR, 0.93 [95% CI 0.88–0.97]) with significantly lower risk of ischemic heart disease, myocardial infarction, stroke, and heart failure. The HR for incident CVD among vegetarians and people who ate both fish and poultry was similar to that of pescatarians, but the CI included 1 for people who ate both fish and poultry. The lower risk of stroke and MI among vegetarians was also of borderline significance. People who ate fish plus poultry did not have a lower risk of MI or heart failure compared with meat eaters. While the HR for incident stroke was similar to fish eaters, the CI also included 1. There was no difference in CVD mortality among the groups. These 2 nutritional studies demonstrate support for the dietary recommendations provided by the 2019 ACC/AHA Guidelines for the Primary Prevention of ASCVD which recommend a diet with a high intake of vegetables, fruits, legumes, nuts, whole grains, and fish to improve control of ASCVD risk factors.³⁴

Walnuts and Healthy Aging

Intake of nuts and seeds is considered an important part of a heart healthy diet, with nut consumption associating with a significant reduction in ASCVD and CVD mortality.³⁴ The Walnuts in Healthy Aging (WAHA) trial studied whether regular walnut consumption improved lipid profiles among 636 participants 63 to 79 years old who were healthy and living independently.²² This was a secondary analysis of a previously published trial whose primary outcome was related to cognition.³⁷ The sample was 67% women and 32% were on a statin. The intervention group was provided with a goal of 30 to 60 g/d

Table 2. Summary of Key Observational Studies and Meta-Analyses Published in 2021 That Address Primary Prevention of ASCVD or Treatment of an ASCVD Risk Factor

Study	Type of study	Study population	Intervention/study setting	Primary outcome	Secondary outcomes	Adverse outcomes
Obesity Syn NL et al ²	Meta-analysis	174,772 adults from 16 highly matched cohort studies and one clinical trial	Compared all-cause mortality of adults with obesity who underwent metabolic–bariatric surgery compared with matched controls who received usual care	<ul style="list-style-type: none"> Metabolic–bariatric surgery associated with a reduction in hazard rate of death of 49.2% (95% CI 46.3–51.9, $P < 0.0001$) Median life expectancy 6.1 y (95% CI 5.2–6.9) longer than usual care 	<ul style="list-style-type: none"> Gain in median life expectancy among adults with T2DM was 9.3 y vs 5.1 y in adults without diabetes NNT to prevent one additional death over 10 y were 8.4 (95% CI 7.8–9.1) for adults with T2DM and 29.8 (21.2–56.8) for those without diabetes 	NA
Cardiometabolic conditions						
PESA (Progression of Early Subclinical Atherosclerosis) Study ⁶	Observational	3973 adults without diabetes, ages 40–54 y	Two-dimensional ultrasound and non-contrast cardiac CT used to detect subclinical atherosclerosis (SA) in carotid and femoral/iliac arteries, infrarenal aorta and coronary arteries	HbA1c showed an association with multiterritorial extent of SA OR 1.05 for HbA1c 4.9–5.0%, OR 1.27 for 5.1–5.2%, OR 1.27 for 5.3–5.4%, OR 1.36 for 5.5–5.6%, OR 1.8 for 5.7–5.8%, OR 1.87 for 5.9–6.0%, OR 2.47 for 6.1–6.4%, respectively; reference HbA1c 4.8%; $P < 0.001$		
Hypertension						
Blood Pressure Lowering Treatment Trialists Collaboration ²³	Meta-analysis	51 primary and secondary ASCVD prevention trials	Included RCTs of pharmacological BP-lowering vs placebo or other classes of BP-lowering medications, or between more vs less intensive treatment, with at least 1000 persons-years of follow-up compared effects of blood-pressure-lowering treatment on ASCVD risk stratified by age and blood pressure at baseline	HR for MACE per 5mm Hg reduction in SBP for each age group: –0.82 (95% CI 0.76–0.88) in adults <55 y, –0.91 (0.88–0.95) adults 55–64 y, –0.91 (0.88–0.95) adults 65–74 y, –0.91 (0.87–0.96) in those aged 75–84 y, and –0.99 (0.87–1.12) in those aged ≥85 y (adjusted P interaction=0.050)	NA	NA

(Continued)

Table 2. (Continued)

Study	Type of study	Study population	Intervention/study setting	Primary outcome	Secondary outcomes	Adverse outcomes
Blood Pressure Lowering Treatment Trialists Collaboration ²⁴	Meta-analysis	22 primary and secondary ASCVD prevention trials	Included RCTs in which specific class or classes of antihypertensive drugs vs placebo or other classes of blood pressure lowering medications that had at least 1000 persons-years of follow-up; studied association of blood pressure reduction with risk of incident T2DM; examined association of specific drug classes with risk of incident T2DM	SBP reduction by 5 mm Hg reduced risk of T2DM across all trials by 11% (hazard ratio 0.89 [95% CI 0.84–0.95]); ACEI (RR 0.84 [95% 0.76–0.93]) and ARBs (RR 0.84 [0.76–0.92]) reduced risk of new-onset T2DM; β blockers (RR 1.48 [1.27–1.72]) and thiazide diuretics (RR 1.20 [1.07–1.35]) increased this risk; calcium channel blockers had not effect (RR 1.02 [0.92–1.13])	NA	NA
Polypill and fixed dose combination treatments						
Polypill meta-analysis ²⁸	Meta-analysis	3 large RCT clinical outcomes trials of fixed-dose combination vs placebo in primary prevention populations	TIPS-3, HOPE-3, Polyrin, n=18 162 participants; mean follow-up 5 y	Composite of cardiovascular death, MI, stroke, or arterial revascularization 3.0% polypill vs 4.9% placebo (HR 0.62 [0.53–0.73]). Greater effects with ASA (HR 0.53 [0.41–0.67]) than without ASA (HR 0.68 [0.57–0.81])	Cardiovasculardeath (HR 0.65=[0.52–0.81]); MI (HR 0.52 [0.38–0.70]); stroke (HR 0.59 [0.45–0.78]); revascularization (HR 0.54 [0.36–0.80])	Dizziness 11.7% polypill vs 9.2% placebo, P<0.0001; GI bleeding 0.4% polypill with aspirin vs 0.2% combined placebo, P=0.15
Diet						
Nurses' Health Study and the Health Professionals Follow-up Study, plus additional cohorts ³⁵	Observational and meta-analysis	66 719 women from the Nurses' Health Study (1984–2014) and 42 016 men from Health Professionals Follow-up Study (1986–2014) who were free from CVD, cancer, and diabetes at baseline repeated analyses in meta-analysis of 24 additional cohort studies	Examined association of fruit and vegetable intake and mortality	Compared with the reference level (2 servings/d), 5 servings of fruit and vegetables/day was associated with HR (95% CI) 0.87 (0.85–0.90) for total mortality, 0.88 (0.83–0.94) for CVD mortality, 0.90 (0.86–0.95) for cancer mortality, and 0.65 (0.59–0.72) for respiratory disease mortality	Dose-response meta-analysis with 1 892 885 participants yielded similar results (summary risk ratio of mortality for 5 servings/d=0.87 [95% CI, 0.85–0.88]; Pnonlinear <0.001)	NA

(Continued)

Table 2. (Continued)

Study	Type of study	Study population	Intervention/study setting	Primary outcome	Secondary outcomes	Adverse outcomes
UK Biobank ³⁶	Observational	422791 participants with dietary data available	Compared incidence and mortality risk for CVD, ischaemic heart disease, MI, stroke, and HF among people with different types of diets—including vegetarians, fish eaters, fish and poultry eaters, and meat-eaters	After a median follow-up of 8.5 y, fish eaters, compared with meat-eaters, had lower risks of incident CVD (HR: 0.93 [95% CI: 0.88–0.97], IHD (HR: 0.79 [95% CI: 0.70–0.88]), MI (HR: 0.70 [95% CI: 0.56–0.88]), stroke (HR: 0.79 [95% CI: 0.63–0.98]) and HF (HR: 0.78 [95% CI: 0.63–0.97]) Risk of adverse outcomes was not different in fish and poultry eaters compared with meat-eaters		
PURE (Prospective Urban Rural Epidemiology) cohort ³⁸	Observational	119575 individuals ages 35–70 y living on 5 continents, from high, medium, and low-income countries ages	Used country-specific food-frequency questionnaires to determine dietary intake and estimate glycemic index; examined the association of glycemic index with incident MACE (cardiovascular death, nonfatal MI, stroke, and HF) or death from any cause	A diet with a high glycemic index was associated with increased risk of MACE or death, both among participants with preexisting CVD (HR, 1.51; 95% CI, 1.25–1.82) and among those without CVD (HR, 1.21; 95% CI, 1.11–1.34)		NA
Framingham Offspring Study ³⁹	Observational	3003 adults free from CVD with valid dietary data at baseline	Data on diet, measured by food frequency questionnaire, anthropometric measures, and sociodemographic and lifestyle factors were collected quadrennially from 1991 to 2008 Examined association of consumption of ultra-processed food and cardiovascular outcomes	On average, participants consumed 7.5 servings per day of ultra-processed foods at baseline Each additional daily serving of ultra-processed foods was associated with a 7% (95% CI: 1.03–1.12), 9% (95% CI: 1.04–1.15), 5% (95% CI: 1.02–1.08), and 9% (95% CI: 1.02–1.16) increase in risk of hard CVD, hard CHD, overall CVD, and CVD mortality, respectively		NA

ASCVD indicates atherosclerotic cardiovascular disease; CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; IHD, ischemic heart disease; MACE, major adverse cardiovascular events; NNT, number needed to treat; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; and T2DM, type 2 diabetes.

(≈15% of energy intake). Over 2 years, participants randomized to walnut consumption had a mean 8.5 mg/dL (95% CI, 11.2–5.4) decrease in total cholesterol with a mean 4.3 mg/dL (6.6–1.6) decrease in LDL-C and no change in HDL-C or triglycerides. There was effect modification by sex for the reduction in LDL-C (7.9% for men versus 2.6% for women, *P*-value for interaction 0.007), which warrants further study. The findings of the WAHA study support the prior data encouraging the consumption of nuts as part of a mostly plant-based diet to improve or maintain cardiovascular health.

Consumption of Foods With High Glycemic Index or Ultraprocessed Foods

In a study from the PURE (Prospective Urban Rural Epidemiology) (*n*=119575) cohort of individuals from high, medium, and low-income countries, Jenkins et al examined the association of glycemic index with incident CVD and all-cause mortality.³⁸ A diet with a high glycemic index was associated with incident CVD over 9.5 years follow-up, among those with prior CVD (HR, 1.51 [95% CI 1.25–1.82]) and without prior CVD (HR, 1.21 [95% CI 1.11–1.34]). This relationship also held true for all-cause and cardiovascular mortality. These data provide a robust confirmation that diets especially rich in refined carbohydrates or similarly rich glycemic content may contribute to the global burden of cardiovascular disease.

Analyzing data from the FOS (Framingham Offspring Study) Juul et al examined the association of ultraprocessed food intake and incident CVD.³⁹ Studying the health effects of ultraprocessed foods is particularly relevant, given that they comprise >50% of the average American diet, and their consumption among youth ages 2 to 19 years has increased from 61.4% of total caloric intake to 67.0% in the past 20 years.⁴⁰ Ultraprocessed foods have been linked to the development of obesity and cardiovascular risk factors, and have numerous potentially harmful properties—they are often high in salt and refined carbohydrates, contain additives that increase oxidative stress, and often displace cardioprotective foods. Examples of ultraprocessed foods include commercially baked goods, hot dogs and sugar-sweetened beverages. FOS participants consumed an average of 7.5 servings of ultraprocessed foods a day. Each additional serving was associated with 7% higher risk of hard CHD and 9% higher risk of hard CVD (see Table 2 for definitions). The results highlight the need for comprehensive population-wide strategies to decrease intake of ultraprocessed foods.

CONCLUSIONS

Prevention of ASCVD has made major strides over the past several decades, resulting in markedly lower rates

of death from MI and stroke. However, these gains have plateaued. Countervailing trends in obesity and accompanying cardiometabolic risks such as diabetes and hypertension have occurred. Thus, the advent of new therapies and new applications of these therapies advanced in 2021 to combat cardiometabolic risk are much welcomed. High blood pressure remains a leading cause of death worldwide and recent studies summarized in this review provide new dietary and medication strategies for hypertension treatment and cement the value of more stringent blood pressure goals. The polypill approach has now progressed beyond a theoretical exercise to a potential viable prevention strategy to lower ASCVD events. As the backbone of prevention, nutrition practices and lifestyle behaviors continue to be investigated, predominantly reports of observational data, but a few informative randomized trials have occurred. All told, 2021 provides much momentum for the field of cardiovascular disease prevention and optimism for what could be accomplished in the coming years.

ARTICLE INFORMATION

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Disclosures

None.

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