



Highlights of Cardiovascular Disease Prevention Studies Presented at the 2022 American College of Cardiology Scientific Sessions

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Accepted: 25 April 2022 / Published online: 28 May 2022

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Abstract

Purpose of Review Focused review highlighting select studies presented at the 2022 American College of Cardiology (ACC) Scientific Sessions.

Recent Findings Included studies assessed the impact of a low-sodium diet on heart failure outcomes (SODIUM-HF); outcomes of pregnant patients with chronic hypertension treated with antihypertensive therapies (CHAP); cardiovascular outcomes in patients with type 2 diabetes and renal impairment treated with sotagliflozin (SCORED); a safety and efficacy study investigating SLN360, a short interfering RNA targeting lipoprotein(a) (APOLLO); a supermarket and web-based intervention targeting nutrition for cardiovascular risk reduction (SuperWIN); a superiority trial comparing myocardial injury following very mild perioperative hypothermia versus aggressive warming after non-cardiac surgery (PROTECT); and 3-year efficacy outcomes of renal denervation on blood pressure reduction from the SPYRAL HTN-ON MED pilot study.

Summary Research presented at the 2022 ACC Scientific Sessions underscores the new potential and meaningful impact of cardiovascular disease prevention and management interventions.

Keywords Heart failure · Hypertension · Cardiovascular prevention · Sotagliflozin · Lipoprotein(a) · DASH diet

Abbreviations

ACC American College of Cardiology
AHA American Heart Association
ASCVD Atherosclerotic CV Disease
BMI Body mass index

BP Blood pressure
CAD Coronary artery disease
cHTN Chronic HTN
CI Confidence interval
CKD Chronic kidney disease
COVID-19 Coronavirus disease 2019
CV Cardiovascular
CVD Cardiovascular disease

This article is part of the Topical Collection on *Reviews and Scientific Meetings and New Research Implications*

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DASH	Dietary approaches to stop hypertension
DBP	Diastolic blood pressure
EF	Ejection fraction
GFR	Glomerular filtration rate
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HR	Hazard ratio
HTN	Hypertension
KCCQ	Kansas City Cardiomyopathy Questionnaire
LDL-C	Low-density lipoprotein cholesterol
NYHA	New York Heart Association
OR	Odds ratio
PCSK9	Proprotein convertase subtilisin/kexin type 9
RRR	Relative risk reduction
SBP	Systolic blood pressure
SGLT-1	Sodium-glucose cotransporter 1
SGLT-2	Sodium-glucose cotransporter 2
T2DM	Type II diabetes mellitus

Introduction

The 2022 American College of Cardiology (ACC) Scientific Sessions featured several notable trials regarding CV disease (CVD) prevention and management. Included studies assessed the impact of a low-sodium diet on heart failure (HF) outcomes (SODIUM-HF); antihypertensive management outcomes of pregnant patients with mild chronic hypertension (cHTN) (CHAP) [1•]; sotagliflozin to treat patients with type 2 diabetes mellitus (T2DM) and renal impairment (SCORED) [2••]; safety and efficacy of SLN360, a short interfering RNA targeting lipoprotein(a) [LP(a)] concentrations (APOLLO); a supermarket and web-based nutrition intervention for CV risk reduction (SuperWIN); a superiority trial comparing myocardial injury following very mild perioperative hypothermia versus aggressive warming after non-cardiac surgery (PROTECT); and 3-year efficacy outcomes of renal denervation on blood pressure (BP) reduction from the SPYRAL HTN-ON MED pilot study. As with prior publications, the significance and clinical implications of select presentations are discussed [3–5]. Finally, a table summarizing the studies discussed is included (Table 1).

SODIUM-HF—the Study of Dietary Intervention Under 100 mmol in HF

Study Overview

Restriction of dietary sodium is a strategy to reduce volume overload in patients with HF. Previous studies have shown mixed results with low-sodium diet. The SODIUM-HF trial re-examined the validity of this long-standing recommendation to limit sodium intake in patients with HF [1•].

This open-label randomized trial involved 26 sites in 6 countries. Participants were ≥ 18 years with chronic HF (NYHA II–III) receiving optimally tolerated guideline-directed medical therapy. Exclusion criteria included average dietary intake of < 1500 mg/day of sodium, serum sodium concentration of < 130 mmol/L, estimated glomerular filtration rate (GFR) < 20 mL/min per 1.73 m² or end-stage renal failure requiring hemodialysis, and hospital admission for a CV cause in the last month. The primary outcome was the composite of all-cause mortality, CV-related hospitalizations, and CV-related emergency department visits. The trial sample size was planned at 992 subjects to achieve 80% power and detect a 30% reduction in primary outcome. Due to the COVID-19 pandemic, the study was stopped early.

Participants were randomized 1:1 to either a low-sodium diet (< 100 mmol or < 1500 mg of sodium intake daily with meal plans provided based on energy requirements and extent of sodium restriction) or usual care (general advice to limit dietary sodium). Investigators, participants, and treating clinicians were aware of the assigned treatment; however, outcome assessors and a Clinical Events Committee that adjudicated outcomes were blinded. Participants received sample menus to promote adherence to a low-sodium diet, and a list of recommended foods was provided for interchange of menu items. Food was individualized to participants' local region/country.

Of 806 participants, baseline characteristics were similar in both groups. The median age was 67 years and 33% were women. Thirty-three percent had a HF hospitalization in the past year, and the median ejection fraction (EF) was 36%. The median sodium intake in the low-sodium group was 1658 mg/day at 12 months, a 28% decrease from baseline. The median sodium intake in the usual care group was 2073 mg/day at 12 months, a 4% decrease from baseline. At 12 months, the median difference in sodium between groups was 415 mg/day. Weight, systolic blood pressure (SBP), caloric, fluid, and potassium intake were not different between groups.

At 12 months, there was no difference in the composite primary outcome between groups, with 60 of 397 patients (15%) in the low-sodium diet group and 70 of 409 patients (17%) in the usual care group (HR 0.89, 95% CI 0.63–1.26). There were no significant differences between groups in the individual components of the primary outcome. However, patients on a low-sodium diet experienced improved quality of life (QOL) and functional status. The Kansas City Cardiomyopathy Questionnaire (KCCQ) scores showed a mean between-group difference of 3.38 points (95% CI 0.79–5.96, $p=0.011$) in the overall summary score, 3.29 points (95% CI 0.74–5.83, $p=0.011$) in the clinical summary score, and 3.77 points (95% CI 0.67–6.87, $p=0.017$) in the physical limitation score. The low-sodium diet group had a greater likelihood of improving by one NYHA functional

Table 1 Summary of major randomized clinical trials on cardiovascular disease prevention at the 2022 American College of Cardiology Scientific Sessions

Clinical trial	Study design and population	Treatment arm	Control arm	Primary outcome	Results
SODIUM-HF	Multinational, open-label, randomized trial with participants recruited from 26 sites in 6 countries of patients aged 18 years or older with chronic HF (NYHA functional class 2–3) receiving optimally tolerated guideline-directed medical therapy	Low-sodium diet, <1500 mg daily (<65 mmol daily)	Usual care	- A composite of all-cause mortality, cardiovascular-related hospitalizations, and cardiovascular-related emergency department visits within 12 months after randomization	- Primary outcome occurred at similar rates in 15% of the low-sodium group vs. 17% of the usual care group (HR [HR] 0.89, $p = 0.53$) - No significant difference between the low-sodium diet versus the usual care groups in all-cause mortality (6% vs 4%, HR 1.38, 95% CI 0.73–2.60), cardiovascular-related hospitalizations (10% vs 12%, HR 0.82, 95% CI 0.54–1.24), and cardiovascular-related emergency department visits (4% vs 4%, HR 1.21, 95% CI 0.60–2.41) at 1 year - KCCQ overall summary score at 12 months was 3.38 points higher in the low-sodium group vs. usual care group ($p = 0.011$) - 6.6 min greater adjusted mean 6-min walk test at 12 months in the low-sodium group vs. usual care group ($p = 0.41$)
CHAP	Open-labeled, multicenter, randomized control trial in pregnant women with mild chronic hypertension (SBP 140–159/DBP 90–104 mmHg)	Antihypertensive treatment to the goal of <140/90 mmHg	No/ discontinuation antihypertensive unless BP > 160/105 mmHg	Composite of pre-eclampsia with severe features, preterm birth before 35 weeks GA, abruptio- tion, fetal/neonatal demise	- 30.2% of patients in the active arm and 37% of patients in the stand- ard arm (RR=0.82[CI 0.74–0.92 $p < 0.001$], NNT = 14.7) - Pre-eclampsia with severe features 22.3% vs. 29.1% in the active vs. standard arm (RR of 0.8 [0.7–0.9]) - Preterm birth < 35 weeks 12.2% vs 16.7% (RR of 0.7 [0.6–0.9]) - Abruptio and fetal/neonatal death were relatively rare and without significant difference
SCORED Trial	Multinational, double-blinded, ran- domized trial from 750 sites in 44 countries in patients aged 18 years or older with type 2 diabetes mellitus (glycated hemoglobin level $\geq 7\%$) and chronic kidney disease (estimated glomerular filtration rate 25 to 60 mL/ min per 1.73 m ² of body surface area) and additional cardiovascular risk factors (at least one major risk factor if 18 years or older or at least 2 minor risk factors if 55 years or older) were included	Sotagliflozin (200 mg once daily with increase to 400 mg once daily if unac- ceptable side effects did not occur)	Placebo	- Total number of deaths from CV causes, hospitalizations for HF, and urgent visits for HF	- Primary outcome for sotagliflozin vs. placebo: 11.3% vs. 14.4% (HR 0.74, 95% CI 0.63–0.88, $p = 0.0004$) - First occurrence of major adverse CV events for sotagliflozin vs. placebo was 8.4% vs. 8.9% (HR 0.84, 95% CI 0.72–0.99, $p = 0.035$) - First occurrence of CV death or HF hospitalization: 8.3% vs. 9.5% (HR 0.77, 95% CI 0.66–0.91, $p = 0.001$) - No significant difference in all-cause mortality or composite renal end- points between the two groups

Table 1 (continued)

Clinical trial	Study design and population	Treatment arm	Control arm	Primary outcome	Results
APOLLO	Single-center phase I randomized controlled trial in primary prevention cohort with elevated LP(a) of at least 150 nmol/L and no known cardiovascular disease	A single subcutaneous dose of study drug SLN360 (30 mg, 100 mg, ≤300 mg, or ≤600 mg)	Placebo	Safety and magnitude of effect on LP(a) concentration	-Dose-dependent reduction in LP(a) with near-complete obliteration of LP(a) at the top 2 doses of the study drug, efficacy maintained at 150 days -LDL cholesterol with 21 and 26% reduction in the two highest doses of the study drug -ApoB was also reduced, and these reductions persisted for about 150 days -No effects on triglycerides or HDL cholesterol
SUPERWin	Multi-site randomized control trial of supermarket and web-based interventions using a novel partnership between a healthcare system and commercial food retailer (Kroger)	Strategy 1: Conventional medical, nutritional, medical therapy + in-aisle data-guided in-store teaching Strategy 2: Conventional medical, nutritional, medical therapy + in-aisle data-guided in-store teaching + training and adoption of online shopping and other technologies	Conventional medical nutrition therapy	DASH diet adherence (DASH score 0–90) Change in score at follow-up and change in score compared between arms	-3 months: DASH score increase in strategies 1 and 2 vs overall increase +4.7 points (0.9–8.5, $p=0.02$). Strategy 2 vs strategy 1 +3.8 [0.8–6.9, $p=0.011$] -6 months: DASH scores continued to increase; however, changes in DASH score between interventional and control arms were not significant and not significant between the two intervention arms
The Protect trial: Effect of aggressive warming on major complications of non-cardiac surgery	Multicenter, parallel-group, superiority trial in patients ≥45 years, with at least one cardiovascular risk factor, scheduled for inpatient non-cardiac surgery expected to last 2–6 h with general anesthesia were included	Patients assigned to aggressive warming had a mean final intraoperative core temperature of 37.1 °C	Patients assigned to the routine thermal management group have a mean intraoperative core temperature of 35.6 °C	A composite of myocardial injury (troponin elevation, apparently of ischemic origin), non-fatal cardiac arrest, and all-cause mortality within 30 days of surgery,	-At least one of the primary outcome components occurred in 246 (9.9%) of 2497 patients in the aggressively warmed group and 239 (9.6%) of 2490 patients in the routine thermal management group -The common effect relative risk of aggressive versus routine thermal management was an estimated 1.04 (95% CI 0.87–1.24, $p=0.69$). Myocardial infarctions occurred in 51 (2.1%) of 2469 patients assigned to aggressive warming and 45 (1.8%) of 2468 patients assigned to routine management ($p=0.54$)

Table 1 (continued)

Clinical trial	Study design and population	Treatment arm	Control arm	Primary outcome	Results
SPYRAL HTN-On MED Trial	Multicenter, single-blind, sham-controlled, randomized trial of 80 patients with uncontrolled hypertension and office systolic blood pressure between 150 and 180 mm Hg and diastolic blood pressure of 90 mm Hg or higher, a 24-h ambulatory systolic blood pressure between 140 and less than 170 mm Hg, while taking one to three antihypertensive drugs with stable doses for at least 6 weeks	Renal angiography and radiofrequency renal denervation	Renal angiography and sham control procedure	The difference in mean 24-h systolic blood pressure at 6 months between the two groups Long-term efficacy was assessed using ambulatory and office blood pressure measurements for 36 months. Drug surveillance was used to assess medication use. Safety events were assessed for up to 36 months	-Mean ambulatory systolic and diastolic blood pressure were significantly lower than in the sham control group, at 24 and 36 months, despite a similar treatment intensity of antihypertensive drugs -At 24 months, mean treatment differences between groups were -11.2 mm Hg (95% CI -21.7 to -0.6; $p=0.039$) for morning SBP and -12.9 mm Hg (-21.1 to -4.7; $p=0.0026$) for night-time SBP -Treatment differences between the renal denervation group and control group at 36 months were -5.9 mm Hg (95% CI -10.1 to -1.8; $p=0.0055$) for mean ambulatory DBP; -11.0 mm Hg (-19.8 to -2.1; $p=0.016$) for morning SBP, and -11.8 mm Hg (-19.0 to -4.7; $p=0.0017$) for night-time SBP -There were no short-term or long-term safety issues associated with renal denervation

class compared to the usual care group (OR 0.59, 95% CI 0.40–0.86, $p=0.0061$). There was no difference in the 6-min walk distance between the groups.

Clinical Implication

Prior studies of dietary sodium restriction and its impact on HF patients are small with mixed results. SODIUM-HF is a large trial utilizing a menu-based system with tools to personalize meals based on cultural and personal preferences. At 12 months, there was no difference in composite outcome or its components. A modest improvement was noted in QOL as measured by the KCCQ and one NYHA functional class improvement in the low-sodium diet group. Future studies investigating greater reduction in sodium intake or higher baseline sodium levels are needed. Still, the findings suggest that a low-sodium diet may still be part of the strategy to improve QOL.

CHAP Trial—Antihypertensive Therapy for Mild Chronic HTN Improves Pregnancy Outcomes: A Pragmatic Multicenter RCT

Study Overview

The CHAP trial was an open-label randomized control trial involving 70 US centers [1•]. Patients with mild cHTN (SBP 140–159/90–104 mmHg), new or pre-existing singleton pregnancy, and <23-week gestation were included. Exclusion criteria included severe cHTN (SBP > 160/105 mmHg), secondary cHTN, high-risk medical co-morbidities, fetal death/anomalies, and medication intolerance. Randomization was based on clinic BPs with untreated BP ranging from 140 to 159/90 to 104 mmHg, and those treated previously on monotherapy with BPs < 159/104 mmHg. The active arm of the trial was treated with a goal target of BP < 140/90 mmHg with either labetalol or nifedipine ER or non-study supplied methyldopa or amlodipine. The standard arm withheld or discontinued medication and only initiated therapy if BP was > 160/105 mmHg and titrated to keep BP < 160/105 mmHg. The primary outcome was a composite of preeclampsia with severe features (up to 2 weeks post-partum), preterm birth before 35 weeks, abruption, and fetal or neonatal death. Safety outcomes evaluated low birth weight with small for gestational age (SGA) birth under the 10th and 5th percentile. Secondary outcomes included composite maternal CV outcomes, preeclampsia, preterm death, and serious neonatal comorbidities.

A total of 2408 patients were enrolled with 1208 in the active arm and 1200 in the standard care arm. Baseline characteristics between arms were well matched. Most patients in the active and standard arm were known to have cHTN on

a medication, Black (47.5%), obese (73% and 76%), and government-assisted insurance/Medicaid (55.7% and 54.7%). The primary outcome was experienced in 30.2% of patients in the active arm and 37% of patients in the standard arm (RR = 0.82 [CI 0.74–0.92 $p < 0.001$], NNT = 14.7). Components of the primary outcome reaching significance included preeclampsia with severe features in 22.3% vs 29.1% in the active vs standard arm (RR of 0.8 [0.7–0.9]) and preterm birth < 35 weeks in 12.2% vs 16.7% (RR of 0.7 [0.6–0.9]). Abruption and fetal/neonatal death were rare in both arms without significant difference. AEs did not differ between the arms, with SGA < 10th percentile noted in 11.2% vs 10.4% (RR 1.07 [0.85–1.36 $p = 0.56$]) in active vs standard arm and SGA < 5th percentile noted in 5.1% vs 5.5% (RR 0.92 [0.65–1.30 $p = 0.63$]). Maternal outcome composite morbidity did not differ between groups. However, secondary outcomes of pre-eclampsia were significantly reduced in the active vs standard arm (24.4% vs 31.1% RR 0.79 [0.69–0.89]), in addition to severe HTN (36.1% vs 44.3% RR 0.82 [0.74–0.90]) and hypertensive organ dysfunction (11.3% vs 15.1% RR 0.75 [0.61–0.92]). Composite neonatal morbidity outcomes did not differ between groups (2.0 vs 2.6% RR 0.77 [0.45–1.3]); however, significant reduction was seen in incidence of preterm birth under 37 weeks (27.45% vs 31.4% RR 0.87 [0.77–0.99]) and low birth weight (19.2% vs 23.1% RR 0.83 [0.71–0.97]).

Clinical Implication

cHTN affects greater than 2% of pregnancies in the USA and leads to maternal and fetal complications [6]. While treatment of hypertensive non-pregnant patients is standard, evidence to treat mild maternal cHTN is lacking [7]. This multicenter trial showed that treating cHTN for BP goal < 140/90 mm Hg reduced adverse pregnancy outcomes without impairing fetal growth or pretending maternal or perinatal harm. Long-term studies are needed to clarify treatment effects on maternal and childhood outcomes.

SCORED Trial—Effect of Sotagliflozin on CV and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at CV Risk

Study Overview

Several studies have examined SGLT2 inhibitors and their cardiorenal protective effects in managing patients with and without HF in regards to HF hospitalizations and CV mortality. Sotagliflozin is an SGLT1 and SGLT2 inhibitor, affecting glucose absorption in the gastrointestinal tract

and kidneys which significantly reduced major adverse CV events (MACE) among HF patients in the SOLOIST-WHF trial [1•]. The SCORED trial evaluated sotagliflozin's effects on MACE in patients with T2DM and CKD, a population at high risk for HF and ischemic events [2••].

This double-blinded randomized trial involved 750 sites in 44 countries. Patients ≥ 18 years with T2DM (glycated hemoglobin $\geq 7\%$) and chronic kidney disease (CKD) (estimated GFR 25 to 60 mL/min per 1.73 m² of body surface area) and additional CV risk factors (at least one major risk factor if ≥ 18 years or at least 2 minor risk factors if ≥ 55 years) were included. Those who planned to start an SGLT2 inhibitor during the trial were excluded. Goal enrollment was achieved at 10,500 patients. The trial was stopped early due to a loss of funding during the COVID-19 pandemic, leading to revisions of the primary and secondary outcomes.

Participants were randomized 1:1 to sotagliflozin (200 mg daily with an increase to 400 mg daily if tolerated) or to placebo, with further randomization stratified based on HF (EF $\leq 40\%$ within the past year or hospitalization for HF during the previous 2 years) and geographic region. The median duration of follow-up was 16 months.

Of 10,584 participants, baseline characteristics were similar in both groups. The median age was 69 years, 44.9% were female, and 82.7% were Caucasian. Of all patients, 19.9% had an EF $\leq 40\%$ within the past year or hospitalization for HF within the previous 2 years (with a median EF of 60%). The median glycated hemoglobin was 8.3% and the median eGFR was 44.5 mL/min per 1.73 m². Among those given sotagliflozin, 74.5% had the dose increased from 200 to 400 mg.

Time-to-event analysis of the revised primary outcome, which was the composite of total deaths from CV causes, hospitalizations for HF, and urgent visits for HF, showed that patients in the sotagliflozin group had significantly reduced event rates compared to patients in the placebo group with 5.6 events per 100 patient-years versus 7.5 events per 100 patient-years respectively (HR 0.74, 95% CI 0.63–0.88, $p = 0.0004$). Time-to-event analysis of MACE, defined as total CV death, non-fatal MI, or non-fatal stroke also showed significantly reduced events in the sotagliflozin group compared to the placebo group with 4.8 per 100 patient-years versus 6.3 per 100 patient-years respectively (HR 0.77, 95% CI 0.65–0.91, $p = 0.002$), with a difference detected by 94 days (HR 0.69, $p = 0.045$).

Time-to-event analysis of first and recurrent MACE in patients with a history of CVD showed significantly reduced rates in the sotagliflozin group compared to the placebo group, 13.4% vs 15.8% (HR 0.79, 95% CI 0.64–0.96, $p = 0.020$). Among patients without a history of CVD, the sotagliflozin group also had significantly reduced event rates compared to the placebo group, 6.7% vs 7.6% (HR 0.74, 95% CI 0.56–0.99, $p = 0.046$).

Prespecified AEs were analyzed, and rates of diarrhea, genital mycotic infections, and diabetic ketoacidosis were significantly higher in the sotagliflozin group compared to the placebo group. However, the proportion of serious AEs was similar between groups.

Clinical Implication

In the SCORED trial, sotagliflozin, an SGLT1 and SGLT2 inhibitor, produced a 26% reduction in the composite total number of deaths from CV causes, hospitalizations for HF, and urgent visits for HF in patients with T2DM and CKD. Furthermore, the drug significantly reduced rates of MACE, defined as total CV death, non-fatal MI, or non-fatal stroke. In patients with and without a history of CVD, sotagliflozin led to significant reductions in first and recurrent MACE, with similar relative risk reductions in both subgroups. While patients on sotagliflozin encountered more AEs, the severity of the effects was similar between groups.

The findings of this study suggest there may be unique benefits of SGLT1 inhibition and sotagliflozin may have a role in the prevention of HF and ischemic disease in high-risk patients.

APOLLO Trial—Magnitude and Duration of Effects of a Short-Interfering RNA Targeting Lipoprotein(a): A Placebo-Controlled Double-Blind Dose-Ranging Trial

Study Overview

Elevated LP(a), found in 20% of people worldwide is a frequently underestimated, genetic, and independent risk factor for premature atherosclerotic CVD (ASCVD) and calcific aortic stenosis [8, 9]. There are currently no FDA-approved pharmacologic treatments approved to target elevated LP(a) concentrations. RNA-based gene silencing pharmacological agents are under development to address this unmet need [10].

Conducted across five medical centers in the USA, UK, and Australia, the APOLLO trial was a double-blinded placebo-controlled single ascending dose study examining the safety and efficacy of gene silencing via a short interfering RNA (siRNA), SLN360, in people with elevated Lp(a) levels [11]. This double-stranded RNA therapy was administered subcutaneously attached to a sugar, GalNaC (to aid transport into the liver), where the RNA is cleaved and one of the strands degrades the messenger RNA and prevents translation of the apo(a) protein essential to LP(a) formation. Participants were ≥ 18 without known CVD and an Lp(a) level ≥ 150 nmol/L. Exclusion criteria included BMI < 18

or > 45 , cirrhosis, or the use of pharmacologic agents impacting Lp(a). The primary outcome was Lp(a) reduction at 150 days. Secondary outcomes were changes in low-density lipoprotein cholesterol (LDL-C), apoB, oxidized LDL, inflammatory markers, plasminogen, and pharmacokinetics. Participants were divided into 4 cohorts. There were 8 participants per cohort of whom 2 received a placebo and 6 received one of four doses (30, 100, 300, or 600 mg) of SLN360 via a single subcutaneous injection. Close monitoring was continued for 24 h after dosing and intermittently for 150 days.

The study included 32 subjects. The mean age was 50 ± 13.5 years (53% female). At baseline, median Lp(a) level was 224 nmol/L, the mean apoB level was 85 mg/dL, and the mean LDL-C level was 108 mg/dL. AEs were mild including headaches and injection site reactions; self-limited elevated neutrophil counts and elevated C-reactive protein levels were noted in a few patients. One serious AE occurred and was considered unrelated to the study. The maximal median reduction in Lp(a) was 20, 89, 185, 268, and 227 nmol/L for those treated with placebo and the four SLN260 doses, respectively. Nearly complete obliteration of Lp(a) was observed in a dose-dependent manner with Lp(a) reduction notably 98% and 96% at the top 2 doses of SNL360 sustained at 150 days. LDL-C was also reduced with a 21 and 26% reduction in the two highest doses and apoB was also reduced. These reductions persisted for 150 days.

Clinical Implication

This study demonstrates the potential to potently and durably lower LP(a) levels. As a phase 1 trial, this study focused on safety and successfully demonstrated no serious related AEs. Potential long-term ramifications of the observed transient inflammatory reaction (elevated hs-CRP) after SLN360 administration are unknown. Current US multisociety guidelines incorporate LP(a) into practice as a risk-enhancing factor, whereas European guidelines advise checking LP(a) at least once in each adult's lifetime [12•, 13•]. The “Lp(a) hypothesis” is currently being tested in the phase 3 Lp(a) HORIZON CV outcomes evaluating the use of an antisense oligonucleotide to lower Lp(a) levels in secondary prevention [9].

SuperWIN—A Multisite, Randomized, Controlled Trial of a Supermarket and Web-Based Intervention Targeting Nutrition for CV Risk Reduction.

Study Overview

The SuperWIN trial was a multisite randomized control trial evaluating the efficacy of supermarket and web-based intervention on DASH diet adherence and CV risk

reduction with a novel partnership between a healthcare system and commercial food retailer (Kroger) [14]. The study design included patients within a university-based primary care network, ages 21–75 years of age, having ≥ 1 CV risk factor (obesity, hypercholesterolemia, HTN), who regularly shop at a Kroger supermarket, not an online grocery shopper, and willing to follow a DASH diet. Participants in the control arm received a 30-min standard-of-care medical nutrition therapy session with a dietician in the store including assessment of nutritional biometrics, DASH diet and calorie weight-loss education, and daily tracking/journaling of meals. The two intervention arms were strategy 1, which included the medical nutrition therapy (control) and the addition of purchasing data guidance with in-aisle nutritional sessions, and strategy 2, which included strategy 1 with the addition of a step-wise introduction of training and adoption of additional technologies (online shopping, home delivery, nutritional apps). Interventions were performed in the supermarket with follow-ups at 3 months and 6 months.

Primary endpoints included DASH diet adherence via a DASH score (0 to 90) with a higher score indicating increased adherence to the DASH diet. The DASH score was evaluated for change from baseline at 3 and 6 months. The DASH score change was used to assess the efficacy of control vs strategies 1 and 2 (data-guided in-store teaching) and strategy 2 vs strategy 1 (addition of online shopping and nutrition apps). Secondary endpoints evaluated BP and BMI at 3 months.

A total of 247 patients were enrolled, 46 in the control group, 100 in the strategy 1 group, and 101 in the strategy 2 group. Baseline characteristics were similar for the three groups with the majority being female, in the fifth decade of life, and with similar initial elevated BP. Baseline DASH scores for control, strategy 1 and strategy 2 were 45.2, 44.4, and 43.2 respectively. At 3-month follow-up, DASH score changes were significantly increased in strategies 1 and 2 (8.6+ and 12.4+) vs control (5.8+) with an overall increase over the control group by 4.7 points (0.9–8.5 $p=0.02$). Online enhancements to in-store teaching also significantly increased DASH scores by 3.8 points (0.8–6.9 $p=0.01$). At 6-month follow-up, DASH scores continued to increase (4.4, 6.6, 8.4 for control and strategies 1 and 2); however, changes in DASH score between interventional and control arms were not significant (3.1 + [− 1.0 to 7.3, $p=0.14$]) and not significant between intervention arms (1.8 + [− 1.9 to 5.5, $p=0.34$]). Secondary endpoints at 3 months did show improvement in BMI and BP, but not significant between the control and the two intervention groups (between-group difference of -0.4 kg/m^2 in BMI [− 0.8 to 0.0, $p=0.08$] and SBP change of -3.4 mmHg [− 3.2 to 5, $p=0.18$]). The COVID-19 pandemic resulted in participants' withdrawal

and decreased educational visit attendance (near 100 to 80% pre- and post-pandemic). COVID impact analysis was notable for a 3-month follow-up intervention of a greater DASH score increase between intervention arms vs the control group (+ 8.3 [3.4 to 13.3 $p<0.001$]).

Clinical Implication

Among participants, a dietary intervention was beneficial and intervention within the supermarket increased the purchase of healthy foods and improved DASH diet adherence. At 6 months, the advantages between the groups were no longer significant. The SuperWIN trial demonstrates the efficacy of dietary interventions harnessing the power of the supermarket's physical environment, in-store dietary counseling, and online shopping, and other technologies to support health. This represents a forward step in addressing guideline nutrition recommendations and implementation mismatch [15]. Further studies in larger and diverse communities are needed to assess generalizability.

Very Mild Perioperative Hypothermia Versus Aggressive Warming and Myocardial Injury After Non-Cardiac Surgery: The PROTECT Trial

Study Overview

PROTECT was a multicenter, parallel-group, superiority trial involving 12 sites in China and the Cleveland Clinic in the USA [16]. Patients were randomly assigned (1:1) to receive either aggressive warming to a target core temperature of 37 °C (aggressively warmed group) or routine thermal management to a target of 35.5 °C (routine thermal management group) during non-cardiac surgery. Inclusion criteria were patients ≥ 45 years, with at least one CV risk factor, scheduled for inpatient non-cardiac surgery lasting 2–6 h with general anesthesia, and having at least half of the anterior skin surface available for warming. Patients requiring dialysis or body-mass index (BMI) exceeding 30 kg/m^2 were excluded. The primary outcome was a composite of myocardial injury (troponin elevation, apparently of ischemic origin), non-fatal cardiac arrest, and all-cause mortality within 30 days of surgery. Secondary outcomes were deep or organ-space surgical site infection within 30 days of surgery, intraoperative transfusion requirement, duration of hospital stay, and hospital readmission within 30 days of surgery.

In total, 5056 participants were enrolled, of whom 5013 were included in the intention-to-treat population (2507 in the aggressively warmed group and 2506 in the routine thermal management group). Patients assigned to aggressive warming had a mean final intraoperative core temperature

of 37.1 °C (SD 0.3) whereas the routine thermal management group averaged 35.6 °C (SD 0.3). At least one primary outcome component (myocardial injury after non-cardiac surgery, cardiac arrest, or mortality) occurred in 246 (9.9%) of 2497 patients in the aggressively warmed group and in 239 (9.6%) of 2490 patients in the routine thermal management group (RR = 1.04 [95% CI 0.87–1.24, $p=0.69$]). Myocardial infarctions occurred in 51 (2.1%) of 2469 patients assigned to aggressive warming and 45 (1.8%) of 2468 patients assigned to routine management ($p=0.54$). Thirty-day incidence of deep or organ-space surgical site infection, red blood cell transfusions, the median length of stay, and 30-day readmissions did not differ significantly between the two groups. Thirty-nine AEs in patients assigned to aggressive warming (17 serious) and 54 in those assigned to routine thermal management (30 serious) occurred.

Clinical Implication

In PROTECT, the incidence of myocardial injury, surgical site infection, and the need for transfusion were similar in patients randomly allocated to intraoperative temperatures of 35.5 °C (routine care, very mild hypothermia) and 37.0 °C (aggressive warming, full normothermia). Keeping core temperature to at least 35.5 °C in surgical patients appears sufficient to prevent major temperature-related complications.

3-Year Efficacy Outcomes from the SPYRAL HTN-ON MED Pilot Study: Long Term Effect of Renal Denervation on Blood Pressure Reduction in Patients on AntiHTN Medication

Study Overview

The SPYRAL HTN-ON MED proof-of-concept trial was a single-blind, sham-controlled, randomized trial of 80 patients [17]. The 6-month outcome of the trial was previously reported with a significant reduction in BP after renal denervation vs control without major AEs [17]. In the final analysis of this population, the changes in BP, antihypertensive medication use, and safety up to 36 months were compared in renal denervation vs control group. The trial enrolled patients from 25 centers in the USA, Germany, Japan, the UK, Australia, Austria, and Greece. Patients with uncontrolled HTN and office SBP between 150 and 180 mm Hg and DBP of 90 mm Hg or higher, a 24-h ambulatory SBP between 140 and 170 mm Hg, while taking one to three antihypertensive medications with stable doses for at least 6 weeks, were included. Patients underwent renal angiography and were randomly assigned (1:1) to radiofrequency renal denervation or a control procedure. The

primary endpoint was the treatment difference in mean 24-h SBP at 6 months between groups. Long-term efficacy was assessed using ambulatory and office BP measurements for up to 36 months. Drug surveillance was used to assess medication use. Safety events were assessed for up to 36 months.

Among 467 enrolled patients, 80 fulfilled qualifying criteria and were randomly assigned to undergo renal denervation ($n=38$) or a sham control procedure ($n=42$). Mean ambulatory SBP and DBP were significantly reduced from baseline in the renal denervation group and were significantly lower than in the control group at 24 and 36 months, despite the similar intensity of antihypertensive medications. At 24 months, mean treatment differences between groups were -11.2 mm Hg (95% CI -21.7 to -0.6 ; $p=0.039$) for morning SBP and -12.9 mm Hg (-21.1 to -4.7 ; $p=0.0026$) for night-time SBP. At 36 months, the ambulatory SBP reduction was -18.7 mm Hg (SD 12.4) for the renal denervation group ($n=30$) and -8.6 mm Hg (14.6) for the control group ($n=32$; adjusted treatment difference -10.0 mm Hg, 95% CI -16.6 to -3.3 ; $p=0.0039$). Treatment differences between the renal denervation group and control group at 36 months were -5.9 mm Hg (95% CI -10.1 to -1.8 ; $p=0.0055$) for mean ambulatory DBP, -11.0 mm Hg (-19.8 to -2.1 ; $p=0.016$) for morning SBP, and -11.8 mm Hg (-19.0 to -4.7 ; $p=0.0017$) for night-time SBP. The medication burden at 36 months was 2.13 medications (SD 1.15) in the renal denervation group and 2.55 medications (2.19) in the control group ($p=0.26$). 24 (77%) of 31 patients in the renal denervation group and 25 (93%) of 27 patients in the control group adhered to medication at 36 months. Adherence meant not missing a single dose of antihypertensive medication. There were no short-term or long-term AEs associated with renal denervation.

Clinical Implication

Radiofrequency renal denervation compared with control produced a meaningful BP reduction up to 36 months of follow-up, independent of concomitant antihypertensive medications and without major AEs. Renal denervation could provide an adjunctive treatment modality besides lifestyle modifications and antihypertensive medications in managing patients with uncontrolled HTN.

Conclusion

The clinical trials discussed above demonstrate noteworthy advancements in CVD prevention and management. Novel applications of existing and innovative procedures, pharmacologic agents, and lifestyle modification hold promise to reduce the burden of CVD which remains the leading cause

of mortality worldwide. While these studies generate optimism for reducing morbidity and mortality in CVD, improving QOL, and diminishing healthcare costs, future studies are warranted to determine applicability of these findings.

Funding Dr. Virani is supported by a Department of Veterans Affairs Health Services Research & Development Service Investigator Initiated Grants (IIR 16–072, IIR 19–069), NIH, Tahir, and Jooma Family Foundation. *The opinions expressed reflect those of the authors and not necessarily those of the Department of Veterans Affairs or the US government.*

Role of the Funder/Sponsor The Department of Veterans Affairs or the US government had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Declarations

Conflict of Interest *Melody Hermel, Stacy Tsai, Luis Dlouhy, Anupama B K, Jamal S. Rana, Sourbha S. Dani:* None. *Salim S. Virani:* Honorarium, American College of Cardiology (Associate Editor for Innovations, acc.org), Section Editor for Current Atherosclerosis Reports.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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