IMPORTANT RECENT ABSTRACTS

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IN HEALTHY NON-OBESE MEN AND WOMEN, A 25% CALORIE RESTRICTION DIET REDUCED CARDIOMETABOLIC RISK FACTORS MORE THAN AN AD LIBITUM DIET AFTER 2 YEARS.

Kraus WE, Bhapkar M, Huffman KM, et al. *2 years of calorie restriction and cardiometabolic risk (CALERIE): exploratory outcomes of a multicentre, phase 2, randomised controlled trial.*Read full-text (not free)View on PubMedRead rater commentsRead user comments

Background: For several cardiometabolic risk factors, values considered within normal range are associated with an increased risk of cardiovascular morbidity and mortality. We aimed to investigate the short-term and long-term effects of calorie restriction with adequate nutrition on these risk factors in healthy, lean, or slightly overweight young and middle-aged individuals.

Methods: CALERIE was a phase 2, multicentre, randomised controlled trial in young and middle-aged (21-50 years), healthy non-obese (BMI 22·0-27·9 kg/m2) men and women done in three clinical centres in the USA. Participants were randomly assigned (2:1) to a 25% calorie restriction diet or an ad libitum control diet. Exploratory cardiometabolic risk factor responses to a prescribed 25% calorie restriction diet for 2 years were evaluated (systolic, diastolic, and mean blood pressure; plasma lipids; high-sensitivity C-reactive protein; metabolic syndrome score; and glucose homoeostasis measures of fasting insulin, glucose, insulin resistance, and 2-h glucose, area-under-the curve for glucose, and insulin from an oral glucose tolerance test) analysed in the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT00427193.

Findings: From May 8, 2007, to Feb 26, 2010, of 238 participants that were assessed, 218 were randomly assigned to and started a 25% calorie restriction diet (n=143, 66%) or an ad libitum control diet (n=75, 34%). Individuals in the calorie restriction group achieved a mean reduction in calorie intake of 11·9% (SE 0·7; from 2467 kcal to 2170 kcal) versus 0·8% (1·0) in the control group, and a sustained mean weight reduction of 7·5 kg (SE 0·4) versus an increase of 0·1 kg (0·5) in the control group, of which 71% (mean change in fat mass 5·3 kg [SE 0·3] divided by mean change in weight 7·5 kg [0·4]) was fat mass loss. Calorie restriction caused a persistent and significant reduction from baseline to 2 years of all measured conventional cardiometabolic risk factors, including change scores for LDL-cholesterol ($p<0·0001$), total cholesterol to HDL-cholesterol ratio ($p<0·0001$), and systolic ($p<0·0011$) and diastolic ($p<0·0001$) blood pressure. In addition, calorie restriction resulted in a significant improvement at 2 years in C-reactive protein ($p=0·012$), insulin sensitivity index ($p<0·0001$), and metabolic syndrome score ($p<0·0001$) relative to control. A sensitivity analysis revealed the responses to be robust after controlling for relative weight loss changes.

Interpretation: 2 years of moderate calorie restriction significantly reduced multiple cardiometabolic risk factors in young, non-obese adults. These findings suggest the potential for a substantial advantage for cardiovascular health of practicing moderate calorie restriction in young and middle-aged healthy individuals, and they offer promise for pronounced long-term population health benefits.

SGLT2 INHIBITORS' INTERACTION WITH OTHER RENOACTIVE DRUGS IN TYPE 2 DIABETES PATIENTS: STILL A LOT TO LEARN.

vanBaar MJB[1], Scholtes RA[1], van Raalte DH[2].

The first cardiovascular (CV) safety trial conducted with a sodium-glucose cotransporter (SGLT)-2 inhibitor, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME), reported not only remarkable risk reductions in CV outcome, but also impressive improvements in renal outcome. Changes in renal hemodynamics could be involved in the benefit of SGLT2 inhibitors on renal outcomes. Considering that all patients of EMPA-REG OUTCOME had established atherosclerotic CV disease at baseline, many patients were also treated with several CV drugs at baseline, including RAS blockers, diuretics, calcium-channel blockers, and nonsteroidal anti-inflammatory drugs. These drugs also impact renal physiology and possibly renal outcome, which could cause relevant drug-drug interactions. This topic is addressed in this issue of Kidney International by Mayer and colleagues. In their manuscript, the impact

of empagliflozin on kidney function, renal outcome, and renal safety is presented with stratification for background therapy. Although the beneficial effects of empagliflozin and its safety profile are consistent among all groups, we wonder, do we really understand the renal effects of all these drugs in type 2 diabetes (T2D) patients as studied in the large outcome trials?

ANALYSIS FROM THE EMPA-REG OUTCOME® TRIAL INDICATES EMPAGLIFLOZIN MAY ASSIST IN PREVENTING THE PROGRESSION OF CHRONIC KIDNEY DISEASE IN PATIENTS WITH TYPE 2 DIABETES IRRESPECTIVE OF MEDICATIONS THAT ALTER INTRARENAL HEMODYNAMICS

Gert J. Mayer[1], Christoph Wanner[2], Matthew R. Weir[3], Silvio E. Inzucchi[4], Audrey Koitka, Weber[2,5,6], Stefan Hantel[5], Maximilian von Eynatten[5], Bernard Zinman[7], David Z.I. Cherney[8,"],

In patients with type 2 diabetes mellitus (T2DM) and cardiovascular (CV) disease, empagliflozin (EMPA) decreased progression of chronic kidney disease (CKD), likely via a reduction in intraglomerular pressure. Due to prevalent comorbidities, such as hypertension and albuminuria, patients often receive other agents that alter intrarenal hemodynamics, including angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARBs), calcium channel blockers (CCBs) and diuretics. Nonsteroidal anti-inflammatory drugs (NSAIDs) may also be used by some individuals. In this exploratory, non-prespecified analysis, we investigated whether the kidney benefits of EMPA are altered in individuals already using the medications in these categories. In the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME®) trial, 7020 patients were essentially equally randomized to EMPA 10 mg, 25 mg or placebo added to their standard care. Differences in risk of incident or worsening nephropathy for pooled EMPA vs placebo across subgroups by baseline background medications (to which patients were not randomized) were assessed using a Cox proportional hazards model. Risk reductions in incident or worsening nephropathy with EMPA were consistent across medication subgroups, with no heterogeneity of treatment effect. As a representative example, the risk for acute renal failure was overall slightly increased in patients using ACEi/ARBs in all groups (placebo, EMPA 10 mg or EMPA 25 mg) but incidence rates were numerically lower in those assigned to EMPA. Similar patterns were observed for other medications included in this analysis. Thus, EMPA may assist to prevent CKD progression in patients with T2DM with CV disease, irrespective of common background medications that alter intrarenal hemodynamics, and without increasing acute renal adverse events.

EFFECT OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURE ON CARDIOVASCULAR OUTCOMES

Alexander C. Flint, M.D., Ph.D., Carol Conell, Ph.D., XiushuiRen, M.D., Nader M. Banki, M.D., Sheila L. Chan, M.D., Vivek A. Rao, M.D., Ronald B. Melles, M.D., and Deepak L. Bhatt, M.D., M.P.H.

Background: The relationship between outpatient systolic and diastolic blood pressure and cardiovascular outcomes remains unclear and has been complicated by recently revised guidelines with two different thresholds (e"140/90 mm Hg and e"130/80 mm Hg) for treating hypertension.

Methods: Using data from 1.3 million adults in a general outpatient population, we performed a multivariable Cox survival analysis to determine the effect of the burden of systolic and diastolic hypertension on a composite outcome of myocardial infarction, ischemic stroke, or hemorrhagic stroke over a period of 8 years. The analysis controlled for demographic characteristics and coexisting conditions.

Results: The burdens of systolic and diastolic hypertension each independently predicted adverse outcomes. In survival models, a continuous burden of systolic hypertension (e"140 mm Hg; hazard ratio per unit increase in z score, 1.18; 95% confidence interval [CI], 1.17 to 1.18) and diastolic hypertension (e"90 mm Hg; hazard ratio per unit increase in z score, 1.06; 95% CI, 1.06 to 1.07) independently predicted the composite outcome. Similar results were observed with the lower threshold of hypertension (≥130/80 mm Hg) and with systolic and diastolic blood pressures used as predictors without hypertension thresholds. A J-curve relation between diastolic blood pressure and outcomes was seen that was explained at least in part by age and other covariates and by a higher effect of systolic hypertension among persons in the lowest quartile of diastolic blood pressure.

Conclusions: Although systolic blood-pressure elevation had a greater effect on outcomes, both systolic and diastolic hypertension independently influenced the risk of adverse cardiovascular events, regardless of the definition of hypertension (e"140/90 mm Hg or e"130/80 mm Hg).

AMBIENT PARTICULATE AIR POLLUTION AND DAILY MORTALITY IN 652 CITIES

C. Liu, R. Chen, F. Sera, A.M. Vicedo Cabrera, Y. Guo, S. Tong, M.S.Z.S. Coelho, P.H.N. Saldiva, E. Lavigne, P. Matus, N. Valdes Ortega, S. Osorio Garcia, M. Pascal, M. Stafoggia, M. Scortichini, M. Hashizume, Y. Honda, M. Hurtado Diaz, J. Cruz, B. Nunes, J.P. Teixeira, H. Kim, A. Tobias, C. Íñiguez, B. Forsberg, C. Åström, M.S. Ragettli, Y.-L.Guo, B.-Y. Chen, M.L. Bell, C.Y. Wright, N. Scovronick, R.M. Garland, A. Milojevic, J. Kyselý, A. Urban, H. Orru, E. Indermitte, J.J.K. Jaakkola, N.R.I. Ryti, K. Katsouyanni, A. Analitis, A. Zanobetti, J. Schwartz, J. Chen, T. Wu, A. Cohen, A. Gasparrini, and H. Kan

Background: The systematic evaluation of the results of time-series studies of air pollution is challenged by differences in model specification and publication bias.

Methods: We evaluated the associations of inhalable particulate matter (PM) with an aerodynamic diameter of 10 ¼m or less (PM10) and fine PM with an aerodynamic diameter of 2.5 ¼m or less (PM2.5) with daily all-cause, cardiovascular, and respiratory mortality across multiple countries or regions. Daily data on mortality and air pollution were collected from 652 cities in 24 countries or regions. We used overdispersed generalized additive models with random-effects meta-analysis to investigate the associations. Two-pollutant models were fitted to test the robustness of the associations. Concentration–response curves from each city were pooled to allow global estimates to be derived.

Results: On average, an increase of 10 ¼g per cubic meter in the 2-day moving average of PM10 concentration, which represents the average over the current and previous day, was associated with increases of 0.44% (95% confidence interval [CI], 0.39 to 0.50) in daily all-cause mortality, 0.36% (95% CI, 0.30 to 0.43) in daily cardiovascular mortality, and 0.47% (95% CI, 0.35 to 0.58) in daily respiratory mortality. The corresponding increases in daily mortality for the same change in PM2.5 concentration were 0.68% (95% CI, 0.59 to 0.77), 0.55% (95% CI, 0.45 to 0.66), and 0.74% (95% CI, 0.53 to 0.95). These associations remained significant after adjustment for gaseous pollutants. Associations were stronger in locations with lower annual mean PM concentrations and higher annual mean temperatures. The pooled concentration–response curves showed a consistent increase in daily mortality with increasing PM concentration, with steeper slopes at lower PM concentrations.

Conclusions: Our data show independent associations between short-term exposure to PM10 and PM2.5 and daily all-cause, cardiovascular, and respiratory mortality in more than 600 cities across the globe. These data reinforce the evidence of a link between mortality and PM concentration established in regional and local studies.

DRUG-INDUCED LIVER INJURY — TYPES AND PHENOTYPES

Jay H. Hoofnagle, M.D., and Einar S. Björnsson, M.D.

Drug-induced liver injury is an uncommon but challenging Clinical problem with respect to both diagnosis and management.1-3 Its incidence is estimated to be 14 to 19 cases per 100,000 persons, with jaundice accompanying 30% of cases.4,5 Drug-induced liver injury is responsible for 3 to 5% of hospital admissions for jaundice6 and is the most frequent cause of acute liver failure in most Western countries, accounting for more than half of cases.7,8Advances have been made in our understanding of viral, autoimmune, and genetic liver diseases, as well as approaches to their prevention and treatment, but progress on these fronts has been modest in the case of drug-induced liver injury.

The diagnosis of drug-induced liver injury is particularly challenging, since it is based largely on exclusion of other causes. The timing of the onset of injury after the implicated agent has been started (latency), resolution after the agent is stopped ("dechallenge"), recurrence on re-exposure (rechallenge), knowledge of the agent's potential for hepatotoxicity (likelihood), and clinical features (phenotype) are the major diagnostic elements.9-11 With few exceptions, there are no specific diagnostic markers for drug-induced liver injury, and special tests (liver biopsy, imaging, and testing for serologic markers) are helpful mostly in ruling out other causes of liver injury. The large number of agents that can cause liver injury highlights these challenges. LiverTox, the National Institutes of Health–sponsored website on hepatotoxicity, has descriptions of more than 1200 agents (prescription and over-the-counter medications, herbal products, nutritional supplements, metals, and toxins), along with their potential to cause liver injury.12

Among the 971 prescription drugs described, 447 (46%) have been implicated in causing liver injury in at least one published case report.11 This brief review cannot cover all aspects of drug-induced liver injury but focuses on general principles, newer concepts, and current challenges, with frequent references to the LiverTox website for further detail.