to receive twice weekly administration of either vehicle (0.02% ethanol), LXA₄ (5µg/kg), or two LXA₄ mimetics – B-LXA₄ (1.7µg/kg) or CT4-43 (1.7 µg/kg) via I.P. (n=24/gp). In the intervention arm, mice received drugs only from week 11 for a total of six weeks. At end-point, mice were culled and kidneys collected for gene expression, ELISA, immunohistochemistry and histology.

Results: Our preliminary results show that diabetic animals demonstrated increased circulating blood glucose, serum glycated haemoglobin, albuminuria, and decreased body weight. Activation of the NLRP3 inflammasome, and increased expression of IL1ß and IL18, were also observed in the kidneys of diabetic mice. Administration of LXA₄ and LXA₄ mimetics to mice in both the 10-week prevention model and 16-week intervention model trended towards a decrease in albuminuria, significantly attenuated glomerular and mesangial matrix expansion (~25%), and significantly reduced mRNA levels of NLRP3 (~50%) and inflammatory markers (IL1ß, TNFα, IL6, ~50%). LXA₄ mimetics also significantly attenuated protein levels of IL1ß and IL18 by ~40%, in both the prevention and the interventional arms of this study.

Conclusions: In this preliminary study, we demonstrated that not only do LXA₄ and LXA₄ mimetics protect the diabetic kidney by reducing inflammatory processes, but also that these novel pro-resolving and anti-inflammatory agents modulate NLRP3 inflammasome activation. These results support our hypothesis that LXs can be used as a novel approach for the treatment of DN. Notably, the protective actions of LX mimetics were effective against chronic inflammation leading to the progression of DN and thus able to reverse inflammatory processes as seen in the intervention study.

SAT-298
EFFECT OF SGLT2 INHIBITORS ON CARDIOVASCULAR, RENAL AND SAFETY OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND CHRONIC KIDNEY DISEASE
Toyama, T¹, NEUEN, B*², Jun, M³, Okumura, T¹, Neal, B¹, Jardine, M¹, Heerspink, H¹, Ninomiya, T¹, Wada, T², Perkovic, V¹
¹The George Institute for Global Health, Renal and Metabolic Division, Sydney, Australia, ²The George Institute for Global Health, Food Policy, Sydney, Australia, ³University of Groningen, Department of Clinical Pharmacy and Pharmacology, Groningen, Netherlands Antilles, ⁴Kyushu University, Department of Epidemiology and Public Health- Graduate School of Medical Sciences, Fukuoka, Japan, ⁵Kanazawa University, Department of Nephrology and Laboratory Medicine, Kanazawa, Japan

Introduction: The use of sodium glucose co-transporter 2 (SGLT2) inhibitors in individuals with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) has been limited, primarily because glycemic efficacy is dependent on glomerular filtration. We conducted a systematic review and meta-analysis to assess the effect of SGLT2 inhibitors on a range of biomarkers as well as cardiovascular, renal, and safety outcomes in individuals with T2DM and CKD, defined as an estimated glomerular filtration rate <60 mL/min/1.73m².

Methods: We searched MEDLINE, EMBASE and the Cochrane Library to August 8, 2018, as well as the websites of the United States, European, and Japanese regulatory authorities to July 27, 2018 for data from randomized controlled trials of SGLT2 inhibitors that included reporting of effects on biomarkers, cardiovascular, renal, or safety outcomes in individuals with T2DM and CKD. Random effects models and inverse variance weighting were used to calculate relative risks with 95% confidence intervals.

Results: Data were obtained from 27 studies with up to 6,590 individuals contributing. The risk of bias in included studies was generally low. Among individuals with T2DM and CKD, SGLT2 inhibitors reduced the risk of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke [RR 0.78, 95% CI 0.65-0.92] and hospitalisation for heart failure [RR 0.58, 95% CI 0.44-0.77]. SGLT2 inhibitors attenuated the annual decline in kidney function (annual mean slope difference of 1.35 µL/min/1.73m²/year, 95% CI 0.78-1.93) but there was no clear effect on the composite renal outcome of doubling of serum creatinine, end-stage kidney disease or renal death [RR 0.82, 95% CI 0.54-1.07]. There was no evidence of additional risks with SGLT2 inhibition in CKD beyond those already known for the class, although heterogeneity was observed across individual agents for some safety outcomes.

Conclusions: In individuals with T2DM and CKD, SGLT2 inhibitors reduced the risk of cardiovascular events and slowed the loss of kidney function, with no evidence of additional safety concerns. Restrictions on the use of SGLT2 inhibitors in this population may warrant review.

SAT-299
CD38 INHIBITION DECREASE RENAL OXIDATIVE STRESS IN DIABETIC KIDNEY DISEASE BY RESTORING OF SIRT3 ACTIVATION.
Ogura, Y¹*, Momoi, I², Koya, D¹
¹Kanazawa Medical University, Department of Diabetology and Endocrinology, Ishikawa, Japan
²University of Sydney, Sydney, Australia

Introduction: Diabetic kidney disease (DKD) is a major cause of end-stage renal disease worldwide. Aging is recognized as one of the risk factors for the development of end-stage renal failure due to chronic kidney disease including DKD. Therefore, investigation of aging-related mechanisms would be needed to discover a novel therapeutic target to treat DKD. Nicotinamide adenine dinucleotide (NAD) levels decrease during aging and are involved in age-related metabolic decline. Previous report demonstrated that expression and activity of the NADase CD38 increase with aging and that CD38 is required for the age-related NAD decline and mitochondrial dysfunction via a pathway mediated at least in part by regulation of sirt3 activity. We already discovered that the expression of CD38 was significantly increased in diabetic kidney and inhibition in Sirt3 activity contributes to mitochondrial oxidative stress by decreasing the activation of anti-oxidative enzymes in the kidney of diabetic model rats. So, we investigated whether the inhibition of CD38 suppress mitochondrial oxidative stress through restoring of Sirt3 activity in diabetic rats and high glucose-incubated human renal tubular epithelial cells (HK2 cells).

Methods: We used Male non-diabetic Zucker Lean (ZL) and type2 diabetes model rats, Zucker Diabetic Fatty rats (ZDFRs). CD38 inhibitor, apigenin or saline were prepared for oral gavage at 20mg/kg/day for 5 times by a week ,continued 4weeks and sacrificed at 28 weeks of age. In vitro study, HK2 cells were cultured in standard or high glucose condition and were treated for 48 hours with 10 µM apigenin or DMSO. Results: At 28 weeks of age, compared to ZL, ZDFRs exhibited elevated HbA1c and heavier kidney weight, increased urinary albumin, liver type fatty acid binding protein (L-FABP), and 8-hydroxy-2’-deoxyguanosine (8-OHdG), excretion, histological tubulo-interstitial fibrosis. In the immunostaining, increased CD38 positive cell in the kidney, particularly tubulo-interstitial area. Expression of mRNA and protein of CD38 were all significantly elevated in renal cortex. Administration of apigenin inhibited mRNA and protein expression of CD38, decreased albumin/L-FABP/8-OHdG excretion and ameliorated tubulo-interstitial fibrosis. Apigenin suppressed overexpression of CD38 in diabetic kidney and may ameliorated tubular cell damage. In addition, ZDFRs showed abnormal mitochondrial morphology, such as swelling and loss of cristae in primal tubular cell. In renal mitochondria, the NAD+/NADH ratio was reduced, and acetylation levels of mitochondrial antioxidant enzymes such as isocitrate dehydrogenase 2 (IDH2) and superoxide dismutase (SOD2), regulated by sirt3 were increased in ZDFRs. While apigenin restored abnormal mitochondrial morphology, increased NAD+/NADH ratio and reduced the acetylation of IDH2 and SOD2. Similarly, high glucose medium incubation in HK2 cell elevated CD38 levels associated with the reduction in NAD+/NADH ratio and increasing acetylation levels of SOD2 and IDH2. Administration of apigenin increased NAD+/NADH ratio, decreased SOD2 and IDH2 acetylation.

Conclusions: Administration of the CD38 inhibitor, apigenin restored the NAD+/NADH ratio, decreased the levels of IDH2 and SOD2 acetylation and renal oxidative stress. Therefore, inhibition of CD38 may be a therapeutic target for the suppression of DKD.

SAT-300
EFFECTS OF DAPAGLIFLOZIN AND DAPAGLIFLOZIN PLUS SAXAGLIPTIN ON HBA1C AND ALBUMINURIA IN PATIENTS WITH TYPE 2 DIABETES AND CHRONIC KIDNEY DISEASE: PHASE II/III DELIGHT STUDY
Pollock, C*, Wheeler, DC*, Rossing, P*, Sjostrom, D⁴, Stefansson, B⁴, Reyner, D³, Langkilde, AM⁴, Heerspink, HJ²
¹Royal North Shore Hospital- University of Sydney, Department of Medicine, C, ²St Leonards, Australia, ³University College London, Department of