MO399 **REMODEL: A MECHANISTIC TRIAL EVALUATING THE EFFECTS OF SEMAGLUTIDE ON THE KIDNEYS IN PEOPLE WITH TYPE 2 DIABETES AND CHRONIC KIDNEY DISEASE**

Petter Bjornstad[1], David Cherney[2], Jack Lawson[3], Camilla Møntegaard[3], Menno Pruijm[4], Katherine Tuttle[5], Blaz Vrhnjak[3] and Matthias Kretzler[6]

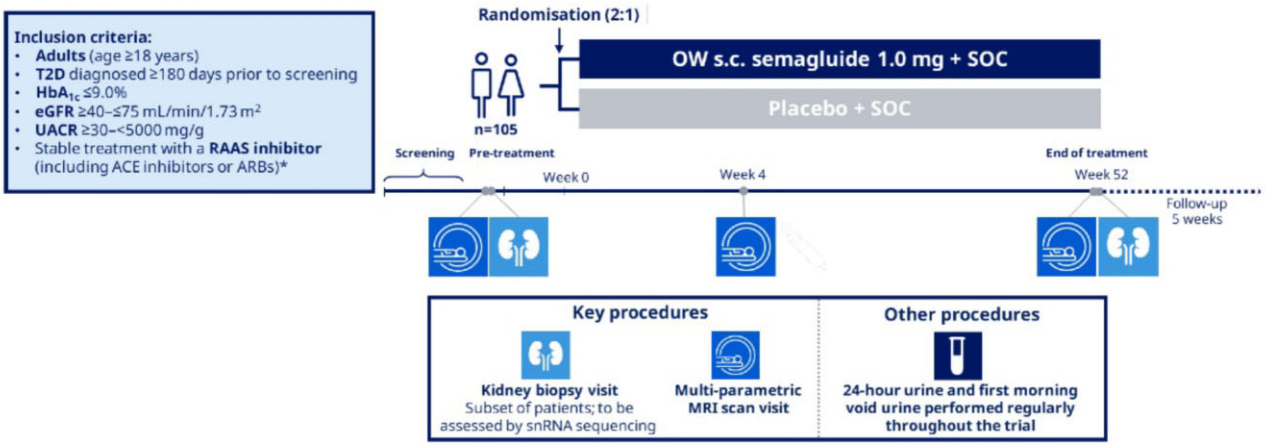
*[1]University of Colorado, Aurora, USA, [2]University Health Network, University of Toronto, Toronto, Canada, [3]Novo Nordisk A/S, Søborg, Denmark, [4]University Hospital of Lausanne and University of Lausanne, Lausanne, Switzerland, [5]University of Washington/Providence Health Care, Spokane, USA and [6]University of Michigan, Ann Arbor, USA*

**BACKGROUND AND AIMS:** Approximately 40% of people with type 2 diabetes (T2D) develop chronic kidney disease (CKD) and, despite current treatment, T2D is the most common cause of progression to kidney failure. This situation underscores the need for additional pharmacotherapeutic options. Analyses of cardiovascular outcomes trials suggest that glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as semaglutide, lower albuminuria and attenuate estimated glomerular filtration rate (eGFR) decline in people with T2D. Previous analyses suggest that GLP-1RAs reduce hypoxia and inflammation and, thereby, have a mode of action on the kidneys that is distinct from other treatments, such as sodium-glucose cotransporter-2 (SGCT-2) inhibitors and renin–angiotensin–aldosterone system (RAAS) blockers. Furthermore, the primary benefit of semaglutide appears to be in people with an eGFR < 60 mL/min/1.73 $m^2$, a group in which there is a significant residual risk of progression and a consequent unmet need for effective treatment. To gain further insights on the kidney-protective mechanism of action of semaglutide, the REMODEL trial is integrating investigative functional kidney magnetic resonance imaging (MRI) and kidney biopsies; recent developments in these techniques permit elucidation of the mechanisms underlying kidney protection with current therapies. Mechanistic findings of the REMODEL trial will complement those of the ongoing FLOW clinical trial, which is designed to evaluate clinical outcomes in people with T2D and CKD treated with once-weekly (OW) subcutaneous semaglutide.

**METHOD:** REMODEL (NCT04865770) is a 52-week, multicentre, international clinical trial (Figure 1). Primary endpoints are MRI-based and include change from baseline to week 52 in kidney oxygenation (measured with BOLD MRI R2*), global kidney perfusion (phase-contrast MRI) and kidney inflammation (T1 Mapping MRI). Secondary endpoints evaluated from kidney biopsies in a nested cohort ($n \sim 45$) include change from baseline to week 52 in intrarenal mRNA expression, assessed by single-nucleus transcriptomics and glomerular basement membrane width, assessed by morphometry. Other secondary endpoints include the apparent diffusion coefficient (estimating renal fibrosis; evaluated with diffusion-weighted MRI), natriuresis, albumin excretion rate and creatinine clearance. MRI outcomes will also be evaluated at week 4 to identify potential early effects of semaglutide in the kidney. Examples of MRI and kidney biopsy single-cell gene expression profile data from participants with CKD are shown in Figure 2 (data not from REMODEL). Safety will be assessed throughout the trial.

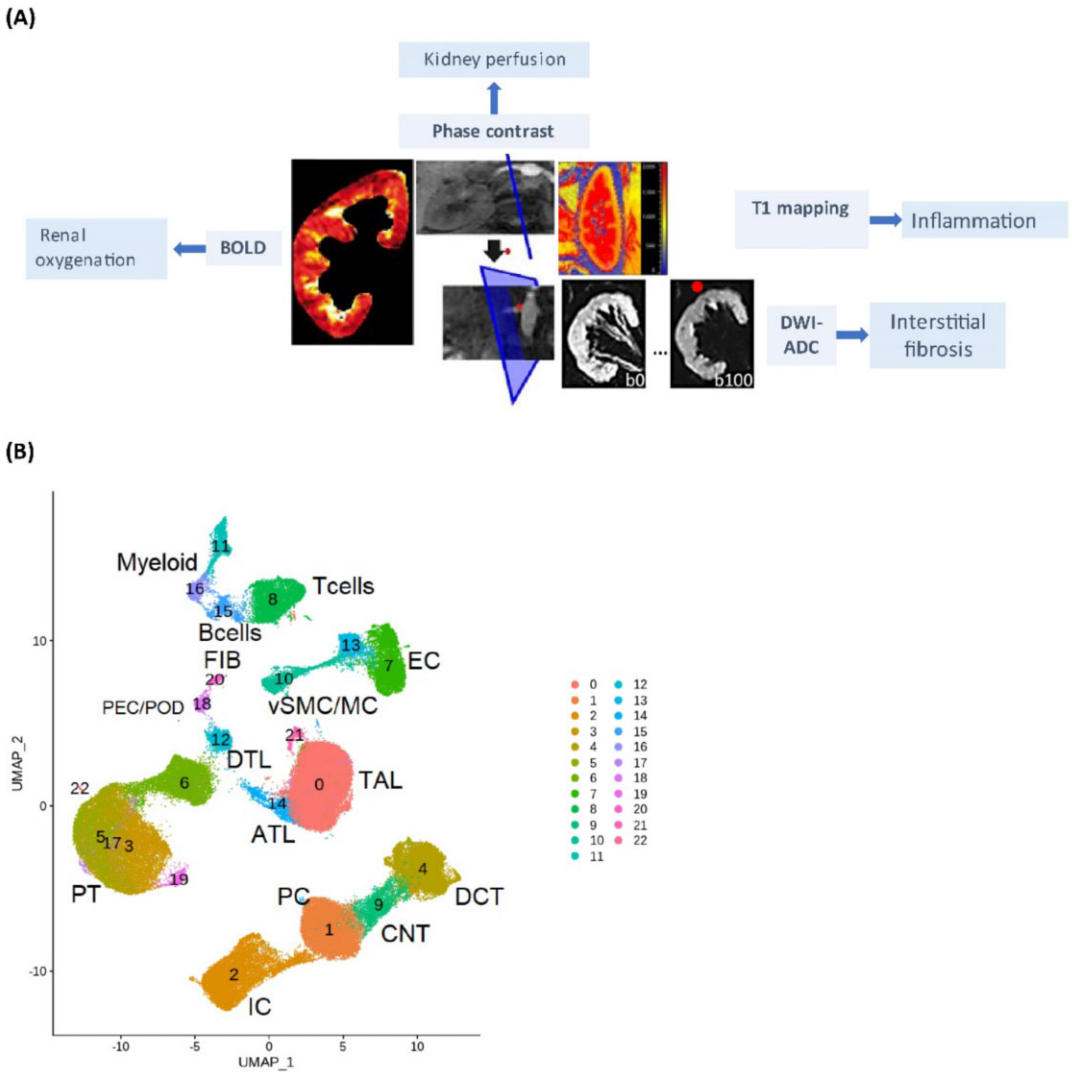
**RESULTS:** REMODEL was initiated in April 2021 and is being conducted in Canada, France, Italy, Poland, South Africa, Spain and USA.

**CONCLUSION:** REMODEL will investigate the effect of the GLP-1RA semaglutide on inflammatory and hypoxia-related pathways in the kidney. The combination of MRI and tissue-level interrogation with biopsies will complement standard laboratory findings, enabling the identification of cells and pathways involved in kidney disease and protection. The trial will provide valuable mechanistic insights on the use of OW semaglutide in people with T2D and CKD and may stimulate the development of a precision medicine approach to the management of such individuals. In addition, REMODEL will complement the findings of the FLOW trial.




**Maximum labelled or tolerated dose. In each trial arm, use of SGLT-2 inhibitors is capped at 50% for both the overall population and the biopsy subpopulation. At least 50% of the trial population will have a UACR ≥100 mg/g. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; eGFR, estimated glomerular filtration rate; $HbA_{1c}$, glycated haemoglobin; OW, once-weekly; RAAS, renin–angiotensin–aldosterone system; s.c., subcutaneous; snRNA, single-nucleus ribonucleic acid; SOC, standard of care; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio.*

**FIGURE 1:** REMODEL trial design.




ATL, ascending thin loop of Henle; CNT, connecting thin tubule; DCT, distal convoluted tubule; DWI-ADC, diffusion-weighted imaging apparent diffusion coefficient; DTL, distal limb of the loop of Henle; EC, endothelial cells; FIB, fibroblast; IC, intercalated; MC, mesangial; POD, podocyte; PC, principal cells; PT, proximal tubule; TA:, thick ascending loop of Henle; vSMC, vascular smooth muscle cells.

**FIGURE 2:** Examples of (A) the renal MRI techniques being performed in the REMODEL study and B single-cell gene expression profile data in CKD.

MO400 **TREATMENT OF RENAL ARTERY STENOSIS: NEPHROLOGY, THE BEST SURGERY**

Álvaro Pérez Fernández, Nuria García Pablos, David Salcedo Herrero, Valentin Delgadillo, María Inmaculada Poveda García and Francisco Javier Gonzalez Martinez

*Hospital Universitario Torrecárdenas, Nephrology, and Almería, Spain*

**BACKGROUND AND AIMS:** Renal artery stenosis causes hypertension in 10–40% of severe cases or refractory to treatment. As a gold standard test for its diagnosis, we have arteriography, which allows the interventional therapeutic option, through angioplasty and/or stenting. There is no consensus on which patient profile would be the optimal candidate for each treatment. We tried to reach an answer by studying a cohort of 25 patients from our centre with a diagnosis of renal artery stenosis in the last 5 years. The objective was to assess the efficacy of isolated or interventional medical treatment with respect to renal function and the number of antihypertensive drugs.
**METHOD:** A retrospective observational cohort study was conducted. The study population was the patients who underwent renal arteriography in the last 5 years in our center ($n = 25$).
We define significant stenosis as greater than 60%, bilateral involvement or of other main arteries. We compared the evolution of glomerular filtration in stages (KDIGO), proteinuria (albumin/creatinine ratio in urine) and number of antihypertensive drugs before and 6 months after the therapy used.
**RESULTS:** Renal arteriography was diagnostic in 18 patients: 13 of them presented significant stenosis, performing angioplasty in 4, stenting in 6 and angioplasty + stenting in 3.
One antihypertensive drug was reduced in 17% of the patients, two in 22%, and one drug was increased in one of them.
In 83% of the patients, the KDIGO stage of renal function did not change after treatment. An improvement was observed in three patients, who only received medical treatment. No differences were found in the evolution of proteinuria.
**CONCLUSION:** There were no statistically significant differences in renal function and the number of antihypertensive drugs between isolated medical versus medical and interventional treatment.
It is necessary to expand the patient database, or start multicenter studies, to improve the significance.