Challenges in generalizability, applicability, and translatability of obesity trials to people with CKD

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Conflicts of Interest Declaration

Consulting/speaker honoraria:

Abbott Laboratories, AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceuticals, Janssen, Menarini-Ricerche, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, Sanofi

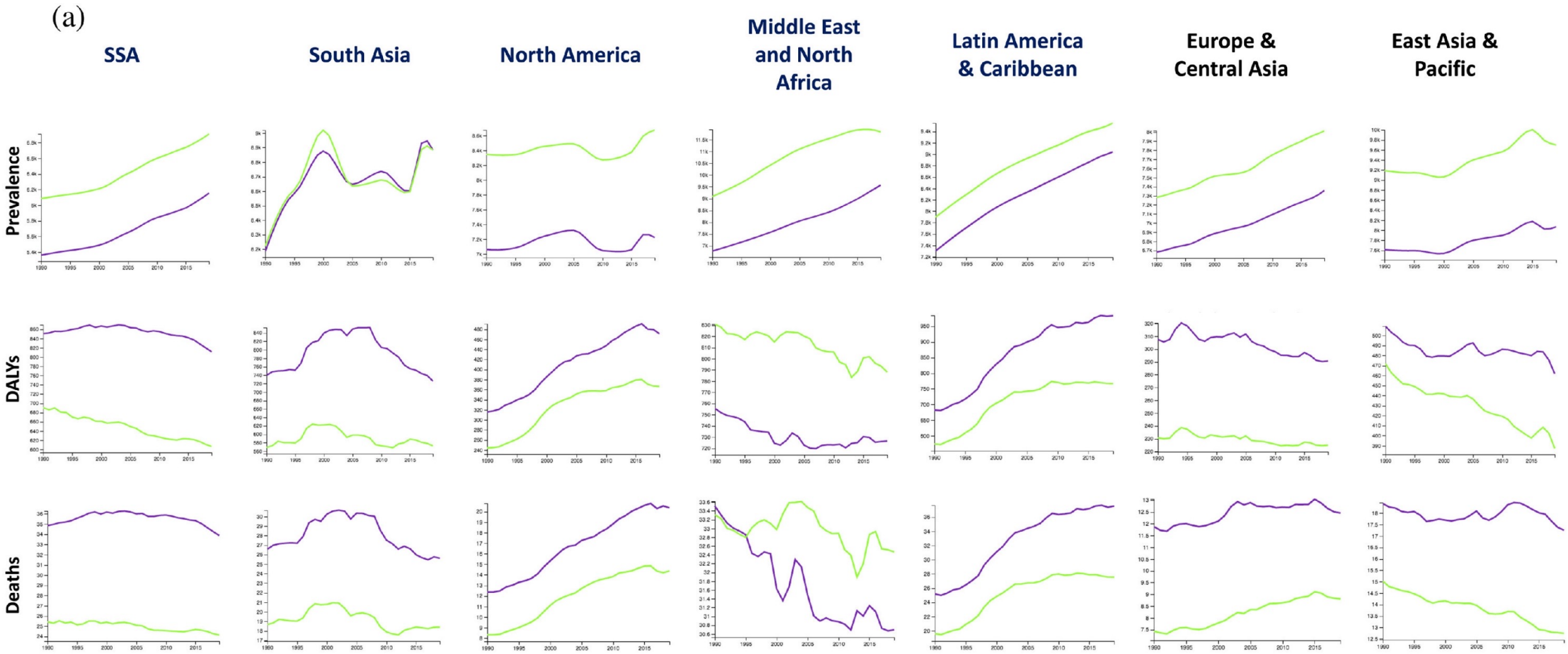
Grant: AstraZeneca, Boehringer Ingelheim, Novartis, Roche Diagnostics

Question asked

- How can we be more inclusive in terms of demographic representation (e.g., people with various degrees of CKD: early vs advanced CKD (dialysis) vs transplant candidates/recipients, comorbidities (e.g., HF, frailty) and socioeconomic/sex/geographic representation?

Certain communities

- Deep suspicion about trials – e.g. South Asians / Afro-Caribbeans
- Need investigators from same communities & advocacy from community leaders – train PI's sub-PI's representative
- Win the hearts and minds of family members – why trial participation can be positive and risks often down even if placebo
- Educational grants for community reach out? More media work? TikTok videos –
- Low SES – less interest - support for travel – trial visits in or near communities? Tricky



SEX : CKD more common in women?? but CKD advances faster in men - more risks - Women with targetable CKD older and frailer? Hard task.

Garcia Garcia et al (2022) Sem In Nephrology

Knowledge of obesity CKD risks?

- Many do not know obesity linked to T2D – yet +++++ HRs>50
- CKD – fewer understand links
- Is obesity paradox still mentioned in CKD circles?
  - Investigator minds? In HFpEF – no longer!
- Point of this meeting: summarise best evidence to foster more wt loss trials – gaps in knowledge

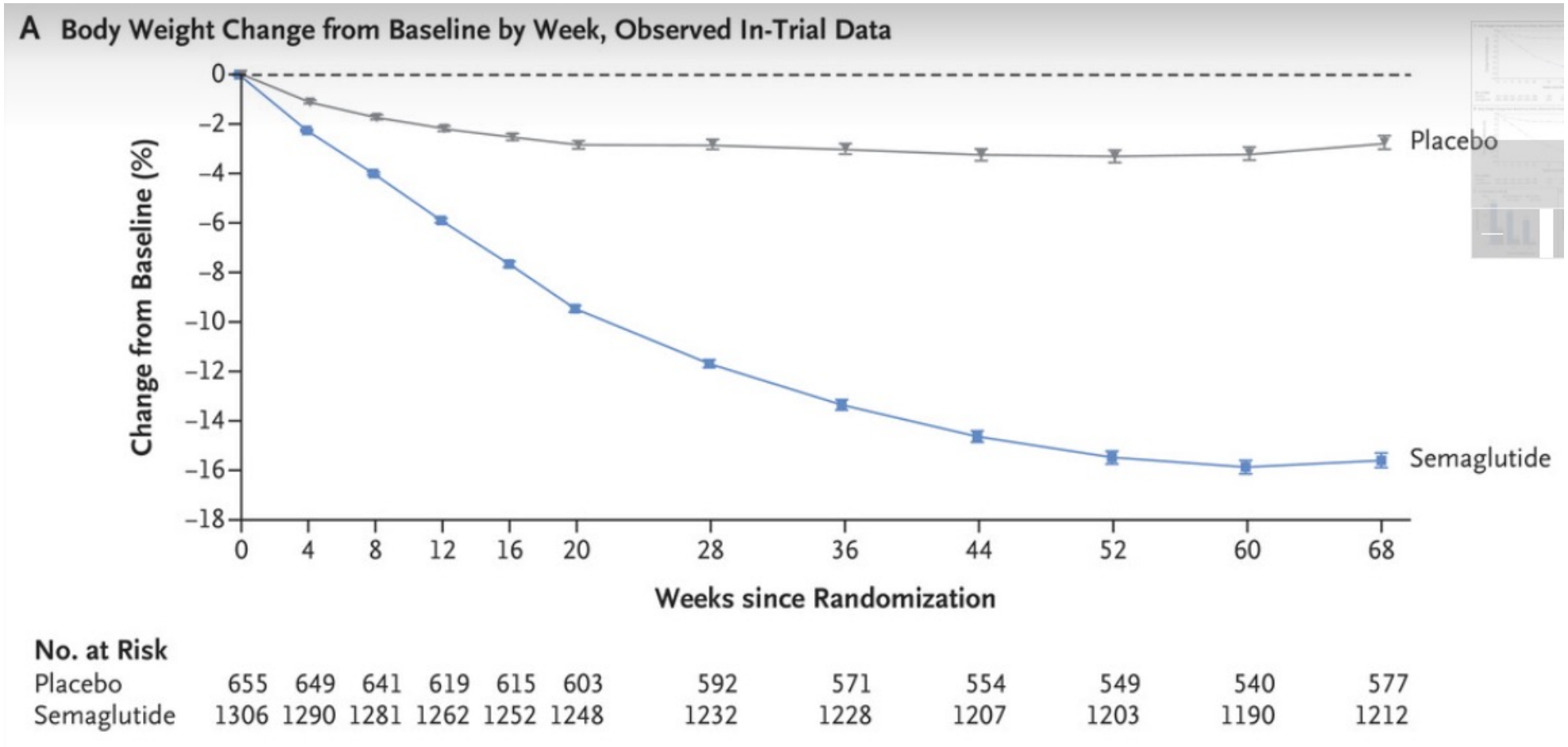
Early CKD - trials

- Early CKD – how long does a trial need to be –
  - Hard outcomes take time….life course
  - Slopes of eGFR sufficient? – need 3 years?
  - Albuminuria in context of intentional weight loss – down really fast

How applicable are Wt loss trials? STEP 1

- Semaglutide 2.4mg
- 70% female / average age 47
- BMI 38, non-DM
- 75% white – 13% Asian, 5% AFC or Black
- eGFR 96 UACR not measured?
- Conditions – HBP 1/3, dyslipidaemia 1/3, OA, Asthma, NAFLD, PCOS, CAD

Weight loss trials



Step 1 Wilding et al (2021) NEJM

SELECT and FLOW baseline criteria

- **SELECT (ASCVD, Non-DM)**
- Age 61, BMI 33 (>27), 3.3 years
- eGFR 82 +/-17
- 72% men
- 83% white, 8% Asian, 4% Black

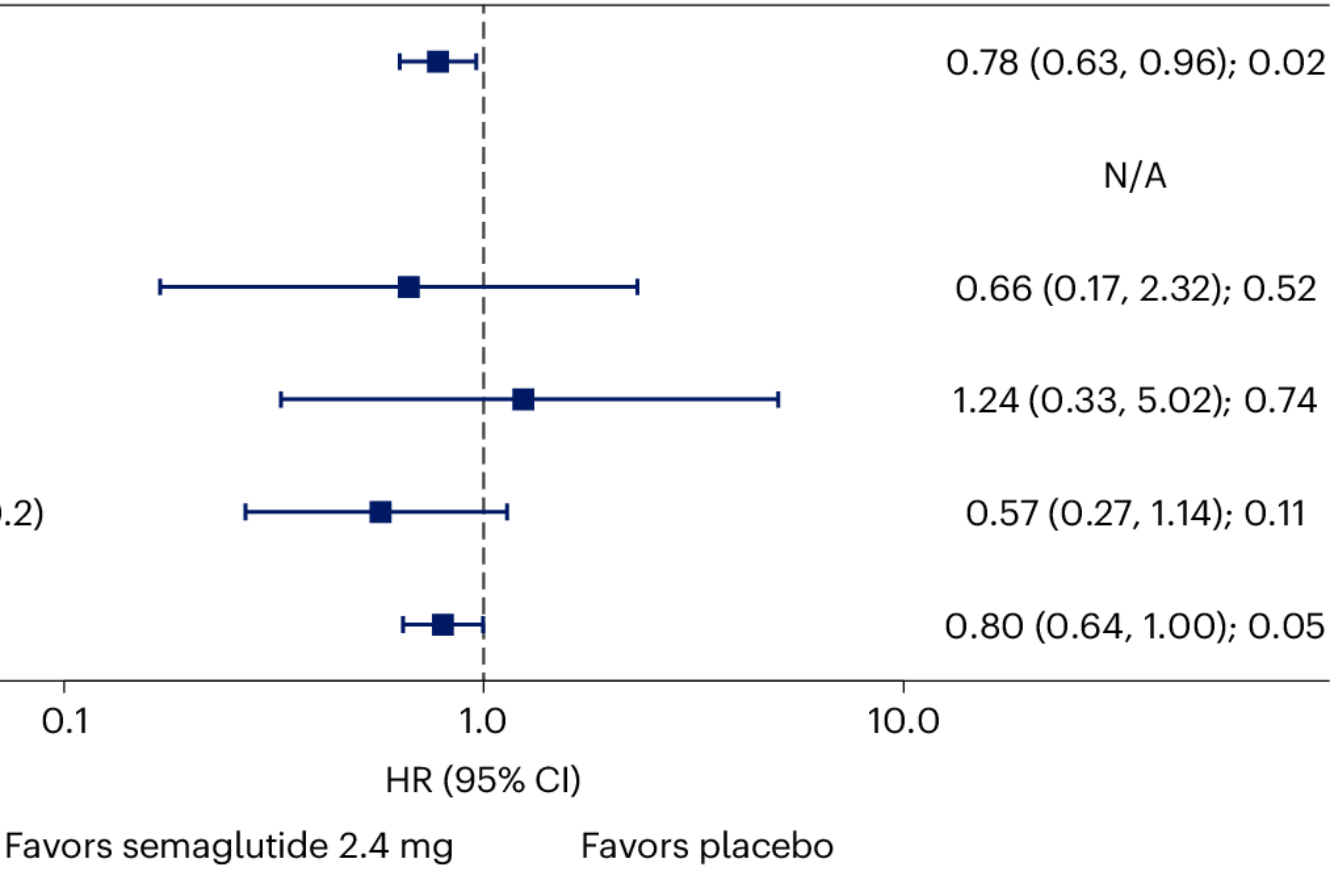
- 2/3 had prior MI

- **FLOW (T2D + CKD)**
- Age 66, BMI 31, 3.4 years
- eGFR 47 +/- 15
- 70% men
- 65% white, 25% Asian, 4% Black

- 1/5 MI; 1/5 HF
- CKD severity or progression faster in men
- Asians – early onset T2D – ↑glycaemia AUC means earlier CKD

SELECT: Kidney outcomes (HbA1c 0.3% improvement)

	Semaglutide 2.4 mg (*N* = 8,803), *n* (%)	Placebo (*N* = 8,801), *n* (%)	HR (95% CI); *P* value
5-component kidney composite endpoint	155 (1.8)	198 (2.2)	0.78 (0.63, 0.96); 0.02
Death due to kidney disease	0	0	N/A
Initiation of chronic kidney replacement therapy[a]	4 (0.0)	6 (0.1)	0.66 (0.17, 2.32); 0.52
Onset of persistent eGFR <15 ml min^{-1} 1.73 m^{-2}	5 (0.1)	4 (0.0)	1.24 (0.33, 5.02); 0.74
Onset of persistent ≥50% reduction in eGFR	12/8,724[b] (0.1)	21/8,742[b] (0.2)	0.57 (0.27, 1.14); 0.11
Onset of persistent macroalbuminuria	144 (1.6)	179 (2.0)	0.80 (0.64, 1.00); 0.05



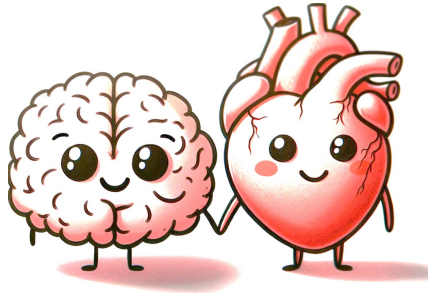
Colhoun HM, et al. *Nat Med* 2024;30:2058–2066.

Question posed

- How can we be more inclusive in terms of demographic representation (e.g., people with various degrees of CKD: early vs advanced CKD (dialysis) vs transplant candidates/recipients, comorbidities (e.g., HF, frailty) and socioeconomic/sex/geographic representation?

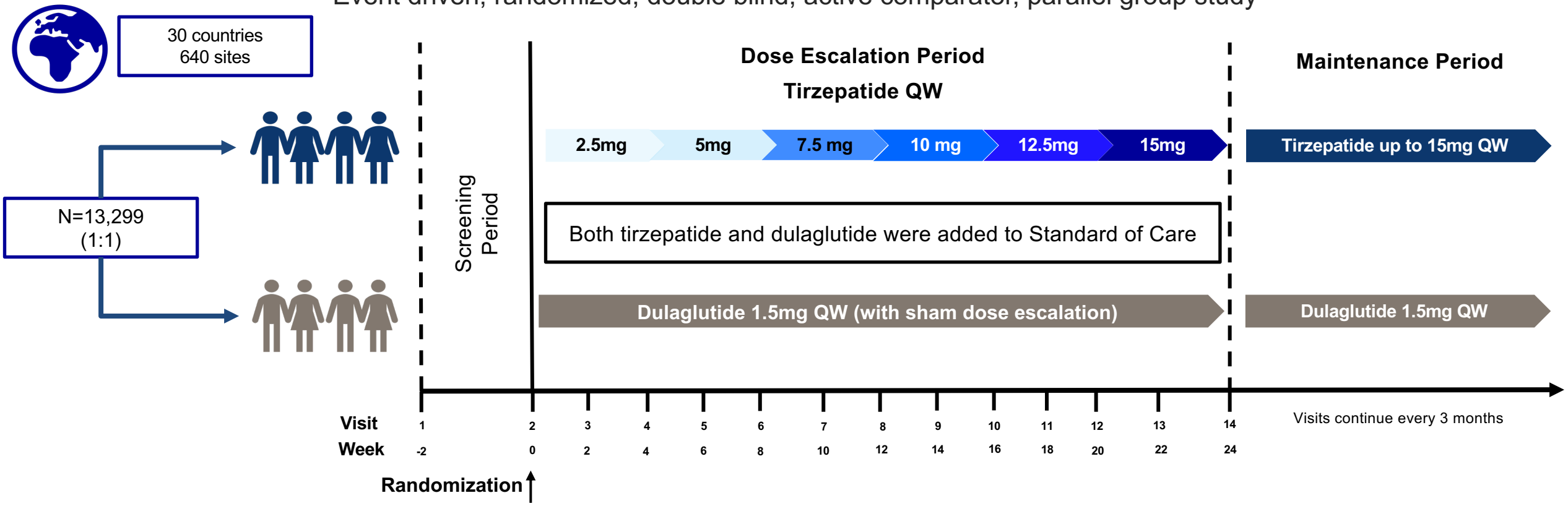
Need outcome data with larger wt loss trials to enhance confidence for advanced CKD?

- Data from FLOW help: 1mg semaglutide & ~4% weight loss
- Larger scale weight loss >=10%? Ongoing trials help?
- Hiddo led SURPASS papers on slopes – short term with TZP
- SURPASS CVOT – DULA vs TZP – 13K
- Age 64, T2D, 14 years duration, 71% men, 10% Asia-Pacific
- 23% eGFR <60,
- UACR 22 (3 to 98) mg/g – 43% Micro or macroalbuminuria



SURPASS CVOT design

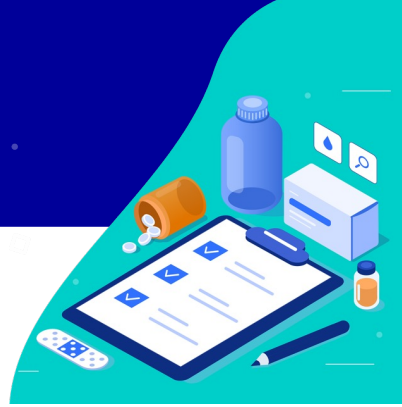
Event driven, randomized, double blind, active comparator, parallel group study



Primary analysis will be conducted to demonstrate non-inferiority of TZP compared to dulaglutide for MACE-3, followed by establishing the superiority of TZP compared to dulaglutide and putative placebo

Nicholls SJ, et al. *Am Heart J* 2024;267:1–11.

Later stage disease



- More concerns wrt obesity paradox in dialysis?
- Concerns about:
  - Side effects – Esp in late-stage disease (uremic) or with Rx (chemo)?
  - Muscle mass – lower to begin with – patients more frail
  - (creatinine vs cystatin C vs gold standard measures – ongoing MOA trials)
- But specialists interested and some ongoing trials with low calorie diets so do need more convincing? Just go do trials?
- Small scale initially? for efficacy / acceptability / side effects / safety signals

Q: Strategies (e.g., inclusive trial designs) facilitate enrichment people + CKD & obesity at ↑ risk for bad outcomes, likely treatment responders?

- Trial designs – inclusive – recruit more patients with CKD as enrichment for CVOTs – AMPLITUDE-O? / with elevated BMI / W /WHtR etc + T2D, BP
- To improve representation make trials
- a) very large,
- b) highly pragmatic, to allow for easier participation and better testing of heterogeneity across underrepresented groups vs safety
- Do we need intensive diet / activity counselling beyond Anti-obesity medicine (AOM) mature wrap around? Start low, go slow
- Oral AOMs would help get to more countries –

Biomarkers to enrich higher risk?

- Biomarkers – UACR / eGFR hard to beat – as end organ damage
  - Rate of change in eGFR over preceding 3-5 years?
  - Kidney failure risk equation? To estimate 5-year risk of kidney failure
  - Risk tools enhanced by the CKD patch/CKD Add-on (developed by the CKD prognosis consortium), or AHA PREVENT
  - Co-existent T2D, HBP, HF etc relevant
  - WHtR or Waist vs BMI? Weight most accurately measured
  - Cardiac biomarkers?
  - Proteomics approach too expensive

Final question

- What are the appropriate outcomes of interest or patient-reported outcome measures (PROMs) in obesity and CKD trials?
- HRQOL – Likert scale for happiness
- Activities of daily living, step count?
- Functional capacity? Grip strength? Step test?
- Fatigue levels, itch, depression?
- Chronic pain?, sleep?