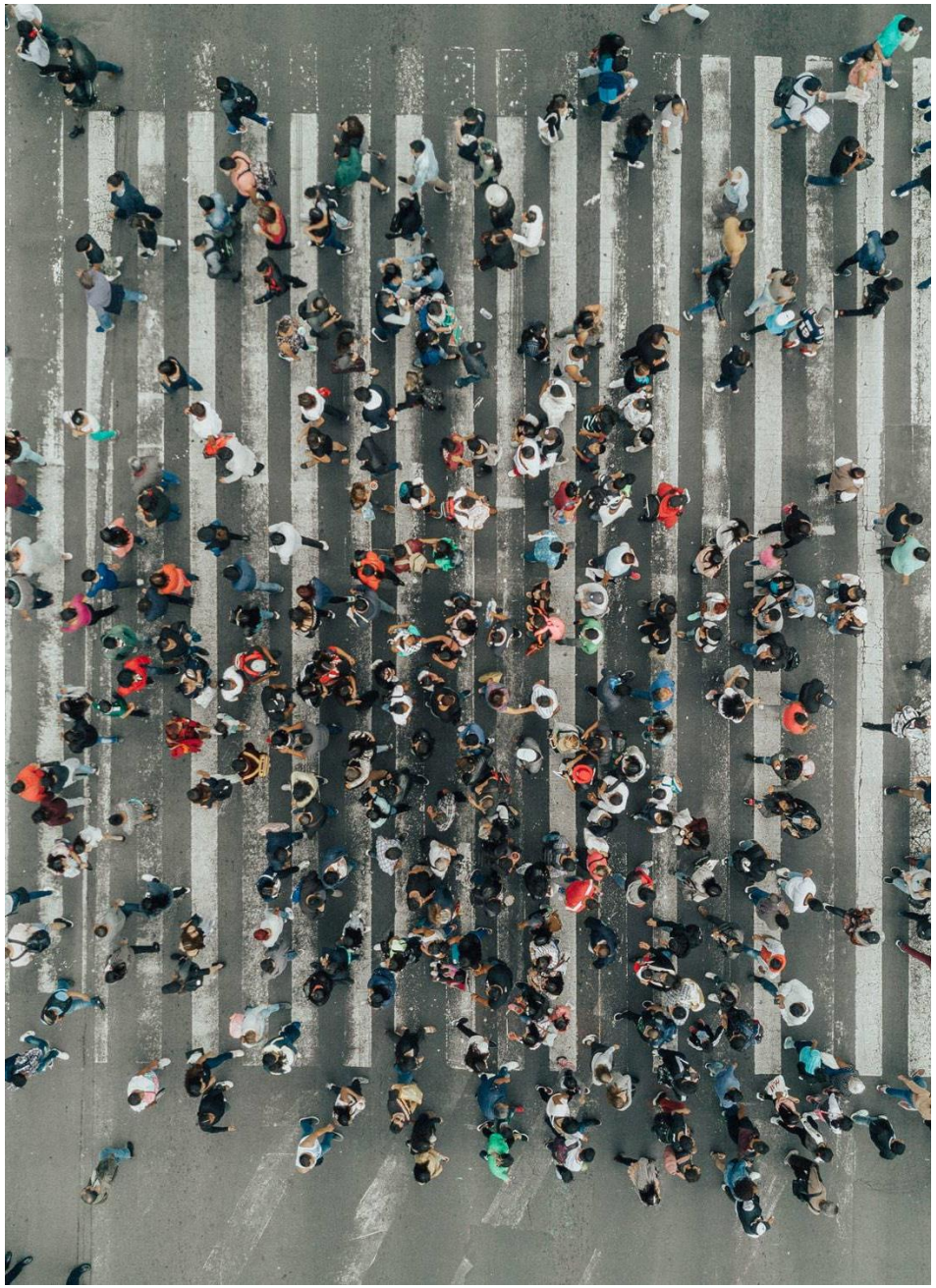


Generalisability and transportability in the context of target trial emulations

Kim Katrine Bjerring Clemmensen

September 2022

Me

- Medical doctor, PhD
- Postdoc at Novo Nordisk A/S, Copenhagen University and Steno Diabetes Center Copenhagen, Denmark

- Involved in the Joint Initiative on Causal Inference

Agenda

Background

Generalizability and transportability

The target trial

An example of a target trial emulation

Background

We need evidence to guide clinical decisions

- Increased complexity with new treatments becoming available
- And how can we answer questions faster and for a wider range of populations
- How do we “translate” evidence from randomized controlled trials (RCTs) into the real world (RW) and our populations of interest (target population)

Generalizability and transportability

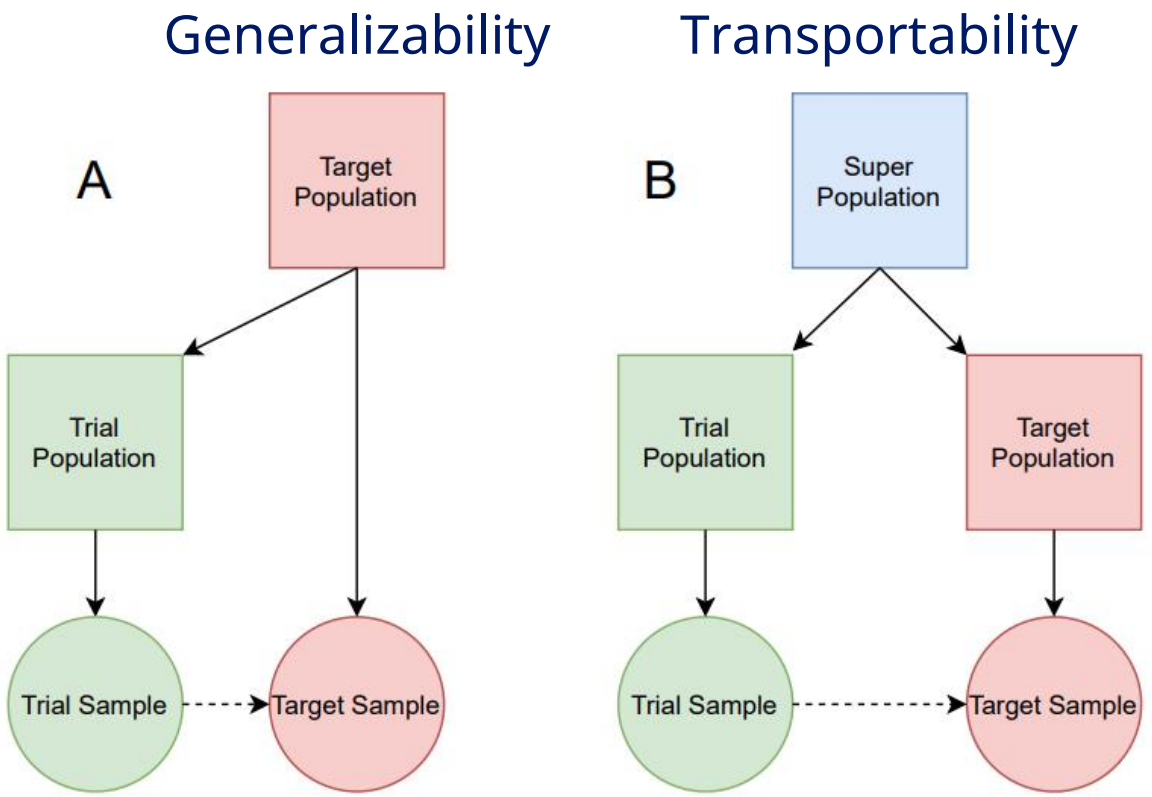


FIGURE 1 Square nodes represent populations whereas circular nodes represent samples. The solid arrow represents a subsetting of the origin node. The dashed line represents the process of generalizability (A) and transportability (B).

Figure from 2002.07899.pdf (arxiv.org) Josey et al.

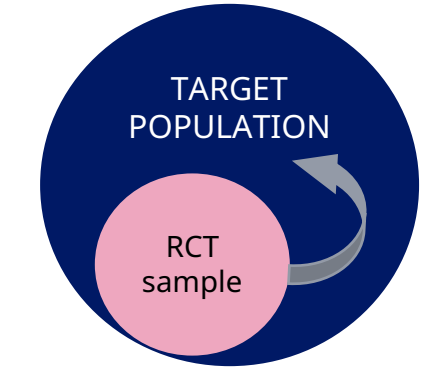
Generalizability and transportability

Answer clinically relevant questions on drug use in real-world data

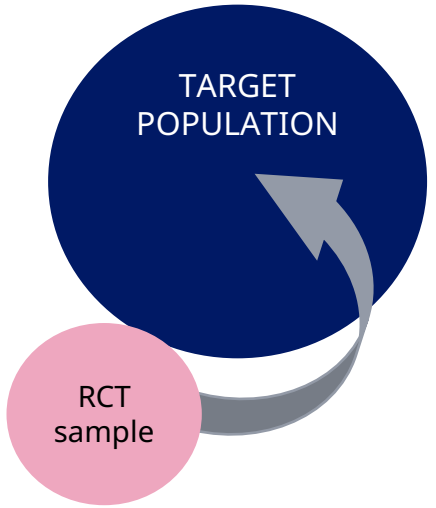
Generalizability of benefits and risks in real world data

Transportability to populations not included in RCTs

GENERALIZABILITY



TRANSPORTABILITY



How do we answer our questions?

The gold standard – a randomized trial

A relevant and well executed randomized trial should be able to answer our causal questions on comparative effectiveness and harm

…but

We cannot always conduct a randomized trial

- Too expensive
- Unethical
- Would take to long
- Unfeasible

So, what do we do?

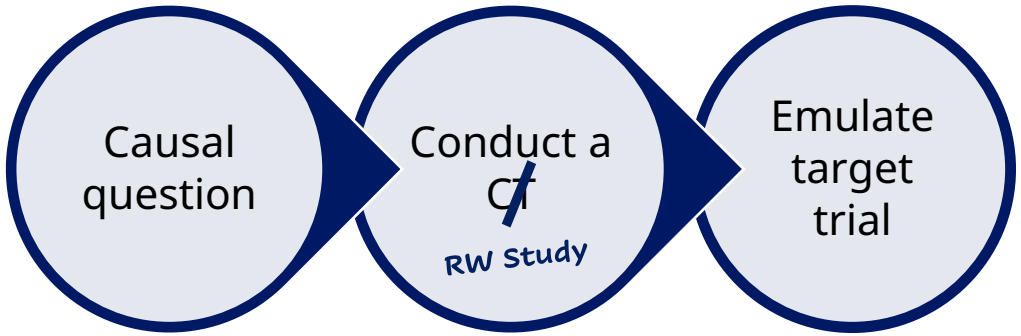
M. Hernan: Causal inference from observational data Emulating a target trial. Duke Margolis Center Workshop: Evaluating RWE from Observational Studies in Regulatory Decision-Making: Lessons Learned from Trial Replication Analyses (duke.edu) and What if https://cdn1.sph.harvard.edu/wp-content/uploads/sites/1268/2021/03/ciwhatif_hernanrobins_30mar21.pdf

The target trial

The (hypothetical) randomized trial that we would have to conduct to answer a causal question

A causal analysis of observational data can be viewed as an attempt to emulate a target trial

If we cannot translate our causal question into a target trial, then the question is not well defined



M. Hernan: Causal inference from observational data Emulating a target trial. Duke Margolis Center Workshop: Evaluating RWE from Observational Studies in Regulatory Decision-Making: Lessons Learned from Trial Replication Analyses (duke.edu) and What if

Benefits of target trial emulations

- Answering causal questions with RWD
- Makes the study design very explicit
- Answer causal questions that are unlikely to be answered with an RCT

- Observational results in a clinician friendly way… example with the LEADER trial

LEADER trial - results

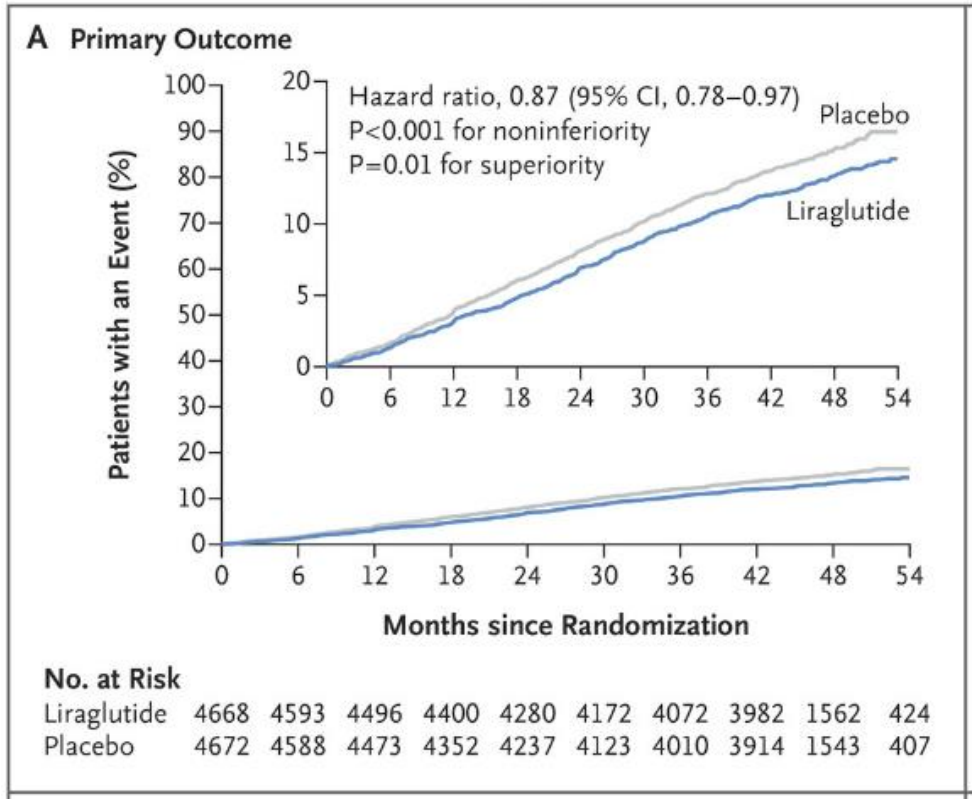
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

Table S2. Baseline characteristics.

	Liraglutide (N=4,668)	Placebo (N=4,672)
Male sex	3011 (64.5)	2992 (64.0)
Age, years	64.2 ±7.2	64.4 ± 7.2
Diabetes duration, years	12.8 ± 8.0	12.9 ± 8.1
Geographic region		
Europe	1639 (35.1)	1657 (35.5)
North America	1401 (30.0)	1446 (31.0)
Asia	360 (7.7)	351 (7.5)
Rest of the world	1268 (27.2)	1218 (26.1)
Glycated hemoglobin, %	8.7 ± 1.6	8.7 ± 1.5
BMI, kg/m^2	32.5 ± 6.3	32.5 ± 6.3
Body weight, kg	91.9 ± 21.2	91.6 ± 20.8
Systolic blood pressure, mm Hg	135.9 ± 17.8	135.9 ± 17.7
Diastolic blood pressure, mm Hg	77.2 ± 10.3	77.0 ± 10.1
Heart failure[a]	835 (17.9)	832 (17.8)
Established CVD (age ≥50)	3831 (82.1)	3767 (80.6)
Prior myocardial infarction	1464 (31.4)	1400 (30.0)
Prior stroke or transient ischemic attack	730 (15.6)	777 (16.6)
Prior revascularization	1835 (39.3)	1803 (38.6)
>50% stenosis of coronary, carotid, or lower extremity arteries	1188 (25.4)	1191 (25.5)

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*



Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes | NEJM

RCT DUPLICATE Initiative

Circulation

ORIGINAL RESEARCH ARTICLE

Emulating Randomized Clinical Trials With Nonrandomized Real-World Evidence Studies

First Results From the RCT DUPLICATE Initiative

BACKGROUND: Regulators are evaluating the use of noninterventional real-world evidence (RWE) studies to assess the effectiveness of medical products. The RCT DUPLICATE initiative (Randomized, Controlled Trials Duplicated Using Prospective Longitudinal Insurance Claims: Applying Techniques of Epidemiology) uses a structured process to design RWE studies emulating randomized, controlled trials (RCTs) and compare results. We report findings of the first 10 trial emulations, evaluating cardiovascular outcomes of antidiabetic or antiplatelet medications.

METHODS: We selected 3 active-controlled and 7 placebo-controlled RCTs for replication. Using patient-level claims data from US commercial and Medicare payers, we implemented inclusion and exclusion criteria, selected primary end points, and comparator populations to emulate those of each corresponding RCT. Within the trial-mimicking populations, we conducted propensity score matching to control for >120 preexposure confounders. All study measures were prospectively defined and protocols registered before hazard ratios

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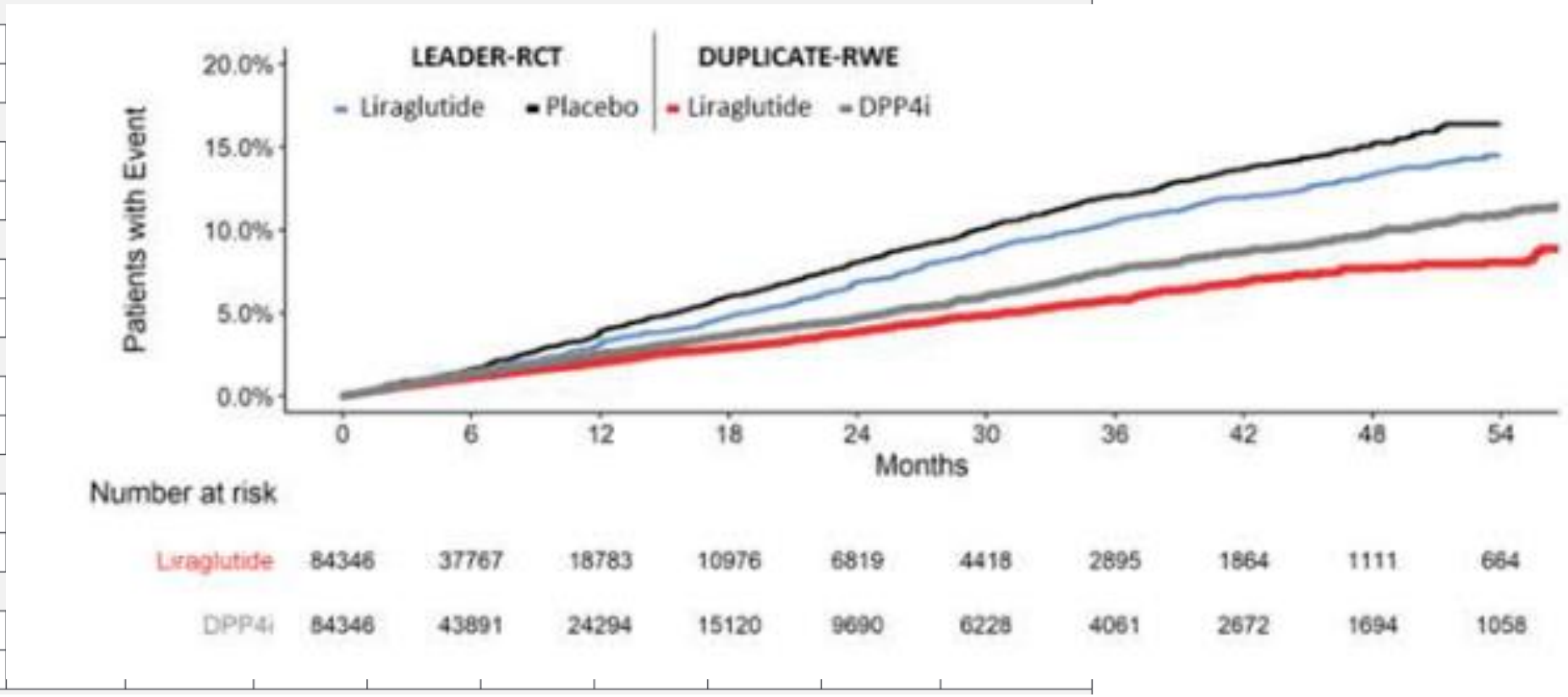
RCT DUPLICATE results

Table 1. Patient Characteristics in the Randomized, Controlled Trials (RCTs) Versus the Corresponding Real-World Evidence (RWE) Emulations

Characteristics	LEADER	DECLARE-TIMI58	EMPA-REG OUTCOME	CANVAS	CARME-LINA	TECOS	SAVOR-TIMI 53	CARO-LINA	TRITON-TIMI 38	PLATO
Age, y, mean±SD										
RCT	64.3±7.2									
RWE	67.7±6.0									
Female, %										
RCT	35.7									
RWE	53.5									
Smoking, %										
RCT	12.1									
RWE	10.2									
History of MI, %										
RCT	30.7									
RWE	13.0									
Hypertension, %										
RCT	90.0									
RWE	97.1									
CHF, %										
RCT	17.9									
RWE	20.9									



Emulating Randomized Clinical Trials With Nonrandomized Real-World Evidence Studies | Circulation (ahajournals.org)

An example
Dual therapy with GLP1 and SGLT2i

Type 2 diabetes

- Blood sugar levels are higher than normal
- The body is not reacting appropriately to insulin – *insulin resistance*
- And there is *insulin deficiency*
- Increasing prevalence

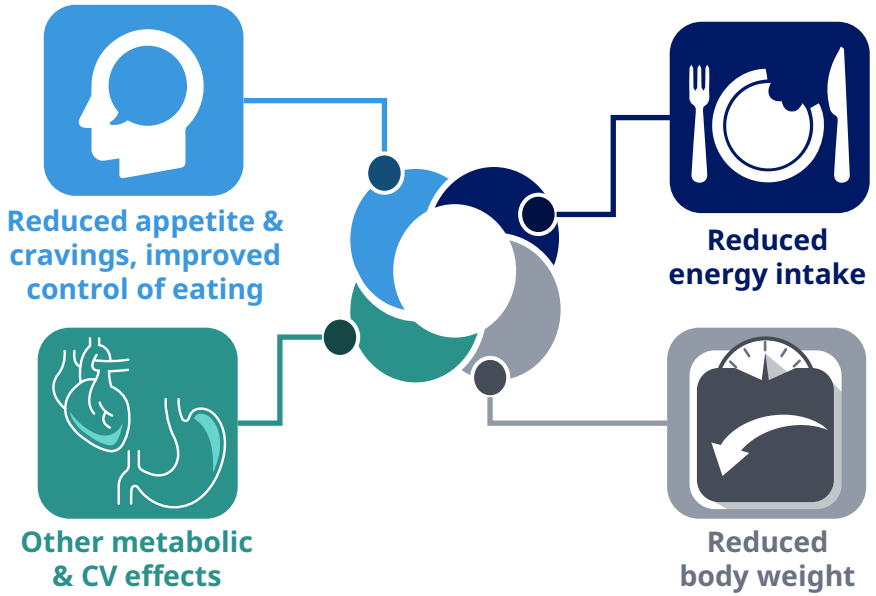
Treatment options

- Lifestyle changes
- Medication

GLP-1 and SGLT2i

GLP-1

Glucagon-like peptide 1 agonists



SGLT2i

Sodium glucose transporter 2 inhibitor

- Increases glucose excretion in the kidneys
  - Plasma glucose ↓
  - Body weight ↓
- CV benefits

Treatments for type 2 diabetes

1

First line treatment

- Metformin

Second line treatments

2

- GLP1
- SGLT2i
- Dipeptidyl peptidase 4 inhibitors (DPP4)
- Sulfonylurea (SU)
- Thiazolidinedione (TZD)

3

Third line treatment

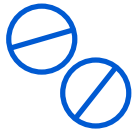
- Insulin

Rationale

Objective

- Generate evidence on added benefit of treating with both SGLT2i and GLP-1RA instead of monotherapy

Scientific Rationale



Different mode of actions
- Added benefits are expected.
- Continuously new data being published for both drug classes.

- **Added benefit on CV outcomes** expected to be shown for the combined treatment.
- **Additional benefits besides renal risk** reduction expected to be shown for the combined treatment.

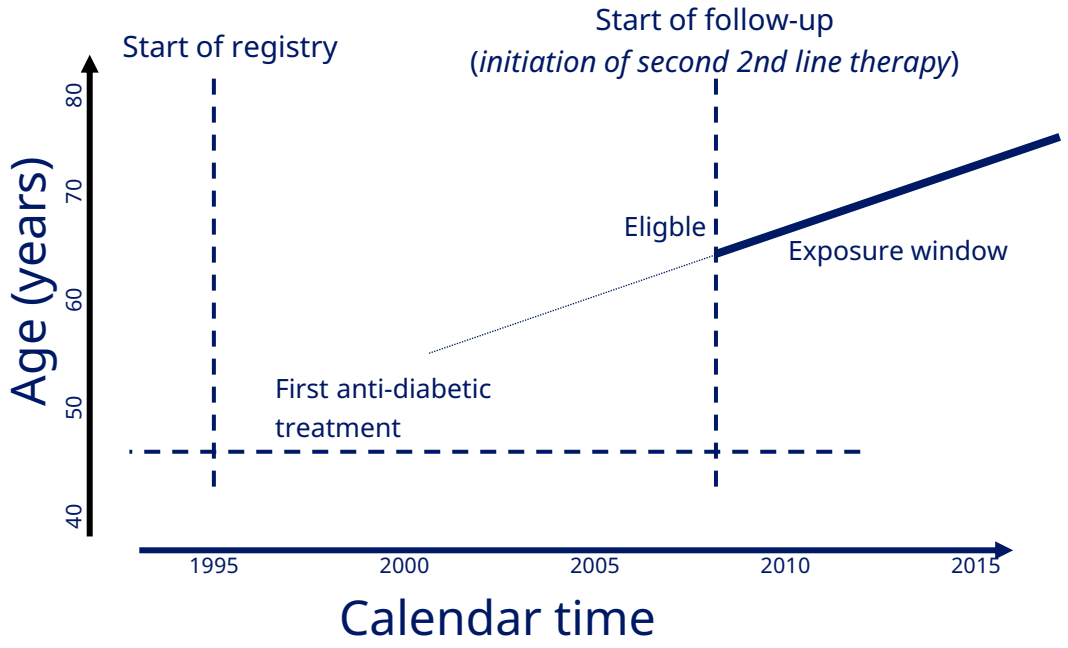
Multi-national register study

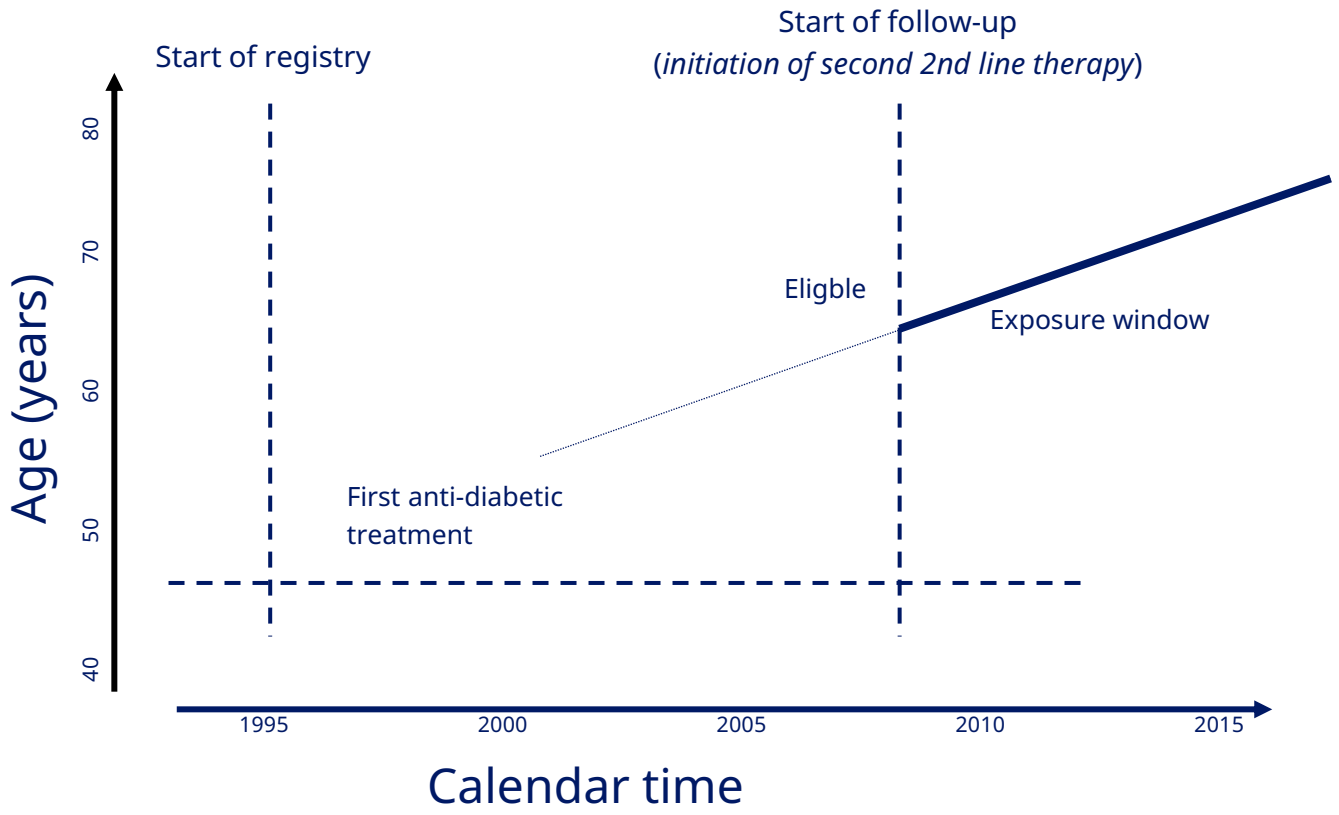
- International retrospective register study with national DK and UK register data

Study population:

- Individuals with type 2 diabetes who have progressed to second 2nd line anti-hyperglycemic drug therapies
- Age ≥ 18 years
- Meets none of the exclusion criteria

Follow-up period is from time of second 2nd line treatment to end of year 2021





Participants exposure time will be categorized as

1. GLP1 + SGLT2i
2. GLP1 + DPP4/SU/TZD
3. SGLT2i + DPP4/SU/TZD
4. DPP4/SU/TZD + DPP4/SU/TZD

Key study comparisons

SGLT2i+GLP1 ***vs.*** SGLT2i+ DPP4/SU/TZD

SGLT2i+GLP1 ***vs.*** GLP-1 RA+ DPP4/SU/TZD

Table 1. A Summary of the Protocol for the Target Trial

Protocol element	Description of hypothetical trial	Trial emulation
Eligibility criteria	Individuals with type 2 diabetes on a second line therapy and meeting none of the exclusion criteria	
Treatment strategies	Initiate an additional treatment with* 1) GLP1 2) SGLT2i 3) DPP4/SU/TZD at baseline and remain on it during the follow-up	
Assignment procedures	Participants will be randomly assigned to one of the strategies at baseline and will be aware of the strategy to which they have been assigned	
Time zero and follow-up period	Starts at date of assignment and ends at diagnosis of the outcome, death, loss to follow-up, or or administrative end of follow-up, whichever occurs first.	
Outcome	First-time heart failure hospitalization following inclusion.	
Causal contrasts of interest	Intention-to-treat effect, per-protocol effect	
Analysis plan	Intention-to-treat analysis Non-naïve per-protocol analysis	
***Starting any of the following second line therapies except not the drug that the individual is currently on**		

Table 1. A Summary of the Protocol for the Target Trial

Protocol element	Description of hypothetical trial	Trial emulation
Eligibility criteria	Individuals with type 2 diabetes on a second line therapy and meeting none of the exclusion criteria	Same as for the target trial
Treatment strategies	Initiate an additional treatment with* 1) GLP1 2) SGLT2i 3) DPP4/SU/TZD at baseline and remain on it during the follow-up	Initiate an additional treatment with* 1. GLP1 2. SGLT2i 3. DPP4/SU/TZD
Assignment procedures	Participants will be randomly assigned to one of the strategies at baseline and will be aware of the strategy to which they have been assigned	We assume randomization conditional on baseline covariates, including but not limited to age, sex, first 2nd line treatment type and length
Time zero and follow-up period	Starts at date of assignment and ends at diagnosis of the outcome, death, loss to follow-up, or or administrative end of follow-up, whichever occurs first.	Same as for the target trial
Outcome	First-time heart failure hospitalization following inclusion.	Same as for the target trial
Causal contrasts of interest	Intention-to-treat effect, per-protocol effect	Observational analogue of the per-protocol effect.
Analysis plan	Intention-to-treat analysis Non-naïve per-protocol analysis	Longitudinal Targeted Maximum Likelihood Estimation (LTMLE), details not included here
***Starting any of the following second line therapies except not the drug that the individual is currently on**		

Perspectives

- Target trial emulations can
  - Answer clinically relevant questions with RWD
  - In hard-to-reach populations

- Evidence in a form that is easier to understand for clinicians that are used to be informed by RCTs

Ideas, questions, comments? Please contact me on kkrc@novonordisk.com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