Trial protocol
REVERsal to normoglycemia by Treating PREDIABETES: the REVERT-PREDIABETES trial

November 2025
Version 4.0

The trial will be carried out in accordance with the protocol, current statutory legislation and the principles of good clinical practice.

Time schedule
Start of trial: November 1, 2025
Estimated completion: October 31, 2029

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Abbreviations

ASCVD – Atherosclerotic cardiovascular disease
ACS – acute coronary syndrome
ADA – American Diabetes Association
BMI – body mass index
CAD – coronary artery disease
CAP – controlled attenuation parameter
CCS – chronic coronary syndrome
eGFR – estimated glomerular filtration rate
GCP – Good Clinical Practice
GDPR – General Data Protection Regulation
GLP-1 – glucagon-like peptide 1
GLP-1 RA – glucagon-like peptide 1 receptor agonist
HbA1c – hemoglobin A1c
IEC – International Expert Committee
MASLD – metabolic dysfunction-associated steatotic liver disease
MI – myocardial infarction
OCT – Optical Coherence Tomography
RVA – Retinal Vessel Analyzer
SGLT-2i – sodium glucose cotransporter 2 inhibitor
T2D – Type 2 Diabetes

Introduction

Background

Prediabetes, a major risk factor for progression to type 2 diabetes (T2D), is far less investigated than T2D. Prediabetes is defined as hemoglobin A1c (HbA1c) 39-47 mmol/mol according to the American Diabetes Association (ADA), whereas the International Expert Committee (IEC) has considered HbA1c 42-47 mmol/mol a particular high-risk prediabetes-equivalent state. In the Danish adult population, the prevalence of prediabetes has been estimated at 7%, with 20% of individuals with prediabetes progressing to T2D within 5 years, using the IEC criterion [1]. In the USA, the prevalence of prediabetes among the adult population is estimated to 34% and, in people aged 65 years or older, as high as 48% when using the ADA criterion. Prediabetes, and its progression to T2D, thereby represents a substantial worldwide issue with expected growth in the future [2].

T2D is associated with micro- and macrovascular complications. In a Danish T2D cohort, 35% of patients already had diabetes-related complications at the time of T2D diagnosis [3]. Thus, microvascular diseases, comprising retinopathy, nephropathy, and neuropathy, which traditionally are thought to develop after years of diabetes-related hyperglycemia, may already be present in persons with prediabetes, challenging the current conventional diagnostic cut-point for T2D, which is based on the risk of developing diabetes-related retinopathy [4, 5]. Accordingly, it has been suggested that intervening before the development of manifest diabetes might be warranted in certain individuals with complications usually considered diabetes-related or whom are at a particular high risk of developing T2D, although efforts must be made to identify the appropriate individuals and treatment approaches [6].

The transition from normoglycemia to prediabetes is associated with increasing body weight, insulin resistance, declining endogenous insulin secretion, decreased endogenous levels of glucagon-like peptide 1 (GLP-1), and increased lipolysis [7]. Interestingly, prediabetes may also be associated with an increased prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD), and, as the two conditions are highly intertwined by mechanisms such as insulin resistance, pursuing reversion of prediabetes to normoglycemia could potentially improve MASLD [8, 9].

Most patients with prediabetes show features of the metabolic syndrome, e.g. dyslipidemia, hypertension, and abdominal obesity [10]. These metabolic risk factors are also strongly associated with the risk of cardiovascular disease. Thus, patients with prediabetes and cardiovascular disease serve as an interesting cohort to examine. Importantly, the prevalence of microvascular diseases in patients with prediabetes and established coronary artery disease (CAD) remains unknown. In patients with cardiovascular disease, a HbA1c within the prediabetes range is highly prevalent and in not yet published data we found that more than one in two with a HbA1c 42-47 mmol/mol, recent MI and BMI ≥27 developed T2D within 5 years. Thus, these individuals potentially represent a high-risk subpopulation of patients which may benefit from early intervention, for example with intensive prophylactic actions on dyslipidemia, hypertension, and lifestyle [11]. Moreover, the use of glucose-lowering agents such as GLP-1 receptor agonists (GLP-1 RA) and sodium glucose cotransporter 2 inhibitors (SGLT-2i), both with a known cardioprotective effect in patients without diabetes, is of particular interest when trying to pursue normoglycemia.

In the SELECT (Semaglutide Effects on Cardiovascular Outcomes in Patients With Overweight or Obesity) trial, patients with preexisting cardiovascular disease (previous myocardial infarction [MI] or stroke >60 days prior, or symptomatic peripheral artery disease) and a body mass index (BMI) of 27 kg/m^2 or greater without a history of diabetes were randomized to receive the GLP-1 RA semaglutide or placebo [11]. 66% had prediabetes according to the ADA criterion. The SELECT trial found that semaglutide reduced the risk of a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke by 20 %. However, based on not yet published results from the Western Denmark Heart Registry, three out of four patients with CAD did not meet the SELECT eligibility criteria. Thus, we want to investigate patients with prediabetes and chronic coronary syndrome (CCS) with documented CAD, irrespective of BMI.

CCS refers to the clinical presentation of CAD during stable periods, thus also following an acute coronary syndrome (ACS). We have found that >30 days after an ACS, as exemplified by primary percutaneous coronary intervention treated ST-elevation myocardial infarction, the excess risk of mortality is very limited when compared to a matched general population [12]. Therefore, we seek to examine patients with CCS with or without a previous MI and with or without a BMI ≥27 kg/m^2; while for patients with MI study initiation will be delayed for at least 30 days.

In this study we aim i) to compare the prevalence of microvascular diseases and MASLD in patients with established CAD and prediabetes versus normoglycemia; ii) to show that it is possible to revert prediabetes to normoglycemia in most patients by the use of glucose-lowering medications with documented cardiovascular protective effects; and iii) to examine the incidence of progression to prediabetes/T2D one year after termination of intervention.
To answer these questions, we have established a collaboration with expert national researchers within epidemiology, T2D, retinopathy, MASLD, and coronary heart disease.

Aims
STUDY I
Working title: Prevalence of microvascular diabetes-related diseases and MASLD in patients with CCS and prediabetes undergoing coronary angiography.
Aim: To compare the prevalence of retinopathy, nephropathy, neuropathy, and MASLD in patients with CCS and prediabetes versus normoglycemia.
Hypothesis: Microvascular diseases and MASLD are more common in patients with CCS and prediabetes compared with normoglycemia.

STUDY II
Working title: Prediabetes, CCS, and medically induced reversal to normoglycemia: a randomized trial.
Aim: To examine effects of intensified medical follow-up and treatment including cardioprotective glucose-lowering drugs on the proportion of patients with angiographically documented CAD that can be reverted from prediabetes to normoglycemia.
Hypothesis: In a randomized setting, it is possible to induce a significantly higher incidence of reversal from prediabetes to normoglycemia in the interventional therapy arm compared with the conventional therapy arm.

STUDY III

Working title: Incidence of recurrence of prediabetes or progression to T2D one year after termination of glucose-lowering medical intervention in patients with CCS and prediabetes at baseline.
Aim: To examine the 2-year effects of intensified medical follow-up and treatment on recurrence of prediabetes or progression to T2D in patients with CCS and prediabetes.
Hypothesis: The prevalence of patients with prediabetes or T2D (HbA1c ≥42 mmol/mol) is no longer substantially different in the interventional and conventional therapy arm at 2-year follow-up due to recurrence of prediabetes or progression to T2D following termination of glucose-lowering medications.

Study populations
The randomized cohort (108 patients; used for Study 1-3)
Patients with angiographically documented CAD and prediabetes as defined by IEC are identified in relation to examination or treatment at the Department of Cardiology at Aarhus University Hospital by staff in the Department (nurses or physicians). These will assess patient files to ensure that patients are eligible for study enrolment.

The baseline comparison cohort (50 patients; Study 1 only)
For study I, patients with angiographically documented CAD with normoglycemia (HbA1c <39 mmol/mol) are identified in relation to examination or treatment at the Department of Cardiology at Aarhus University Hospital by staff in the Department (nurses or physicians).

Potentially eligible patients will either receive oral and written information by an investigator; or be asked by the staff at the Department of Cardiology if they accept to be contacted at a later time regarding study participation, which will be noted in the patient files. Everyone assessed who meet our inclusion and exclusion criteria are invited to participate at a screening visit (*Table 4*), where informed consent is obtained by an investigator. Patients will be given a sufficient amount of time to consider their participation and discuss with relatives if needed. All patients need to be capable of giving informed consent as assessed by the investigator in order to be eligible, thus, patients must speak the national language to participate.

After collection of informed consent to study participation, a HbA1c measurement is repeated to confirm a HbA1c of 42-47 mmol/mol or <39 mmol/mol. If eligibility is confirmed, the participant will be invited for the baseline visit. At the baseline visit 108 trial subjects with HbA1c 42-47 mmol/mol will be randomized 1:1 to either the interventional therapy arm or conventional therapy arm. Patients deemed not eligible after visit 1 will be registered as screen failure, and the reason will be registered. An additional comparison cohort of 50 patients with normoglycemia will undergo evaluation of baseline microvascular diabetes-related diseases and MASLD and will be compared with the randomized cohort.

Investigational medicinal products
GLP-1 RA: semaglutide subcutaneous once-weekly titrated to a maximum of 2.4 mg or the maximum tolerable dose. Needles will be provided.
The dose of a maximum of 2.4 mg per week is in accordance with the current recommended maximum dose for the treatment of overweight or obesity.

SGLT-2i: dapagliflozin 10 mg oral tablet daily. This is in accordance with the generally recommended dose.

Treatment of dyslipidemia and hypertension will be conducted according to guidelines, and will thus not be further explained in this section.

Risk-benefit assessment

Risks

The examinations are further described below. Blood samples will provide much information and are rarely linked to prolonged discomfort. The eye examination requires administration of mydriatic eye drops (duration 3-4 hours), which might lead to a burning sensation (seconds) and blurred vision (hours). Very rarely an allergic reaction to the preservative in the eye drops occurs, which can be treated unproblematically by anti-allergic eye drops.

For trial subjects randomized to the interventional arm, treatment optimization regarding hypertension and dyslipidemia will be conducted according to guidelines. The potential adverse effects, generally associated with the specific therapeutic choices, will be considered as part of the treatment strategy.

Risks regarding treatment with semaglutide:

- Gastrointestinal disorders: Such as diarrhea, nausea, and vomiting. This is the most frequently reported adverse reaction in clinical trials, generally of mild or moderate severity [11, 13]. The risk is minimized by starting at a low dose followed by gradual escalation of dose.
- Cholelithiasis/gallbladder-related disorders: In some studies, with overweight patients without T2D, the risks of cholelithiasis or cholecystitis are marginally higher compared to placebo. In other studies, however, there is not found an increased risk of gallbladder-related disorders or cholelithiasis [11, 13, 14].
- Allergic reactions: As for all medications, participants are at risk of developing allergic reactions.
- Pregnancy: Animal studies have shown reproductive toxicity. Only limited data exist from the use of the medication in pregnant women. In pregnant patients with T2D, periconceptional use of GLP-1 RA is associated with a significantly higher risk of major congenital malformations as compared to non-exposure to antidiabetic medications [15]. Thus, semaglutide should not be used while pregnant. Consequently, females who are pregnant, breast-feeding, intends to become pregnant, or is of child-bearing potential and not using a highly effective contraceptive method will be excluded from the trial.
- Hypoglycemia: No significantly increased risk of hypoglycemia in patients without diabetes [16].
- Cancer: Pancreatic cancer has been classified as a potential class risk for all marketed GLP-1 RA, however, there has not been established a causal association with semaglutide. In a number of trials, there were found no significant differences between rates of neoplasms in patients treated with semaglutide or placebo [11, 14].
- Acute pancreatitis: Has been observed with the use of drugs from the GLP-1 RA. For this reason, subjects with a history of pancreatitis will not be enrolled. Further, in the case of suspicion of pancreatitis, semaglutide will be discontinued.

Risks regarding treatment with dapagliflozin:

- Genital mycotic infection: For patients with diabetes, treatment with a SGLT-2i is associated with an increased risk of genital mycotic infection. The risk for patients without diabetes remains less clarified but is described to be lower than for those with diabetes [17].
- Urinary tract infections: Is an expected adverse effect, however, data from large, randomized clinical studies have not yet found evidence of an elevated risk hereof [18, 19].
- Ketoacidosis: In patients without T2D there is a minimal risk of ketoacidosis as there has been reported a very few numbers of cases [17].
- Pregnancy: Only limited data exist from the use of the medication in pregnant women. However, in a study of pregnant patients with T2D, periconceptional use of SGLT-2i was associated with a higher risk of major congenital malformations as compared to non-exposure to antidiabetic medications, although not significant [15].Consequently, females who are pregnant, breast-feeding, intends to become pregnant, or is of child-bearing potential and not using a highly effective contraceptive method will be excluded from the trial.
- Allergic reactions: As for all medications, participants are at risk of developing allergic reactions.

Benefits
All patients will be examined for presence of microvascular diseases and MASLD at baseline. These examinations are not routinely performed in individuals with prediabetes or normoglycemia and might serve a potential benefit for the patients.

For patients randomized to the interventional arm, their medical treatment of dyslipidemia and hypertension will be monitored beyond the conventional ≈ 3 months cardiac rehabilitation program in Denmark and they may thus have a greater chance of reaching target goals. They will also be provided sustained counseling on diet, alcohol intake, smoking cessation, and exercise on top of the cardiac rehabilitation program beyond the standard ≈ 3-month rehabilitation program. Further, by initiating treatment with semaglutide and potentially dapagliflozin, we aim to achieve normoglycemia in patients, which in the SELECT-eligible patients were beneficial and may thus also be of benefit in the approximately three-quarters of patients with prediabetes in this study who would not fulfill the SELECT inclusion criteria. The glucose-lowering drugs, in particular GLP-1 RA, used in this study have documented cardiovascular risk reduction and, further, have documented secondary benefits including, but not limited to, improvements of high-sensitivity C-reactive protein (hs-CRP), LDL cholesterol, triglycerides, renal function, and body weight [11, 20-22]. All glucose-lowering treatments will be supplied free of charge for the patients.

Trial participants within the conventional therapy arm will receive the current practice at their local hospital or general practitioner, therefore their participation in this trial will not in any way negatively impact their management.

Risk-benefit conclusion
We conclude that the abovementioned risks do not outweigh the potential benefits of this study in trial subjects with established cardiovascular disease and prediabetes, considering the established exclusion criteria.

Trial plan and design

Primary and secondary endpoints

To compare the effect of glucose-lowering treatment, optimization of blood pressure and lipids, and lifestyle counseling as compared with conventional follow-up and medical intervention in trial subjects with CCS and established CAD as well as prediabetes.

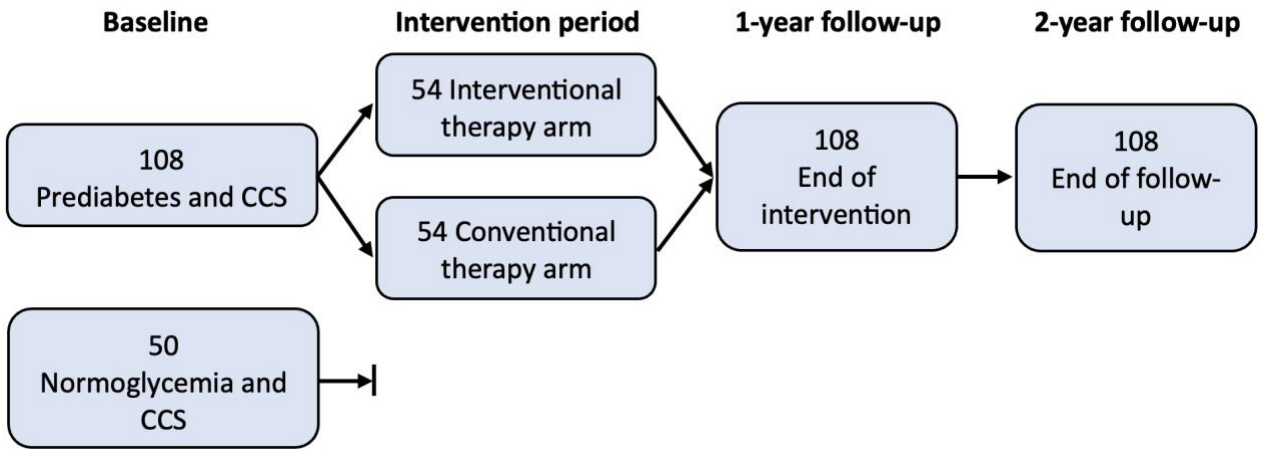

Figure 1. Overview of study design.

At baseline, all randomized trial subjects will be examined for the presence of potential microvascular diseases commonly associated with diabetes, i.e., retinopathy (eye examination), nephropathy (urine and blood samples), and neuropathy (monofilament test and Vagus device test) (Table 1); nephropathy also assessed at 1-year follow-up. Further, a fibroscan with transient elastography with controlled attenuation parameter (CAP) will be conducted at baseline and 1-year follow-up for MASLD severity (liver steatosis and fibrosis). The examinations are further described below.

Blood samples at baseline, 1-year, and 2-year follow-up will elucidate levels of HbA1c, hemoglobin, creatinine, cystatin-C, sodium, potassium, hs-CRP, lipids (LDL, HDL, triglycerides, cholesterol, non-HDL), c-peptide, fasting insulin and glucose, amylase, alanine aminotransferase, FIB-4, ADAPT-score, PRO-C3, and CD163. Insulin resistance will be estimated by the homeostasis model assessment of insulin resistance (HOMA-IR).

In the cases of PRO-C3, CD163, c-peptide and insulin, blood samples are stored in a biobank for later batch analyses. PRO-C3 is analyzed by a third party. All other samples are analyzed within the clinical laboratory.

A maximum of 33 ml blood will be collected per visit. At baseline and 1-year follow-up, this amount will be collected. At 2-year follow-up, a maximum of 23 ml will be collected. At other visits a maximum of 13 ml will be collected. All randomized participants are expected to undergo study related blood collection four times, for those in the interventional arm at least one additional sampling is expected. Further blood samples may be conducted at the discretion of the investigator.

Those with normoglycemia and CCS are seen only at screening and baseline. They will undergo blood sampling (two collections), urine sampling, interview, vital measures, body metrics and composition, nerve examination, eye examinations, and fibroscan.

Table 1

Outcomes	
STUDY I (Baseline)	
Primary - Presence of a composite of retinopathy, nephropathy, neuropathy, and MASLD	Secondary Presence of - Retinopathy - Nephropathy - Neuropathy - MASLD Presence of a composite of retinopathy, nephropathy, and neuropathy.
STUDY II (1-year follow-up)	
Primary - Incidence of normoglycemia defined as HbA1c <39 mmol/mol	Secondary - Incidence of normoglycemia defined as HbA1c <42 mmol/mol - Change in HbA1c - Change in eGFR - Change in cystatin-C - Change in hs-CRP - Change in lipid parameters - Change in c-peptide - Change in HOMA-IR - Change in Fib-4 - Change in CD163 - Change in PRO-C3 - Change in MASLD severity - Change in urine albumin-creatinine ratio - Change in weight - Change in waist circumference
STUDY III (2-year follow-up)	
Main outcome of interest - Prevalence of HbA1c ≥42 mmol/mol	Secondary - Incidence of T2D - Prevalence of prediabetes defined as HbA1c 42-47 mmol/mol - Prevalence of prediabetes defined as HbA1c 39-47 mmol/mol - Change in HbA1c - Change in eGFR - Change in cystatin-C - Change in hs-CRP - Change in lipid parameters - Change in c-peptide - Change in HOMA-IR - Change in Fib-4 - Change in CD163

	- Change in PRO-C3 - Change in weight - Change in waist circumference

All secondary outcomes are considered exploratory.

Design

The trial will be conducted as a non-blinded randomized controlled trial and the conventional therapy arm adheres to current practice at the subject's local hospital or general practitioner without any study visits after screening apart from baseline, 1-year, and 2-year follow-up examinations. For this reason, there will be no placebo treatment.

Baseline blood samples will be obtained from all trial subjects.
Within the interventional therapy arm, trial subjects will through monthly visits be treated to optimal levels of glycemia, blood pressure, and lipids, hereafter visits every 3 months according to Table 2. Regarding hypertension and dyslipidemia, treatment will be according to current guidelines.

Hyperglycemia:

- Semaglutide titration according to the recommended dose titration for semaglutide to a maximum maintenance dose of 2.4 mg once-weekly or maximum tolerable dose (Table 2). HbA1c is measured at visit 5. If normoglycemia is not reached, it will be possible to add dapagliflozin.
  In case of significant gastrointestinal side effects at a specific dose, postponement of dose escalation as well as a dose reduction should be discussed.

Table 2

Week	1-4	5-8	9-12	13-16	17-
Dose	0.25 mg	0.5 mg	1.0 mg	1.7 mg	2.4 mg

Due to the varying definitions of prediabetes, we will consider normoglycemia at HbA1c <39 mmol/mol, which is according to ADA, despite alone including patients with HbA1c 42-47 mmol/mol, which is prediabetes according to IEC, as this is considered a particular high-risk subgroup.

Optimization of medical therapy (individualized treatment strategy according to current guidelines):

- Dyslipidemia: goal non-HDL<2.2 mmol/l and/or LDL ≤1.4 mmol/l and at least 50% reduction of LDL.
- Hypertension: goal clinical blood pressure at 125-135/75-85 mmHg, as optimally measured blood pressure in a clinical situation generally lies 5/5 mmHg higher than home measurements.

When medical treatment is fully titrated according to the mentioned goals and sufficient lifestyle counseling is provided, intervention period visits will be replaced by visits every 3 months for the remainder of the 1-year intervention period. Overview of expected study visits and examinations are presented in Table 3, although visit numbers depend on when the goals are reached, thus number and timing of visits might vary. A safety telephone visit (visit 10) is scheduled for the interventional therapy group five weeks after end of treatment to allow for registration of adverse events.

Conventional therapy will be conducted according to current practice at the trial subject's hometown hospital or general practitioner. These trial subjects are seen only at screening, baseline, 1-year and 2-year follow-up with no additional visits. At inclusion, it will be discussed that initiation of a GLP-1 RA during the first year is discouraged in the case another equal medication or management can be initiated instead.

Table 3. Trial overview for participants with prediabetes and CCS.

	Baseline Screening		Intervention period						1-year follow-up	Safety	2-year follow-up
Visit	1	2	3	4	5	6	7	8	9	10	11
Timing of visit (weeks)		0	4	8	12	16	28	40	52	57	104
Visit window (days)			±7	±7	±7	±7	±7	±7	±14	±7	±14
Medical history	x	X									
Evaluation/ adjustment of medical treatment		X	x	x	x	x	x	x	X		
Blood samples A		X							X		x
Blood samples B	x		(x)	(x)	x	(x)	(x)	(x)			
Urine sample		X							x		
Vital measures		X	x	x	x	x	x	x	x		x
Body metrics and composition		X							x		x
Eye examinations		X									
Nerve examination		X									
Fibroscan		X							x		
Lifestyle counseling			x	x	x	x					
Adverse events			x	x	x	x	x	x	x	x	
Dispensing of medication		X	x	x	x	x	x	x			
Discontinuation criteria		X	x	x	x	x	x	x			
Concomitant medication		X	x	x	x	x	x	x	x		

Medical history: at screening/baseline patients are interviewed on their health status and previous or current concomitant diseases, supplemented by information from patient files. Information on average alcohol use and smoking habits are reported.

Blood samples A: HbA1c, hemoglobin, creatinine, cystatin-C, sodium, potassium, hs-CRP, lipids (LDL, HDL, triglycerides, cholesterol, non-HDL), c-peptide, fasting insulin and glucose (HOMA-IR), amylase, alanine aminotransferase, FIB-4, ADAPT-score, PRO-C3, and CD163.

Blood samples B:
When clinically relevant, for instance:

- At screening/if treatment of hyperglycemia has been adjusted (after 12 weeks): HbA1c, hemoglobin.
- If treatment of hypertension has been adjusted (primarily ARB or thiazide): creatinine, sodium, and potassium.
- If treatment of dyslipidemia has been adjusted: alanine aminotransferase and lipids.
- Further blood samples may be conducted at the discretion of the treating physician.

Urine sample: albumin and creatinine for calculation of albumin-creatinine ratio. Two samples from two different days are analyzed at both baseline and 1-year follow-up. A sample kit will be provided before the visit.

Vital measures: blood pressure and pulse.

Body metrics and composition assessment: Height, weight and waist circumference are measured in centimeter and kilograms. Further, a non-invasive bioelectrical impedance analysis is conducted to estimate body composition.

Eye examinations: Visual acuity is measured by reading letters on a visual acuity chart. Subsequently, the pupils are dilated using mydriatic eye drops (Mydriacyl 1% and Metaoxedrin 10%) used routinely for imaging of the retina. The retinal morphology will be documented by fundus photography and the thickness by Optical Coherence Tomography (OCT) scanning. Retinal reactivity (changes in vessel diameter) is assessed using the Retinal Vessel Analyzer (RVA).

Nerve examination: Firstly, a monofilament test, where the subject's sensitivity to the touch of a monofilament on the skin of the feet is evaluated. Secondly, using a handheld Vagus Device, which evaluates the heart rate and variability by guiding the subject through standardized tests to assess for cardiac autonomic neuropathy [23].

FibroScan: Liver transient elastography with Controlled Attenuation Parameter (CAP) is a non-invasive diagnostic tool that uses ultrasound technology, which is conducted to assess liver steatosis and fibrosis. Trial subjects should remain fasting 3 hours before the scan is conducted.

Lifestyle counseling: Counseling on diet, alcohol intake, smoking cessation, and exercise will be provided when relevant.

Dispensing of medication: Medication will be dispensed until next study visit. Further, compliance to study medication will be assessed.

Interview: During visits, trial subjects will be asked to provide information on potential adverse effects and events, which might have occurred since their last visit. Further, they will be asked about any concomitant medication. It will be ensured that no discontinuation criteria are present.

Data will be reported in an electronical Case Report Forms (eCRFs) in REDCap. Data not previously written down or elsewhere electronically registered will be recorded directly into REDCap and considered to be source data. This could be vital measures, height, weight, waist circumference, as well as the results of nerve examination, and fibroscan.

Randomization
Trial subjects with prediabetes will be randomized 1:1 to the interventional therapy arm or the conventional therapy arm. Randomization will be non-blinded due to the trial design as previously described. However, statistical analyses and evaluation of the results are performed blinded to the randomization group.

The randomization will be performed with the use of the eCRFs system REDCap. To ensure balanced sex distribution between arms, randomization will be stratified by sex. Further, randomization will be done in permuted blocks of varying size (4, 6 or 8), to avoid any predictability of the randomization. The allocation lists will be uploaded in REDCap by the Research Data Management at Institute for Clinical Medicine, Aarhus University, an independent party. To ensure allocation concealment, the randomization sequence will be concealed from investigators and study personnel involved in participant enrolment and assignment until the point of allocation. This process safeguards against selection bias and maintains the integrity of the randomization.

Trial duration
The intervention period will terminate at 1 year, where glucose-lowering treatments are discontinued. Afterwards, follow-up without further interventions will continue until 2 years after inclusion.

Neither temporary nor permanent discontinuation of medical treatment will lead to withdrawal from the trial. A trial subject may withdraw consent at any time. Indications for discontinuation of study products will be discussed below.

Trial period
Trial period completion is defined as

- When the trial subject has completed the final scheduled visit at year 2, at baseline for those with normoglycemia

Or

- When the trial subject has died during trial.

End of trial is defined as the date of the last visit of the last trial subject.

Investigational medicinal products
Semaglutide
Is authorized for clinical use in the European Union. The current authorized indications for once-weekly subcutaneous use in the European Union is

- As Wegovy: along with diet and physical activity to help people lose weight and keep it under control. Either in patients with a BMI of 30 or greater or a BMI of at least 27 mg/kg^2 with concomitant weight-related health problems such as diabetes, hypertension, abnormal lipids, obstructive sleep apnea, documented CCS, previous MI, stroke or peripheral artery disease.
- As Ozempic: treatment in adults whose T2D is not satisfactorily controlled. Either as add-on to other diabetes medications or on its own in patients who cannot take metformin.

In our cohort, the medication is not used at an authorized indication *per se* when the BMI is <27 mg/kg^2. Further, the glucose-lowering medications are expensive and currently not eligible for

subsidies in Denmark unless you have T2D. However, it has been shown to reduce the risk of cardiovascular outcomes in patients with BMI ≥27 mg/kg^2 without diabetes and is used in patients with T2D with a BMI <27 mg/kg^2. Due to the large amount of safety data in these cohorts, we find it reasonable to use it in a prediabetes and CCS cohort when using the IEC criteria for prediabetes, as the current diabetes diagnosis threshold is defined according to the risk of retinopathy. Further, it has been proposed to intervene before the development of manifest diabetes in certain individuals with diabetes-related complications or at a particular high risk of developing T2D.

The target dose of a maximum of 2.4 mg subcutaneously once-weekly is chosen based on the current maximum dose to treat patients for overweight or obesity, and previously used in clinical trials such as SELECT. To minimize gastrointestinal side effects, gradual dose escalation is conducted as previously described.

Trial subjects will be instructed to inject the medication once-weekly (preferably the same day of the week), by a pre-filled pen-injector. Injections may be administered in the upper arm, abdomen or thigh at any time of the day, with or without meals. Needles will be provided.

If one dose is missed, it should be administered as soon as possible, except if the time to next dose is <48 hours. In the last case, the missed dose should not be administered. The regular dosing day of the week should not be changed due to a missed dose.

Dapagliflozin
Is authorized for clinical use in the European Union.
The current authorized indications for dapagliflozin use in the European Union are:

- T2D: Individuals from 10 years of age whose diabetes is not satisfactorily controlled
- Chronic heart failure: in symptomatic patients with a reduced ejection fraction
- Chronic kidney disease: in adult patients

In our study cohort, the medication is not used at an authorized indication. However, as for semaglutide, there is a large amount of safety data in patients with T2D, renal disease, or heart failure, and we find that it is reasonable to use in a prediabetes and CCS cohort without expecting safety issues beyond that of the established indications. Again, the current diabetes diagnosis threshold is defined according to the risk of retinopathy. Further, it has been proposed to intervene before the development of manifest diabetes in certain individuals with diabetes-related complications or at a particular high risk of developing T2D.

Generally, the recommended dose is 10 mg once daily. Therefore, we have chosen this dose as standard in the current trial. The dose is taken orally as a tablet.

Accountability and administration
Only trial subjects that are enrolled may use and self-administer the trial products. Further, only authorized site staff may supply or administer trial product. Both semaglutide and dapagliflozin are acquired especially for the current trial. Products will be provided at each visit for the period until next visit.

The investigator is responsible for drug accountability and record maintenance, which should be done at pen level. Any returned, expired, or damaged products must be stored separately from non-allocated trial products.

Trial subjects

Inclusion and exclusion criteria

We will include patients aged 18 to 80 years, CCS, and prediabetes (HbA1c 42-47 mmol/mol) or normoglycemia (HbA1c <39 mmol/mol). Patients with a recent MI are seen at baseline minimum 30 days after MI. Prediabetes or normoglycemia is ensured by a measurement within six months before screening and repeated at screening. Both measurements must be within the indicated range. HbA1c is not valid if a person has anemia or a recent blood transfusion, therefore such persons are excluded. Anemia is defined as a hemoglobin <7.3 mmol/l for women and <8.3 mmol/l for men. We want to examine persons without diabetes, the latter defined as any HbA1c >47 mmol/mol, a previous diabetes diagnosis, or current/previous usage of any diabetes medications; thus, these are excluded.

The following exclusion criteria are due to (relative) contraindications to initiation of treatment with either semaglutide or dapagliflozin: previous pancreatitis, current pregnancy, breastfeeding or fertile women who do not use birth control, or strongly reduced liver function. For women with childbearing potential (following menarche and until becoming post-menopausal unless permanently sterile), a negative pregnancy test must be performed prior to inclusion. Highly effective contraception must be used until 5 weeks after discontinuation of medical treatment and appropriate methods include combined hormonal contraception or progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence.

Due to a potential indication for initiation of SGLT-2i and a potential influence on the validity of the HbA1c measurement, patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 are excluded. Owing to a potential influence on the validity of the HbA1c measurement, patients with chronic alcohol abuse, known hemoglobinopathy, or intake of mediations known to affect HbA1c, will be excluded. Finally, patients with heart failure and NYHA class III or IV are excluded due to unreliability of the fibroscan in these patients.

Table 4

Inclusion criteria	Exclusion criteria
- Chronic coronary syndrome with documented coronary artery disease. In the case of previous MI, at least 30 days between the event and randomization is required. - Prediabetes defined as HbA1c 42-47 mmol/mol (IEC criteria) OR normoglycemia defined as HbA1c <39 mmol/mol - Age 18 to 80 years	- eGFR <30 mL/min/1.73 m^2 - Previous diabetes diagnosis, previous HbA1c >47 mmol/mol, or current/previous usage of diabetes medication - Anemia, recent bleeding or blood transfusion (<3 months) - Previous pancreatitis - Pregnancy, breastfeeding, or fertile women who do not use highly effective contraception - Strongly reduced liver function - Chronic alcohol abuse - Known hemoglobinopathy and other conditions with effect on erythrocyte lifespan - Intake of medications with known effect on HbA1c validity such as: antiretroviral medications,

	trimethoprim, sulfamethoxazole, sulfasalazine hydroxyurea, dapsone, acetylsalicylic acid (>3 g/daily), high dose vitamin C and E. - Heart failure with NYHA class III or IV

Trial subjects must be capable of giving informed consent as assessed by the investigator.
Patients with BMI<25 kg/m^2 will be assessed individually by an investigator for eligibility (e.g., whether initiation of a GLP-1 RA with potential weight loss is clinically justifiable).

Withdrawal of consent
A trial subject may withdraw consent at any time.
If withdrawal is considered, the subject will as an alternative be offered a more flexible participation in the trial, such as fewer visits or conversion to phone contacts if possible. Alternatively, treatment pause could be suggested. Nonetheless, completing the baseline, 1-year and 2-year visit should always be encouraged.

There is no obligation to give a reason for withdrawal, however the investigator should make a reasonable effort to try to uncover the reason(s), as the primary reason for withdrawal in such case should be sought specified, while respecting the trial subject's rights.

Trial subjects leaving the study will not be replaced by new subjects.

Discontinuation of study treatment
Semaglutide
Temporarily/permanent in case of
1) Suspected pancreatitis
2) Pregnancy or breastfeeding
3) Intention to become pregnant (discontinuation at least 5 weeks before end of contraceptive method)
4) Treatment with another GLP-1 RA
5) Diagnosis of type 1 diabetes
6) Diabetic ketoacidosis
7) Other safety concerns, at the discretion of the investigator

For re-initiation of medication, the start dose should be considered at a reduced dose if at least 4 consecutive doses are missed.

Dapagliflozin
Temporarily/permanent in case of
1) Recurrent cystitis or genital mycosis
2) Diabetic ketoacidosis
3) Diagnosis of type 1 diabetes
4) Pregnancy or breastfeeding
5) Intention to become pregnant
6) Hypovolemia, dehydration or hypotension
7) Other safety concerns, at the discretion of the investigator

Neither temporary nor permanent discontinuation of medicinal treatment will lead to withdrawal from the trial.

Treatment of trial subjects

Investigational medicinal products

Wegovy active substance: semaglutide.
Forxiga active substance: dapagliflozin propanediol monohydrate (international common name: dapagliflozin)

After the end of trial, trial subjects are to be treated at the discretion of the investigator. Generally, glucose-lowering medications will be discontinued, whereas any initiated treatments for dyslipidemia and hypertension should be continued.

The delivery of products to the trial site, the inventory at the site, the use of medicine by each subject, and the return of used/unused products will be recorded continuously. Records will include dates, quantities, batch/serial numbers, expiration dates, and the unique code number of the investigational product and trial subjects.

Patient compliance to semaglutide will be assessed by tracking delivery of medication to each trial subject as well as any returned medicine and packaging.

Semaglutide
During the intervention period, the medication is administered once-weekly subcutaneously at a maximum dose of 2.4 mg. Needles used must be authorized.
Trial product must be stored in a refrigerator (2-8 °C) until use of each pen is initiated. The pen under current use may be stored for a maximum of 6 weeks at room temperature (below 30 °C), or in a refrigerator (2-8 °C). Medication should be protected from light and not let to freeze.

Dapagliflozin
During the intervention period, the medication is administered daily orally as a tablet at a maximum dose of 10 mg if indicated. There are no requirements for trial product storage.

Concomitant treatment

Medical treatment initiated before and during the trial is recorded in eCRFs upon study visits.

Efficacy assessment

Blood samples: HbA1c, hemoglobin, creatinine, cystatin-C, sodium, potassium, hs-CRP, lipids (LDL, HDL, triglycerides, cholesterol, non-HDL), c-peptide, fasting insulin and glucose (HOMA-IR), amylase, alanine aminotransferase, FIB-4, ADAPT-score, PRO-C3, and CD163.
Samples of plasma and serum for a biobank, for batch analyses of PRO-C3, CD163, c-peptide and insulin.
The samples will be analyzed at baseline, 1-year and 2-year follow-up, and changes will be assessed statistically. Apart from HbA1c - our primary outcome in STUDIES II and III - blood samples are generally indicated due to potential medications for the interventional arm, or used as secondary study outcomes to elucidate changes and differences between the two cohorts.

Urine sample: albumin and creatinine for calculation of albumin-creatinine ratio. A ratio of 30-300 mg/g creatinine indicates moderate albuminuria and a ratio >300 mg/g creatinine indicates severe albuminuria.

Vital measures: blood pressure and pulse. These will be measured by conducting three measurements, whereof the mean of the second and third measurement is recorded. The information is used to adjust the medical treatment in the case of hypertension in the intervention group. At baseline, 1-year and 2-year follow-up it provides information on prevalence of participants reaching treatment goals.

Body metrics and composition assessment: Height is measured without shoes (centimeters). Body weight is measured without shoes and wearing light clothing only (kilograms). Waist circumference is measured midway between the lower rib margin and the iliac crest in standing position while breathing normally (centimeters). The measuring tape should touch the skin but not compress tissue. Information is obtained to gain knowledge on any weight loss or gain, crude and as BMI, as well as related changes in waist circumference. Body composition is assessed non-invasively using a bioelectrical impedance analysis at 50 kHz conducted with a stand-on multi-frequency stand-on body composition analyzer (Seca mBCA 515, Seca GmbH, Hamburg, Germany).

Eye examinations: visual acuity, fundus photographs and OCT scans are assessed by experienced specialists regarding grade of diabetic retinopathy according to International Clinical Disease Severity Scale for diabetic retinopathy, and presence of diabetic macular edema. Grade 0 denotes no diabetic retinopathy. Grade 1-3 involves different stages of non-proliferative diabetic retinopathy. Grade 4 represents proliferative diabetic retinopathy [24]. Retinal reactivity (changes in vessel diameter) as examined by RVA is evaluated by experienced specialists.

Nerve examination: We will conduct a monofilament test, which is a sensory test where the examiner applies a 10 g monofilament perpendicular until it bends to the skin of the feet in predefined locations. Wounds and hyperkeratotic areas are to be avoided. If the touch is not registered in one location, the tactile sensation is considered reduced. The number of touches that the participant sense and correctly locate will be registered.
Further, cardiac autonomic neuropathy will be assessed using a handheld Vagus™ Device (Medicus Engineering), which evaluates the heart rate and the heart rate variability via the palm of the hands as the device measures electrical signals generated by each heartbeat. First, a 5-minute baseline heart rate measurement during rest is done. Subsequently, the device guides the subject through standardized tests of three situations lasting one minute each: changing position from supine to upright, expiration and inspiration, and during forced expiration (Valsalva) [25]. Test results are compared with available reference values from Medicus Engineering. One abnormal test result indicates early signs of cardiac autonomic neuropathy categorized borderline, whereas at least two abnormal test results confirm cardiac autonomic neuropathy.

FibroScan: Liver transient elastography with CAP simultaneously assess liver steatosis and fibrosis by combining two key parameters: CAP, which quantifies the level of liver steatosis, and the Liver Stiffness, which evaluates liver fibrosis, as indicators of MASLD severity. Steatosis will be graded as S0-S3, fibrosis as F0-F4.

Safety evaluation

The safety of all randomized trial subjects is continuously monitored based on information recorded at each visit from the initiation of medication to the end of treatment (five weeks after discontinuation of semaglutide). In this information, potential adverse events (AE) and serious adverse events (SAE) are identified.

An AE is any untoward medical event (symptom or illness) of a trial subject after initiation of study medication. There is not necessarily a connection between the AE and the trial treatment.

A SAE is defined as an adverse event that fulfill at least one of the following criteria: results in death, is life threatening, require inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity or results in a congenital anomaly/birth defect.

The investigator will assess the severity and likely causality between the trial medication and the incident. To judge the latter, the latest product resumé will be consulted. In case of a likely causality with a SAE this is defined as a serious adverse reaction (SAR). Whether it is a suspected or unexpected serious adverse reaction (SUSAR) is assessed by product resumé consultation.

All adverse reactions will be followed up by the investigator until resolution or stabilization. The type of follow-up will depend on the nature and severity of the adverse reaction and may include physical examination, laboratory testing, or specialist evaluation.

Concomitant illness is any illness present at the start of the trial. Only significant worsening of such will lead to recording. Outpatient visits will generally not be recorded if related to a known concomitant illness.

Reporting procedure

All SAE, SAR and SUSAR must be reported to the sponsor by the investigator within 24 hours of first gaining knowledge about the event.

The sponsor is obliged to immediately report suspected serious unexpected adverse reactions (SUSARs) that occur in connection with the clinical trial.
The deadline for the sponsor's reporting of SUSARs must consider the seriousness of the side effect, and must be as follows:

a) in the case of fatal or life-threatening suspected serious unexpected side effects, as soon as possible and in any case no later than seven days after the sponsor has become aware of the side effect.

b) in the case of suspected serious unexpected side effects that are not fatal or life-threatening, no later than 15 days after the sponsor has become aware of the side effect.
Sponsor must report SUSARs to the Eudravigilance database.

In Central Denmark Region/Aarhus University, the GCP unit at Aarhus University Hospital has the correct user access and training in reporting SUSARS to Eudravigilance database and will take care of reporting SUSARs in collaboration with the sponsor.

Once a year an annual safety report will be submitted to CTIS.

The sponsor shall via CTIS notify about serious breaches. A ‘serious breach’ means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

Statistics

Sample size determination

We estimated a reversal rate from prediabetes to normoglycemia of 62% in the intervention therapy arm and 30% in the conventional therapy arm. Semaglutide has previously demonstrated an ability to induce reversal to normoglycemia in 70.8 % of patients with BMI $\geq$ 27 kg/m^2 and HbA1c 42-47 mmol/mol at three years, with the lowest HbA1c observed within the first year [26]. In the present trial, participants with a lower BMI are also eligible for inclusion. Accordingly, the estimated reversal rate in the intervention arm has been conservatively set, despite the potential addition of Forxiga to the treatment regimen. In the same reference trial, a reversal rate of 19% was observed in a comparable placebo group. This has been used to set a conservative estimate for the conventional therapy arm in the current study.

Assuming an alpha cut-off of 5% and power of 90%, 49 trial subjects are needed in each arm. To account for withdrawal of consent or a fatal event prior to end of 1-year follow-up, a total of 108 trial subjects will be randomized.

Analysis population

The intention-to-treat population will consist of all participants randomized and examined at baseline. The as-treated population will examine the treatment actually received by the participant. We intent to primarily use the intention-to-treat population for our analyses, secondarily the as-treated population.

The trial will be terminated after 2 years of follow-up for all trial subjects.
Analyses for STUDY I will be conducted after all participants have completed the baseline examination, for STUDY II after all participants have completed 1 year of follow-up, and STUDY III after all participants have completed 2 years of follow-up.
Missing information of any of the variables included the multivariable Poisson regression analysis (sex, smoking, hypertension, alcohol intake, peripheral artery disease, and BMI) will be handled through multiple imputations using chained equations assuming data are missing at random[27, 28] The number of imputations will be determined according to the proportion of participants with missing information. We will include all prespecified covariates intended for the multivariable regression analysis in the multiple imputation model, as well as the primary outcome variable in the model to reduce bias.
In case of loss to follow up due to emigration, death or withdrawal, participants will be censored.

Baseline characteristics

Categorial data will be presented as numbers and proportions. Continuous data will be presented as either the arithmetic mean ± standard deviation (SD) in the case of normal distribution, or as the median and the interquartile range in the case of non-normality. Q-Q plots and histograms will be used to assess normal distribution.

STUDY I

Hypothesis: Microvascular diseases and MASLD are more common in patients with prediabetes compared with normoglycemia.

Primary outcome:

- The baseline prevalence of a combined endpoint of nephropathy, neuropathy, retinopathy and MASLD will be reported for both those with prediabetes and normoglycemia. Risk ratios will be estimated by Poisson regression, both crude and adjusted for sex, smoking, hypertension, alcohol intake, PAD, and BMI using normoglycemia as reference.

Secondary outcomes (exploratory):

- The baseline prevalence of nephropathy, neuropathy, retinopathy, or MASLD, respectively, will be reported for both cohorts. Further, the risk ratio will be estimated by Poisson regression, both crude and adjusted for sex, smoking, hypertension, alcohol intake, PAD and BMI.
- The baseline prevalence of a combined endpoint of nephropathy, neuropathy, and retinopathy will be reported for both those with prediabetes and normoglycemia. The odds ratio will be estimated as described above.

STUDY II

Hypothesis: In a randomized setting, it is possible to induce a significantly higher incidence of reversal from prediabetes to normoglycemia in the interventional arm compared with the conventional therapy arm.

Primary outcome:

- The null hypothesis of no difference 1-year incidence of normoglycemia assessed by *chi-square test*. P-value <0.05 is considered significant.
- In exploratory analysis, we will estimate risk ratio using Poisson regression model using a robust variance covariance estimator with the control arm as reference.
- To account for the competing risk of death during 1-year follow-up, we will use the Fine-Gray model to estimate the sub-distribution hazard ratio, and the Aalen-Johansen estimator to calculate 1-year incidence and 1-year risk difference of normoglycemia in sensitivity analysis.

Secondary outcomes (exploratory):

- Secondary outcomes include *T2D* (defined as HbA1c ≥48 mmol/mol) and *normoglycemia* (here defined as HbA1c<42 mmol/mol). The outcomes will be analyzed as described for the primary outcome.

Continuous data:

- Differences from baseline to 1-year follow-up will be estimated in each group. Differences will be presented as either the arithmetic mean ± standard deviation (SD) in the case of normality, or as the median and the interquartile range in the case of non-normality.
- Normally distributed data: a paired t-test will be used to assess the differences within each cohort
- Non-normally distributed data: a Wilcoxon signed-rank test or bootstrapping method will be applied
- An ANCOVA model with intervention as the fixed factor and the baseline of the outcome as a covariate will be used to investigate the association between the interventional arm and the

specific outcome differences as compared to the control arm in the case of normality. In the case of non-normality, a rank-based ANCOVA model will be used.

Other categorical data:

- Differences in prevalence from baseline to 1-year follow-up within groups will be estimated. The null-hypothesis will be tested by McNemar's test within each cohort.
- Risk ratio will be estimated by a Poisson regression model using a robust variance covariance estimator with the control arm as reference.

STUDY III

Hypothesis: The prevalence of patients with prediabetes or T2D (HbA1c ≥42 mmol/mol) is no longer substantially different in the interventional and conventional therapy arm at 2-year follow-up due to recurrence of prediabetes or progression to T2D following termination of glucose-lowering medications.

Main outcome of interest:

- 2-year incidence of HbA1c ≥42 mmol/mol.
- The null hypothesis of no difference 2-year incidence of normoglycemia assessed by *chi-square test*. P-value <0.05 is considered significant.
- In exploratory analysis, we will estimate risk ratio using Poisson regression model using a robust variance covariance estimator with the control arm as reference.
- To account for the competing risk of death during 2-year follow-up, we will use the Fine-Gray model to estimate the sub-distribution hazard ratio, and the Aalen-Johansen estimator to calculate 2-year incidence and 2-year risk difference of HbA1c ≥42 mmol/mol in sensitivity analysis.

Secondary outcomes (exploratory):

- Secondary outcomes include 2-year prevalence of *T2D* (defined as HbA1c ≥48 mmol/mol), *prediabetes* (defined as both HbA1c 42-47 mmol/mol and HbA1c 39-47 mmol/mol) and *normoglycemia* (defined as HbA1c <39 mmol/mol). The outcomes will be analyzed as described for the main outcome of interest.

Continuous data:

- Differences from 1-year follow-up to 2-year follow-up will be estimated in each cohort. Differences will be presented as either the arithmetic mean ± standard deviation (SD) in the case of normality, or as the median and the interquartile range in the case of non-normality.
- Normally distributed data: a paired t-test will be used to assess the differences within each cohort
- Non-normally distributed data: a Wilcoxon signed-rank test or bootstrapping method will be applied
- An ANCOVA model with intervention as the fixed factor and the baseline of the outcome as a covariate will be used to investigate the association between the interventional arm and the specific outcome differences as compared with the conventional therapy arm in the case of normality. In the case of non-normality, a rank-based ANCOVA model will be used.

General considerations

Each of the sub-studies have one prespecified primary outcome/main outcome of interest. Hypothesis testing for this outcome used a two-sided significance level of 0.05. No multiplicity

adjustment will be applied to the primary analysis. All secondary outcomes are considered exploratory, why no adjustments for multiple testing will be applied, as such, p-values should be interpreted descriptively and the results are considered hypothesis generating.

Two-sided 95 % confidence intervals (CI) and p-values will be presented. P-values of <0.05 will be considered indicative of statistical significance.

For studies II and III, analyses will be repeated after stratification for HbA1c at 1-year follow-up in 4 strata: <39 mmol/mol, 39-41 mmol/mol, 42-47 mmol/mol, or >47 mmol/mol, when appropriate. The statistical analyses outlined above will be used.

Any deviations from this statistical analysis plan will be documented as "post hoc" analyses in the publications.

Ethical considerations and data management

The trial will be conducted under monitoring by the local unit of Good Clinical Practice (GCP), to ensure the rights of trial subjects, that data are accurate, complete, and verifiable from source documents, and in compliance with the approved protocol and applicable regulatory requirements. Before initiation of the trial, all necessary approvals will be obtained.

At screening for study participation eligibility, all trial subjects will be identified in relation to examination or treatment at the Department of Cardiology at Aarhus University Hospital due to suspected or known CAD. The investigators at the Department of Cardiology will screen patient files for presence of prediabetes defined by HbA1c 42-47 mmol/mol or normoglycemia defined as HbA1c <39 mmol/mol, angiographically verified CAD, age between 18 and 80, or any exclusion criteria. Patients who meet the inclusion and exclusion criteria, will receive written and oral information on the trial, and informed consent will be collected.

For patients meeting the inclusion criteria, a screening log will be filled out including information on initials, sex, age, inclusion (yes/no), screening date, the responsible physician and if not included, the reason for exclusion. No additional information will be recorded in the eCRF before written consent is obtained. Written consent includes the acceptance of investigator access to the trial-relevant information in electronical patient files. As stated in the participant information document, the trial subjects' consent to the access to source documents and relevant medical records for trial-related monitoring, audits, Independent Ethics Committee review, and regulatory inspection. Patients are informed that their participation is voluntary, and withdrawal is possible at any time. Neither decline to participate nor withdrawal will influence the future treatment of the patient.

All trial subjects have established CAD, thus optimization of treatment of dyslipidemia and hypertension in the interventional therapy arm is indicated and conducted according to guidelines. Further, all randomized trial subjects have prediabetes and a potential diabetes-related macrovascular complication in the form of CAD, which is the rationale for initiating glucose-lowering treatment in the interventional therapy arm. Semaglutide is generally considered safe to use, although with a higher prevalence of gastrointestinal side effects such as diarrhea, nausea and vomiting [11]. Addition of a SGLT-2i is considered safe in patients with T2D [29].

Besides blood samples, none of the examinations are invasive.

For randomized patients their general practitioner is informed of study participation according to the participation information document.

Perspectives
Prediabetes is highly prevalent in the western world. It is strongly associated with obesity and progression to T2D, and may be associated with diabetes-related microvascular diseases. The increasing global burden of obesity and T2D highlights the importance of preventing disease at an early stage and to pursue initiation of timely management.

Our future study results may suggest that the diagnostic cut-point of T2D should be re-defined to a lower HbA1c level, or at least that prophylactic intervention in some cohorts should be initiated already at the stage of prediabetes, as this could be a window of opportunity to intervene at an early stage to prevent further progression to diabetes or development of related complications in high-risk patients.

Data management
Patient data is protected by the General Data Protection Regulation (GDPR).
The primary investigator is responsible for ensuring the accuracy, completeness and contemporary registration of data. According to the European Union regulation, the trial master file will be stored for 25 years after the end of the trial.

Quality of data
In accordance with the ICH-GCP guidelines, the project will be monitored by the local GCP unit. The monitor will closely follow the conduct of the trial, this through periodical visits as well as telephonically/written contact with the investigator.

Financing and insurance

Financing
The study is partly financed by The Novo Nordisk Foundation (grant number NNF22OC0074083).

Conflicts of interests
Sponsor-Investigator and the current trial is supported by a research grant from the Novo Nordisk Foundation (grant number NNF22OC0074083).
Outside this trial, the Sponsor-Investigator has received lecture and/or advisory board fees from Novo Nordisk, has received research grants from Philips, Bayer, and Novo Nordisk, has ongoing institutional research contracts with Novo Nordisk, Philips, Janssen, and ResoTher, and has minor shareholder equity positions in Eli Lilly & Company and Novo Nordisk.

Insurance
In case of any injury related to the trial, patients can seek compensation by contacting "Patienterstatningen". All patients will receive a standard letter of information besides the participant information.

Publication policy

We commit to communicate and disclose the study results regardless of outcome (i.e., whether considered positive, neutral, or negative). This includes publication of manuscripts in English in a peer-reviewed scientific journal. The results will be reported in an objective and accurate manner, and strengths and limitations will be discussed.

As soon as possible and no later than one year after the trial has ended, the summary of the results will be submitted to the CTIS portal.

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