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Protocol for the specialist supervised Individualized multifactorial treatment of new clinically diagnosed type 2 diabetes in general practice (IDA)

– A prospective controlled multicenter open-label intervention study

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ABSTRACT

Introduction. We present the protocol for a multifactorial intervention study designed to test whether individualized treatment, based on pathophysiological phenotyping and individualized treatment goals, improves type 2 diabetes (T2D) outcomes.

Methods and analysis. We will conduct a prospective controlled multicentre open-label intervention study, drawing on the longitudinal cohort of the Danish Centre for Strategic Research in Type 2 Diabetes (DD2). New clinically diagnosed T2D patients in the intervention group will be assigned to receive individualized treatment by their general practitioner. Intervention patients will be compared with a matched control cohort of DD2 patients receiving routine clinical care. Among intervention patients, we will first do pathophysiological phenotyping to classify patients into WHO-defined T2D or other specific types of diabetes (monogenic diabetes, secondary diabetes, etc.). WHO-defined T2D patients will then be further sub-characterized by their beta cell function (BCF) and insulin sensitivity (IS), using the revised homeostatic assessment model, as having either insulinopenic T2D (high IS and low BCF), classical T2D (low IS and low BCF), or hyperinsulinemic T2D (low IS and high BCF). For each sub-type a specific treatment algorithm will target the primary pathophysiological defect. Antihypertensive treatment will be similarly targeted at the specific underlying pathophysiology, characterized by impedance cardiography (relative importance of vascular resistance), intravascular volume, and cardiac inotropy. All treatment goals will be based on individual patient assessment of expected positive versus adverse effects. Web-based and face-to-face individualized lifestyle intervention will also be implemented to empower patients to make a sustainable improvement in daily physical activity and to change to a low-carbohydrate diet.

Ethics and dissemination. The study will use well-known pharmacological agents according to their labels; patient safety is therefore considered high. Study results will be published in international peer-reviewed journals. The study is registered at ClinicalTrials.gov, number NCT02015130.

STRENGHTS AND LIMITATIONS

Strenghts

- The IDA study is a nationwide intervention study in primary care, based on a close cooperation between hospital-based diabetes specialists and general practitioners
- The study includes patients who are newly diagnosed with type 2 diabetes and enrolled consecutively without selection
- Endocrinological assessment of pathophysiological phenotypes will form the basis for individual treatment algorithms, made readily available to primary health care providers.
- The study will clarify if an individualized approach to the pharmacological and lifestyle treatment of type 2 diabetes with individualized treatment goals is associated with a range of improved hard outcomes in everyday clinical practice, including micro- and macrovascular complications and death

Limitations

- The study is not randomized, and potential differences in prognostic factors between intervention and control patients need to be addressed by rigorous statistical methods
- Existing high-quality healthcare registries will be used for assessment of outcomes, rather than primary adjudication of end-points

INTRODUCTION

The importance of individualized glycemic control

Although current advances in the T2D treatment have reduced mortality [1] and possibly complications[2] among T2D patients, they still suffer excess mortality compared to people without diabetes[3]. Poor glycemic control has been linked to cardiovascular morbidity, even below the threshold for diabetes [4],

and increased mortality is seen in the lowest 10th percentile of HbA1c values [5]. This has led to several trials testing intensive glucose-lowering against moderate glucose-lowering strategies [6-8]. Their results have been inconclusive. A meta-analysis of trials of intensive glucose-lowering found no effects on mortality (RR 1.04, 0.91-1.19) or cardiovascular mortality (RR 1.11, 0.86-1.43), while a significant effect (risk ratio 0.85, 0.74-0.96) was observed for non-fatal myocardial infarction, although in analyses restricted to high quality studies there was no favorable effect on all myocardial infarctions (RR 1.34, 0.77-2.35). In addition a potential effect was observed for new or worsening retinopathy (RR 0.85, 0.71-1.03)[9 10]. On the other hand, intensive glucose control was associated with a significant increase in severe hypoglycemic events (RR 2.33, 1.62-3.36) [9] The analyzed trials are heterogeneous with respect to diabetes duration and achieved HbA1c. In UKPDS study intensive glucose lowering to Hba1c of 53 mmol/mol in newly diagnosed T2D was associated with reduced all-cause mortality [11-13]. Intensive glucose lowering of HbA1c to 6.4 in the ACCORD trial treating patients with longer duration of diabetes was associated with an increased risk of all-cause and cardiovascular mortality[6 14]. Post-hoc analyses of the ADVANCE study, which sought to determine the effect of intensive glucose-lowering compared to standard glucose lowering treatment on cardiovascular disease, have shown that patients with severe hypoglycemic events have a higher incidence of micro- and macrovascular events, as well as mortality [15]. These results indicate the necessity for an individualized approach, with differentiated goals for glycemic control. A tight glycemic goal of 48 mmol/mol seems relevant for many patients with newly diagnosed T2D, while patients with former CVD, neuropathy and high risk of hypoglycemic events arguably could aim for Hba1c below 58 mmol/mol[16]. Frail patients should aim for relief of hyperglycemic symptoms and treatment should confer a very low hypoglycemic risk[16].

Improved glycemic control through better pathophysiological phenotyping

Diabetes is classified into type 1 diabetes, Type 2 diabetes, other specific types of diabetes, and gestational diabetes[17]. It has become increasingly clear that diabetes is a more heterogeneous disease [18]. Data

from the Danish Centre for Strategic Research in Type 2 Diabetes (DD2) show that in clinical practice patients with other specific types of diabetes than T2D (for example, glucocorticoid-induced, LADA or secondary diabetes) are often misclassified as classical WHO-defined T2D patients. As the pathophysiology of other specific types of diabetes is potentially different from classical WHO-defined T2D[19] poor glycemic control could be a consequence if the given treatment does not address the underlying pathophysiological defect. Moreover, DD2 data also show that the classical WHO-defined T2D population is heterogeneous and may be further classified according to pathophysiological phenotypes, with potential implications for appropriate glucose-lowering treatment[20].

The importance of individualized blood pressure control

Elevated blood pressure in patients with T2D is associated with cardiovascular death, starting with a systolic blood pressure of 120 mmHg[21]. A recent meta-analysis concluded that when systolic blood pressure was below 140 mmHg, further reduction in blood pressure was associated with increased risk of cardiovascular death in patients with diabetes[22]. However, even under optimal conditions, blood pressure control is very difficult to achieve, with only 50% of patients reaching a systolic blood pressure below 140 mmHg. Impedance cardiography has been shown to increase the proportion of patients who achieve blood pressure control[23], although a recent study in a specialized hypertension clinic could not replicate this finding. However, the incidence of adverse events was significantly reduced in patients in the impedance group[24]. Impedance cardiography offers an assessment of cardiac contractility, vascular resistance, and intravascular volume. In the IDA study, these estimates will be used to guide selection of anti-hypertensive treatment in order to obtain better blood pressure control and to reduce side-effects.

The importance of individualized lifestyle changes

Lifestyle changes are the first-choice treatment for patients with newly diagnosed T2D. However, such changes are often difficult to implement and also costly, if they need to be supervised. Promoting individualized lifestyle changes will be an important part of this study. Our aim is to provide evidence-based

lifestyle interventions that are feasible to implement on an everyday basis. We hope to empower patients to implement changes in their everyday life via face-to-face consultations and novel individualized supportive E-health solutions. We plan to identify and describe patients who will benefit clinically from the E-health solutions being offered and to use this knowledge for large-scale implementation of individualized E-health technology in daily clinical practice.

The importance of multifactorial management of type 2 diabetes

The Steno 2 study underlined the importance of multifactorial intervention in type 2 diabetes with a marked and durable reduction in morbidity and mortality associated with multifactorial intervention[1]. A multifactorial approach is also emphasized in the current diabetes guidelines [16 25]. In the current study we therefore aim to develop specific individualized approaches to the various components of a multifactorial intervention.

The importance of diabetes management in general practice

Primary health care providers have an integrated knowledge of the medical history, social status, and family relationships of their patients, together with a general knowledge of treatment. “The Individualized treatment of newly clinical diagnosed T2D in general practice study” (IDA) is designed to integrate specialist knowledge and examinations into the treatment of patients in primary care. Endocrinological assessment of pathophysiological phenotypes will form the basis for individual treatment algorithms, made readily available to primary health care providers.

HYPOTHESIS

We hypothesize that individualized treatment based on pathophysiological traits and a new guidance strategy will improve glycemic and blood pressure regulation and reduce complications in clinically diagnosed T2D patients, compared with outcomes under current guidelines. We hypothesize that individualized treatment will reduce side-effects and polypharmacy, thereby improving patient compliance

and quality of life. Furthermore, we hypothesize that an individually tailored approach has the potential to improve the cost-benefit ratio of T2D treatment.

AIM

The study's aim is to investigate the effect of a new treatment concept for patients with T2D based on personalized treatment in general practice supervised by specialists. Treatment goals, lifestyle interventions, and pharmacological treatment will be individualized. Medication choices will be based on pathophysiological measurements of possible underlying causes of hyperglycaemia and hypertension in individual patients.

OBJECTIVES

The primary objective of the study is to assess the effect of individualized, multifactorial, interactive, and supervised treatment in patients with T2D, compared to treatment based on contemporary guidelines. The composite clinical outcome measure will encompass all-cause mortality, micro- and macrovascular complications, cancer, and hypoglycemia. Secondary objectives are to assess effects on individual clinical outcomes, socioeconomic costs and quality of life.

METHODS AND ANALYSIS

Setting and design

The study is designed as a prospective controlled multicenter open-label study of a controlled intervention, in the longitudinal DD2 cohort. Newly diagnosed T2D patients are enrolled prospectively in the population-based DD2 cohort. At baseline, the DD2 project collects interview data and biobanks blood and urine samples [26 27]. Following enrolment, each participant is followed over time using data in nationwide registries [28]. This study is one of several planned studies drawing on the cohort [29].

The study setting will be community-based. Patients in the intervention group will be recruited and treated by their general practitioners (GPs). Patients in the control group will be passive study participants, followed longitudinally using information from the DD2 cohort and biobank and linked longitudinal to national registries. Patients in the intervention group will be recruited over 3 years, with clinical examinations at baseline and after 2, 4 and 10 years. The project timeline is shown in Figure 1.

The project builds on the concept of shared care, where specialist knowledge is expanded into the primary care sector. For GPs participating in the study, specialist input will be available by phone during the day and also delivered electronically to each patient's electronic health record (EHR).

Patients and Recruitment

A flowchart of GPs participating in DD2 and IDA is provided in Figure 2. Patients in the intervention group will be recruited from GPs in the region of southern Denmark and the region of Zealand participating in both the DD2 cohort and the IDA study. Patients in the control group will be recruited from GPs participating in the DD2 cohort but not in the IDA study. The selection process for patients in the two groups will be different and adjustment for differences in prognostic factors at baseline is therefore warranted as described in the statistical section.

Intervention patients

A flowchart of recruitment is provided in Figure 3. Participating IDA GPs will be responsible for the initial patient contact, including collection of brief general patient information. If a DD2 patient is interested in the study, the GP automatically will register the patient in the DD2 website, triggering contact by a study nurse who will give the patient detailed study information. This will occur either by phone or during an initial informational meeting. Collection of in-depth patient information, informed consent, and additional screening will take place at central study hospitals prior to the baseline examination.

The following patient inclusion criteria will be used:

1. Member of the DD2 cohort [30]
2. Patient at a GP participating in the IDA study
3. Not diagnosed with Type 1 Diabetes, defined as age <30 years, fasting C-peptide<300pM, and Gad65-ab>20IU/ml (see below)
4. Life expectancy above 2 years
5. No participation in other clinical trials
6. Willing to provide written informed consent

Control patients

Patients for the control group will be recruited from DD2 clinics throughout Denmark not participating in the IDA study (Figure 2). Availability of valid biobanked samples for measuring GAD-ab, P-glucose, and C-peptide will be required to join the control group. As the control group will be created within DD2, neither GP nor patient will be informed, ensuring that the control group is truly blinded.

Patient examination before intervention

Screening will take place at the following four central study sites: Odense University Hospital, Hospital of Southwest Denmark, Næstved Lægecenter, and Holbæk Hospital. A written informed consent will be signed at the baseline visit prior to initiating examination of study participants.

Phenotype evaluation will be performed at the central sites at baseline and after 24 and 48 months. Medical history, medication use, and measures used in the phenotype evaluation will be obtained from the patient. Fasting plasma glucose, GAD65-antibody, and fasting C-peptide will be ascertained from the DD2 database. Repeat measures of cardiac impedance and unobserved automated blood pressure will be taken at the central sites at the following time points, determined by prior blood pressure values:

1) BP≤135/85: impedance measurement repeated after 24 months,
2) 135/85<BP≤145/95: impedance measurement repeated after 12 and 24 months,

3) BP>145/95: impedance measurement repeated after 6, 12 and 24 months.

The results of the phenotype evaluation will be assessed at Odense University Hospital and the results sent to the patient's general practitioner via the electronic health record.

Treatment and implementation of the phenotype evaluation will take place at the GP's office every third month or at the discretion of the GP. The GP will measure HbA1c, the lipid profile, the albumin creatinine-ratio, creatinine, and BMI annually.

Daily physical activity

To measure daily physical activity level, a Axivity AX3 accelerometer (Axivity, Newcastle, UK) will be taped on the thigh and on the lower back. The AX3 is a 11g and 23x32.5x7.6 mm weatherproof accelerometer with a 512MB internal memory and clock. Accelerometers will be fixed directly on the skin using waterproof taping. Subjects will be instructed to wear the accelerometers at all times (including water activities and sleep) during a 10-day period and additional tape will be provided to patients at examination. The accelerometer on the back will be placed on the right side, above the upper point of the posterior iliac crest and next to the spine with its positive x-axis pointing downward and its negative z-axis pointing forward. The accelerometer on the thigh will be placed on the medial front of the right thigh, midway between the hip and knee joints, with its positive x-axis pointing downward and its negative z-axis pointing forward[31]. A sampling rate of 50 Hz will be used and data stored in in the original cwa Axivity file format, but also converted into a binary gt3x compatible file format using a custom made add-on to OmGui Axivity software.

Cardiovascular surrogate markers

Patients with clinically diagnosed T2D within 2 years of their baseline examination will be invited to participate in additional evaluation of the following cardiovascular surrogate markers:

1) *24-hour ambulatory blood pressure monitoring (24ABPM)*

24ABPM will be implemented by means of brachial oscillometric measurements, using the Mobil-O-Graph® system (IEM GmbH, Stolberg, Germany). The device will be set to measure BP every 15 minutes during the day (0700-2300 hours) and every 30 minutes during the night (2300-0700 hours). The patient will be instructed to record when s/he went to bed and got up.

2) *Skin auto fluorescence (SAF) to evaluate advanced glycosolated end-products*

SAF will be measured using the AGE Reader™ (DiagnOptics Technologies BV, Groningen, the Netherlands). Technical details of this non-invasive device have previously been described in detail,[32].

3) *Low-dose non-contrast CT scan to detect coronary artery calcification*

The atherosclerotic plaque burden in the coronary, carotide, aortic, and femoral arteries will be estimated by measuring calcium during a 64-slice CT scan (Discovery VCT; GE Healthcare, Milwaukee, WI, USA) conducted at Odense University Hospital. The scan will be performed with the following parameters: gantry rotation time 500 ms, 16 · 2.5mm collimation, 120 kV tube voltage, 200 mA tube current and a prospectively EGC-triggered scan acquisition gating at 50% of the R–R interval. Scan data will be acquired during an inspiratory breath hold. The CAC Agatston score is computed by summing the CAC scores of all foci in the epicardial coronary system.

4) *Ultrasound of the carotid arteries to evaluate intima media thickness (IMT) and plaques*

IMT will be measured by B-mode ultrasound (Model IE33, Koninklijke Philips Electronics N.V, Eindhoven, The Netherlands), using a linear array transducer (L11-3 with a frequency up to 11 MHz), with acquisition of multi-insonation angles for subsequent analysis with automated edge detection software according to current guidelines,[33].

5) *ECG for approximation of left ventricular hypertrophy*

ECG will be measured digitally (EC Sense Lexor, Cardiolex AB, Solna, Sweden). The following measures of LVH will be calculated:

- Cornell voltage-duration product, defined as the sum of voltage of SV3 and RaVL multipled by QRS duration (in women 0.6mV is added to the voltage)
- Sokolow-lyon voltage, defined as the sum of SV1 and R in V5 or V6, depending on which is larger.

6) *Fundus photo to evaluate retinal vascular changes*

Retinal vascular changes will be assessed through retinal imaging. Two methods will be employed to assess diabetic retinopathy and vascular damage:

- Diabetic retinopathy will be graded using the Early Treatment of Diabetic Retinopathy Study (ETDRS) classification,[34]. Grading is performed in 7 standard fields. The assessed characteristics are graded in specific fields and/or multiple fields. The grading encompasses the following characteristics: microaneurysm, hemorrhages, hard exudates, soft exudates, intraretinal microvascular abnormalities, venous abnormalities, new vessels on disc or elsewhere, preretinal hemorrhage, vitreous hemorrhage, scars of prior photocoagulation, and clinically significant macular edema.
- The retinal arteriolar and venular caliber as described by Hubbard *et al*.[35] All venules and arterioles in the area half to one disc diameter from the disc margin of the diameter are measured

and an averaged measure is derived. The ratio of the venular and arteriolar diameters also is derived.

- Retinal photos will be taken after dilation of both eyes with 1 drop 10% metaoxedrin and mydriacyl 5mg/ml. After 10 min this will be repeated. After a total of 20 minutes, six pictures will be taken of each eye.

  All photographs will be assessed for retinopathy locally as part of the patients' regular screening. Trained ophthalmologists at the Department of Ophthalmology, Odense University Hospital then will assess retinopathy with the methods described above.

Surrogate marker evaluation will take place at baseline and again at two and four years follow-up.

Study interventions

Patients in the control group will not receive study-related interventions, but rather will be treated by their GP according to national guidelines. Patients in the intervention group will receive multifactorial individualized treatment as outlined below.

Anti-diabetic treatment based on pathophysiological phenotypes

Pathophysiological phenotyping will provide the basis for individually guided treatment. At inclusion patients with "other specific forms of diabetes" will be identified. The remaining classical WHO-defined T2D patients will be characterized according to their insulin sensitivity (IS) and beta cell function (BCF).

Other specific types of diabetes are defined as follows:

1) Maturity-onset diabetes of the young (MODY). Patients will be screened for 10 monogenic causes of diabetes.
2) Late autoimmune diabetes of the adult (LADA). Defined as GAD65-ab≥20 IU/ml.
3) Secondary diabetes. Defined as low BCF (HOMA2-beta < 115.3%) and a history of pancreatitis or pancreas resection.

4) Steroid-associated diabetes, defined as use of oral glucocorticosteroids within 3 months of diabetes diagnosis. Genuine-steroid induced diabetes is present when it is known with certainty that diabetes was not present in the 3 months prior to steroid initiation. Patients with known prior T2D or with uncertainty about the timing of diabetes onset and steroid use will be allocated to one of the additional phenotypes described below.

Genuine WHO-defined T2D:

5) Insulinopenic type 2 diabetes. Defined as low BCF (HOMA2-beta < 115.3%) and high IS (HOMA2-S ≥ 63.5 %)
6) Classical type 2 diabetes. Defined as low BCF (HOMA2-beta< 115.3%) and low IS (HOMA2-S< 63.5 %)
7) Hyperinsulinemic type 2 diabetes. Defined as high BCF (HOMA2-beta≥ 115.3%) and low IS (HOMA2-S< 63.5 %)

The classification is hierarchical. The phenotypes have been described previously [20]. BCF and IS will be assessed using the HOMA2 model, calculated based upon fasting C-peptide and fasting plasma glucose. HOMA2-beta is an estimate of the beta-cell function and HOMA2-S is an estimate of the IS. In a healthy population without diabetes or impaired glucose tolerance, median HOMA2-beta was found to be 115.3% and median HOMA2-S was 63.5%. In the study population, values of HOMA2-beta or HOMA2-S above these medians will be defined as “high”, while values below the median will be defined as “low”.

Proposed treatment strategies in the study according to diabetes phenotypes are as follows:

1) MODY. (A) Types 1 and 3 MODY should be treated with glimepiride or repaglinid. (B) Type 2 MODY should be treated with diet. Secondarily, basal insulin can be used. (C) Type 5 MODY should be treated with basal insulin. (D) Rare types of MODY should be treated individually according to specialist assessment.

2) LADA.

   In patients who have IS and BCF equivalent to insulinopenic and classic T2D:

   A) Metformin if BMI>25 kg/m2. B) Basal insulin and meal-time insulin.

   In patients who have IS and BCF equivalent to hyperinsulinemic T2D:

   Treatment equivalent to hyperinsulinemic T2D (see below), with additional information on risk of rapid BCF deterioration and possible absolute need for insulin therapy.

3) Secondary diabetes. Basal and meal-time insulin.

4) Steroid associated diabetes. A) Meal-time insulin. B) Metformin. C) Basal insulin if fasting blood glucose is above 7.0.

5) Insulinopenic type 2 diabetes. A) Metformin. B) Basal insulin. 3) Meal-time insulin.

6) Classical type 2 diabetes.

   In patients without CVD: 1) Metformin. 2) GLP-1 analogue*. 3) Basal insulin. 4) Meal-time insulin.

   In patients with former CVD: 1) Metformin. 2) SGLT-2 inhibitor. 3) GLP-1 analogue*. 4) Basal insulin. 5) Meal-time insulin.

7) Hyperinsulinemic type 2 diabetes. In patients with BMI>35 kg/m2, gastric bypass should be considered according to current national criteria and patient preference. Pharmacological treatment:

   In patients without CVD: A) Metformin. B) GLP-1 analogue*. C) Pioglitazone. D) Basal insulin. E) Meal-time insulin.

   In patients with former CVD: A) Metformin. B) SGLT-2 inhibitor. C) GLP-1 analogue*. D) Pioglitazone. E) Basal insulin. F) Meal-time insulin.

Pioglitazone is not recommended for patients with heart failure or known osteoporosis.

*DDP-4 inhibitors can be used if the patient does not want a GLP-1 analogue. It is recommended that a DDP-4 inhibitor be discontinued if insulin is initiated.

Type of drug within drug classes, dosing, and titration will be chosen at the discretion of the treating physician. Suggestive algorithms will be available to the physicians.

Treatment of hyperglycemia will proceed according to the following individual goals:

1) Optimal control of HbA1c < 48 mmol/mol;
2) Acceptable control of HbA1c < 58 mmol/mol; or
3) Free of symptoms, with best possible HbA1c achieved within this constraint.

All treatment algorithms will be applied according to these predetermined goals. GPs will be free to choose the goal applicable to an individual patient. In patients with neuropathy or pre-existing cardiovascular disease, careful goal assessment is needed. If a patient has a severe hypoglycemic event, has repeated measures of blood glucose below 4.0 mmol/l, or is therapy resistant, the goal should be reassessed. For an in-depth discussion of the motivation for the glucose-lowering algorithm we refer to the supplemental material.

Anti-hypertensive treatment

Treatment of hypertension will be guided by measurements of thoracic impedance, which provide estimates of vascular resistance, intravascular volume, and cardiac inotropy. These measurements will be used to guide the pharmacological treatment of arterial hypertension. Principles of drug class choice will be as follows:

1) When hypertension or microalbuminuria are present, patients should be treated with an ace-inhibitor (or a angiotensin-2-antagonist), regardless of the result of the impedance measurement.
2) High vascular resistance, as the only abnormal impedance measure, should be treated with a calcium-channel antagonist (dihydropyridins) (CCBs) in addition to an ace-inhibitor.

3) High intravascular volume, as the only abnormal impedance measure, should be treated with a thiazide in addition to current anti-hypertensive treatment. If the patient already is receiving a thiazide in maximum dose, an aldosterone receptor antagonist should be added.
4) In cases of high vascular resistance and high intravascular volume (more than double the vascular resistance in relative terms), diuretics (thiazide or secondarily aldosterone receptor antagonist) should be increased, comparable to the maximum dose of one new drug. As a next step, a CCB should be added. Finally, an aldosterone receptor antagonist should be increased to its maximum dose.
5) In cases of high vascular resistance and high intravascular volume (but less than double the vascular resistance in relative terms), an ACE inhibitor or CCB should be added, depending on initial treatment. As a second measure, diuretics (thiazide or, less often, an aldosterone receptor antagonist) should be increased comparable to the maximum dose of one new drug. As a third measure, CCB should be titrated to its maximum dose. Finally, an aldosterone receptor antagonist can be increased to its maximum dose.
6) High inotropy is addressed only when the patient receives an ACE-inhibitor, thiazide, and CCB and the impedance measurement is made while the patient is receiving this treatment. Other abnormalities need to be addressed first. Carvedilol up to 50mg is recommended.

The maximum dose of bendroflumethiazide is considered to be 5.0 mg, that for hydrochlorthiazide is 50 mg, and that for spironolactone is 50 mg. In cases in which the eGFR is below 30 mL/min/1.73m^2, high ceiling diuretics are substituted for thiazides. Non-hypertensive indications for anti-hypertensive medication overrule this algorithm.

Impedance measurements also are used to downgrade anti-hypertensive treatment, in the following situations:

1) When inotropy is decreased, beta-blockers are terminated, or the dose reduced.

2) When hypovolemia is present, diuretics are terminated or the dose reduced.

3) When inotropy is decreased, vascular resistance is normal, and blood pressure is regulated, CCBs can be reduced or terminated.

For patients with macroalbuminuria, the goal of anti-hypertensive treatment will be to achieve a blood pressure <130/80 on 3 drugs, measured as home blood pressure or with an automated blood pressure device. For other patients, the goal is blood pressure<135/80 on 3 drugs. In cases in which control of blood pressure is not achieved with 3 anti-hypertensive drugs, the patient will be referred to a specialist clinic. Blood pressure below 120/70 should be avoided, if necessary by means of down-titration, unless other considerations are present.

Hypertension at study inclusion will be defined by presence of anti-hypertensive treatment or a blood pressure measurement above or equal to 135/80 in the office under standardized conditions using an automated blood pressure device (Mobilograf).

Treatment of dyslipidemia

Treatment with atorvastatin or simvastatin 40mg will be recommended for all patients, regardless of LDL-C. If the treatment goal is not met, atorvastatin 80 mg or rosuvastatin 40 mg will be recommended. Combining lipid-lowering drugs will not be recommended. The treatment goal will be LDL cholesterol ≤2.5mM and LDL cholesterol ≤2.0mM in patients with established cardiovascular disease.

Termination of inefficient medication

The effect of a specific anti-diabetic, antihypertensive, or cholesterol-lowering treatment will be measured. The following efficacy requirements after titration to the full tolerable dose will need to be met:

1) Decline in Hba1c exceeding 0.5 % within 3 months.

2) Decline in systolic blood pressure exceeding 5 mmHg within 1 month.

3) Decline in LDL-cholesterol exceeding 0.5 mM within 1 month.

If the target is not met, the specific treatment should be terminated and replaced by another drug according to the algorithm. The missing effect on blood pressure should be validated by home blood pressure measurements according to national guidelines. For anti-hypertensive medication, another drug within the same class can be tried.

Lifestyle interventions

Supportive individualized M-health initiatives and face-to-face consultations for promoting changes in lifestyle will be used in this study. The aim is to empower patients to achieve sustainable reductions in carbohydrate intake and increase the daily physical activity level.

In the current study, we will integrate dietician-supported self-management by using a commercially Internet platform (Liva) to facilitate interactive communication between dieticians and users, as well as by peer-to-peer support. The platform will be further developed to support individualized education, goal setting and evaluation of diet and exercise behavior as described below. In addition, interactive communication between patient and a personal healthcare professional will allow for asynchronous contact when needed, in the form of video, text, or spoken messages. The advanced interactive platforms will be supported further by an individualized number of face-to-face consultations between the patient and the personal healthcare professional, with whom the patient will be acquainted from the interactive platform.

The current study aims to empower patients to decrease the amount of carbohydrates in their diet (40E% fat, 40E% carbohydrates, and 20E% proteins), while keeping energy intake unchanged or slightly decreased in cases in which the patient seeks weight reduction. We will support individualized changes towards a sustainable increased number of low-carb meals each week. To support these changes, we have designed an Internet and smartphone platform (www.dd2mad.dk) that easily allows individuals to plan, purchase

groceries, and cook low-carb meals for all daily meals, including snacks. A dietician developed the recipes, and the macro-nutritional composition of each recipe has been calculated using "DANKOST" software (Dankost Aps, Copenhagen, DK). The platform is updated monthly with new recipes and will be developed further using a user-driven iterative process. We will implement this platform in the modified Liva.

We aim to empower patients to make a sustainable increase in physical activity level by implementing interval walking. To enable the patients to engage in and maintain correct individualized interval walking we have developed a smartphone application (InterWalk). The application is designed to individually guide duration and intensity of the training in real time based on a small test at the first use of the application. During use, the app automatically monitors exercise intensity, training duration, and walking distance. Following each training session, the app sends the data to a central server[36]. The training data will be available for the patient and the healthcare professionals making it possible to provide evidence-based training feedback to patients, using physical fitness data[37], training duration, and compliance from the App[36]. The InterWalk App will be implemented in the Liva platform. For a discussion of the motivation of the lifestyle intervention see the supplemental material.

Outcomes

The study's primary outcome measure is time to a composite outcome of all-cause mortality, non-fatal myocardial infarction, coronary revascularization, cardiac arrest with resuscitation, hospitalization for heart failure, non-fatal stroke, development or progression of nephropathy or retinopathy (see below), severe hypoglycemia leading to hospitalization, and development of cancer. Development or progression of nephropathy is defined as renal failure (defined by the need for chronic dialysis), development of macroalbuminuria, or doubling of baseline s-creatinine to a level above 200uM. Development of retinopathy is defined as proliferative retinopathy or macular edema that requires laser therapy or vitrectomy, or diabetes-related blindness (Snellen visual acuity below 0.1). Information on deaths will be obtained from the Civil Registration System. Individual diagnoses, operations, and procedure codes will be

obtained from the Danish National Patient Registry (See Table 1). S-creatinine values and albumin-creatinine-ratios will be obtained through the Danish Diabetes Database for Adults.

Secondary outcome measures are all-cause mortality, socioeconomic costs, and quality of life. Quality of life will be assessed with SF-12 and Q-5 questionnaires at study inclusion and after 2 and 4 years.

Tertiary outcome measures are the individual endpoints in the composite endpoint. Other endpoints are

1) time to fatal acute myocardial infarction
2) time to fatal stroke
3) time to lower-limb amputation
4) time to other revascularization procedures and peripheral thrombosis (not cardiac or cerebrovascular events)
5) Overall hospitalizations per 1000 patient-years
6) Treatment adherence, defined as reimbursement of prescriptions, compared to intended treatment dose
7) Time trends of HbA1c, blood pressure, and LDL cholesterol
8) Individual time trends of daily physical activity

Cause of death will be obtained from the Danish Cause of Death Register. Reimbursement of prescriptions will be ascertained through the Danish National Prescription Registry. Intended treatment dose will be obtained through the electronic medicine chart "FMK".

Power calculations

The power calculation was performed using Lakatos normal approximation for a log-rank test of two survival curves. The estimated sample size of 1123 patients will have 80% power to detect a reduction of 20% of the incidence rate of the primary endpoint, with a type 1 error of 5%, during 10 years of follow-up. A composite yearly event rate of 5% is estimated, based on estimated incidence rates of 2.5% per year of

macro- and microvascular complications, 1.5% per year for cancer, and approximately 1% for overall mortality. The hypoglycemic event rate is expected to be less than 0.4%. Due to the database approach, loss to follow-up should be minimal.

Statistical analysis

The advantage of our pragmatic study approach is that our results will reflect effectiveness, harms and costs of individualized treatment in daily practice in primary care, improving generalizability compared to single-exposure RCTs typically conducted among heavily selected patient and clinic populations. On the other hand, GP practices and their patients are self-selected to participating in the IDA intervention in our study, and will be non-blinded to receiving this treatment. The main methodological challenge for our proposed study will therefore be to address possible confounding caused by imbalance of prognostic factors in participants versus controls. We will use appropriate statistical methods for dealing with confounding, including regression analyses and propensity score matching.

Confounders

Covariates expected to be confounders will be selected according to available evidence and knowledge, and will include the following:

1) *General variables:* Age, gender, diabetes onset, DD2 enrollment year, time from DD2 enrollment to IDA study entry, GP and place of residence (municipality)
2) *Lifestyle variables:* Smoking, alcohol consumption, physical exercise (self-reported and accelerometer measurements)
3) *Comorbidity:* Each of the individual strata of the Charlson Comorbidity Index, except diabetes, hospitalization for hypoglycemia, chronic dialysis, laser treatment of retinopathy/maculopathy, vitrectomy, chronic heart disease, angina pectoris, any revascularization procedure, lower-extremity amputation, atrial fibrillation and history of psychiatric disease (8 covariates defined by ICD-10: DF1 to DF8)

4) *Socioeconomic variables:* Education, employment, income, social support
5) *Clinical variables:* Blood pressure, BMI, waist circumference, LDL-C, HDL-C, triglyceride level, creatinine level, urine albumin creatinine ratio, diabetes phenotype
6) *Medication use:* Aspirin, statins, anti-coagulating drugs, thiazides, ACE-inhibitors or angiotensin 2 antagonists, calcium channel antagonists, beta-blockers, potassium-sparing diuretics, metformin, sulfonylurea, DD4-inhibitors, GLP-1 analogues, SGLT-2 inhibitors, insulin, oral corticosteroids, and number of redeemed drugs (including the above drugs)

Ascertainment of confounder variables will be through the DD2 cohort and registries. Comorbidity is defined as all diagnoses registered from 1977 until enrollment. Socioeconomic variables are defined as the values recorded in the enrollment year. Medication use is defined as redeemed prescriptions 1 year prior to enrollment. Clinical variables are defined by the value measured closest to enrollment, no more than 1 year prior to enrollment and 1 month after enrollment.

Cox regression analysis

Follow up will extend for 10 years from the date of IDA intervention start until first of any of the individual composite outcome events, emigration out of Denmark, or end of study 1.January 2018, whichever comes first. For patients in the control group the entry date will be the date of DD2 enrollment or date of the overall IDA study initiation 1.January 2015, whichever comes last. We will construct survival curves for intervention and control patients and compute cumulative incidence rates. We then compute incidence rate ratios (IRRs) with 95% confidence intervals (CIs) for intervention patients compared with controls using Cox regression analysis and controlling for confounders described above. Stratified analyses will be performed by gender, age below/above 60 years, eGFR below/above 60, former CVD, and diabetes phenotype with test for interaction.,.

Propensity score analysis

In a second analysis, we will use propensity score matching. For this analysis, we will compute the probability of each DD2 cohort non-IDA-intervention patient being included in the IDA intervention arm in a logistic regression analysis, conditioned on the patient's covariate profile. Next, we will match each intervention patient to a DD2 control patient with the closest propensity score in a 1:3 fashion and eliminate the remaining controls. The matching will be performed in a random sequential order. After determining that the covariates are balanced, between the two treatment groups (see supplemental material), we will conduct a matched Cox regression analysis without further adjustment. If any covariate is not balanced a model with adjustment for non-balanced covariates will be made. The assumption of proportional hazards in the Cox models will be assessed graphically.

ETHICS AND DISSEMINATION

The study will use well-known pharmalogical agents and bariatric interventions. Thus the safety of the patients is considered high. Patients in the intervention group will provide written informed consent before participation. The study will be conducted in compliance with the principles set forth in the Declaration of Helsinki and the Good Clinical Practice (GCP) Guidelines. The study has been approved by the Regional Committee on Medical Health Ethics (Region of Southern Denmark S-20120186), the Danish Data Protection Agency, and the Danish Health and Medicines Authority (journal nr. 2012120204).

All subjects will be identified by an unambiguous subject code that can be linked to the civil registration number. The subject code will be used as a pseudo-anonymization code throughout the study. Handwritten source data (CRFs) or hard-copy source data will be securely safeguarded against unauthorized access and kept under lock, with access only by authorized persons. Electronically reported source data will conform to good clinical practice standards by using the RedCap data collection system and the DD2-established data

collection system. Both systems have a high level of security and use data verification and detailed logging during reporting.

Most study data will be stored in OPEN – a custom-designed study database secured against unauthorized access. OPEN is a research service provided by the University of Southern Denmark that enables researchers to store research data in accordance with national legislation and requirements for data logging, password security, and backup.

Study results will be made public via articles in national and international peer-reviewed journals, which will be accessible at www.dd2.nu. Positive, negative, and inconclusive results will be published according to the Vancouver Principles. The results will be disseminated through www.clinicaltrials.com and the Danish Diabetes Association.

PERSPECTIVES

IDA is one of the first studies to formalize a specific implementation of individualized medicine in treating T2D. The ultimate goal is to improve quality of life and reduce complications in T2D patients –in a manner requiring less medication and fewer resources.

Competing interests statement

JEH is a member of the MSD and Boehringer National Advisory board. HBN has received personal lectures fees from Novo Nordisk, outside the submitted work. MHO has received a clinical research grant from the Novo Nordisk Foundation. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of those studies have any relation to the present study. All other authors declare no competing interests.

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Authors' contributions

The study concept was developed by HBN and JEH. HBN, JEH, MHO, JVS, JSN, TBO, RWT and SF designed the study. Principal Manager of the DD2 study is JSN. JVS drafted the article and JSN, RWT, HBN and MHO revised the draft. All authors participated in the critical revision of the intellectual content of the report.

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Table 1. Endpoint definitions.

ICD-10 codes for diagnoses and operation codes were obtained from the Danish National Patient Registry, as follows:

Non-fatal myocardial infarction	I21-23, T822A, T823 (without death within 30 days)
Coronary revascularization	KFNG, KFNA, KFNB, KFNC, KFND, KFNE, KFNF, KFNH, KFNW, KFLF
Cardiac arrest with resuscitation	I46
Hospitalization for heart failure	I50, I11.0, I13.0+2 (only as a-diagnosis)
Non-fatal stroke (including cerebral hemorrhage)	I61, I63, I64, KAAL10, KAAL11 (without death within 30 days)
Development of nephropathy	BJFD2 (chronic dialysis) or UACR>300g/mg or Doubling of creatinine (if creatinine >=200uM)
Development of retinopathy	KCKC10, KCKC15 (Laser therapy) or KCKD65 (vitrectomy) or H540+1+4 (blindness)
Severe hypoglycemia leading to hospitalization	E15, E160-2, T383A
Cancer (except basocellular carcinoma)	C00-99 (except when ZM809xx are added)
Amputation of the lower limbs:	KNEQ, KNFQ, KNGQ, KNHQ
Revascularization procedures and peripheral thrombosis (not cardiovascular or cerebrovascular disease)	I74, N280, K550-1, K558-9, H340-2 KPBE+F+H+N+P+Q, KPBW, KPGH10. KPGE+F+H+N+P+Q, KPGW99, KPGW20, KPEE+F+H+N+P+Q+W, KPFE+H+N+P+Q+W,

	KPGH20+21+22+23+30+31+40+99, KPDU74+82+83+84, KPEU74+82+83+84, KPFU74+82+83+84, KPAE+F+H+N+P+Q, KPAW99, KPAU74, KPCE+F+H+N+P+Q, KPCW99, KPCW20, KPCU74+82+83+84, KPGU74+83+84+99, KPGW, KPWG
Fatal acute myocardial infarction	I21-23, T822A, T823, R96-99 with death within 30 days
Fatal stroke	I61, I63, I64 with death within 30 days

Figure 1. Study timeline.

Figure 2. Recruitment flowchart at GP level

Figure 3. Study timeline.

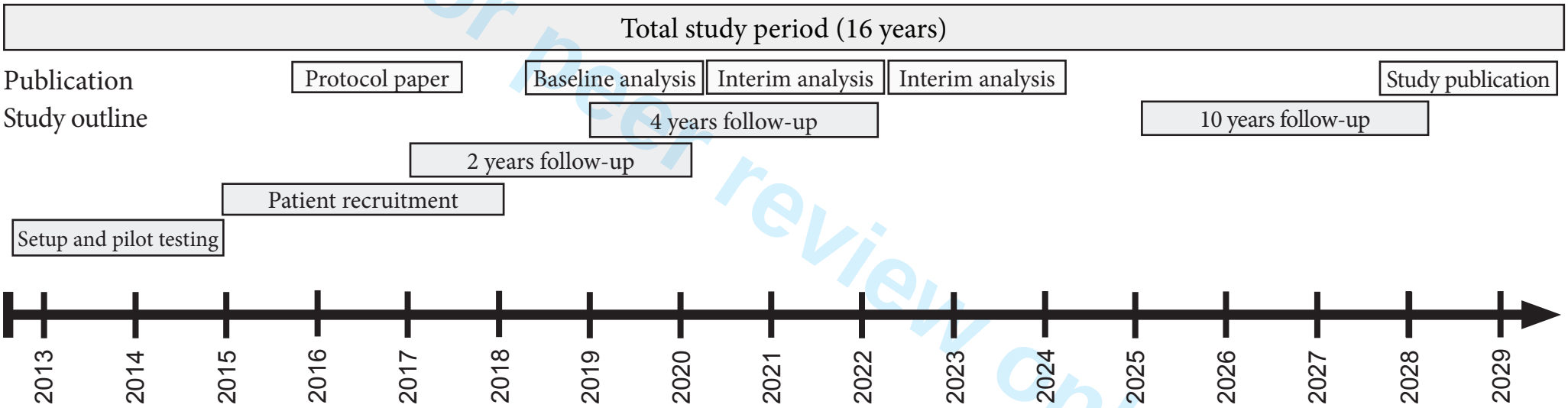
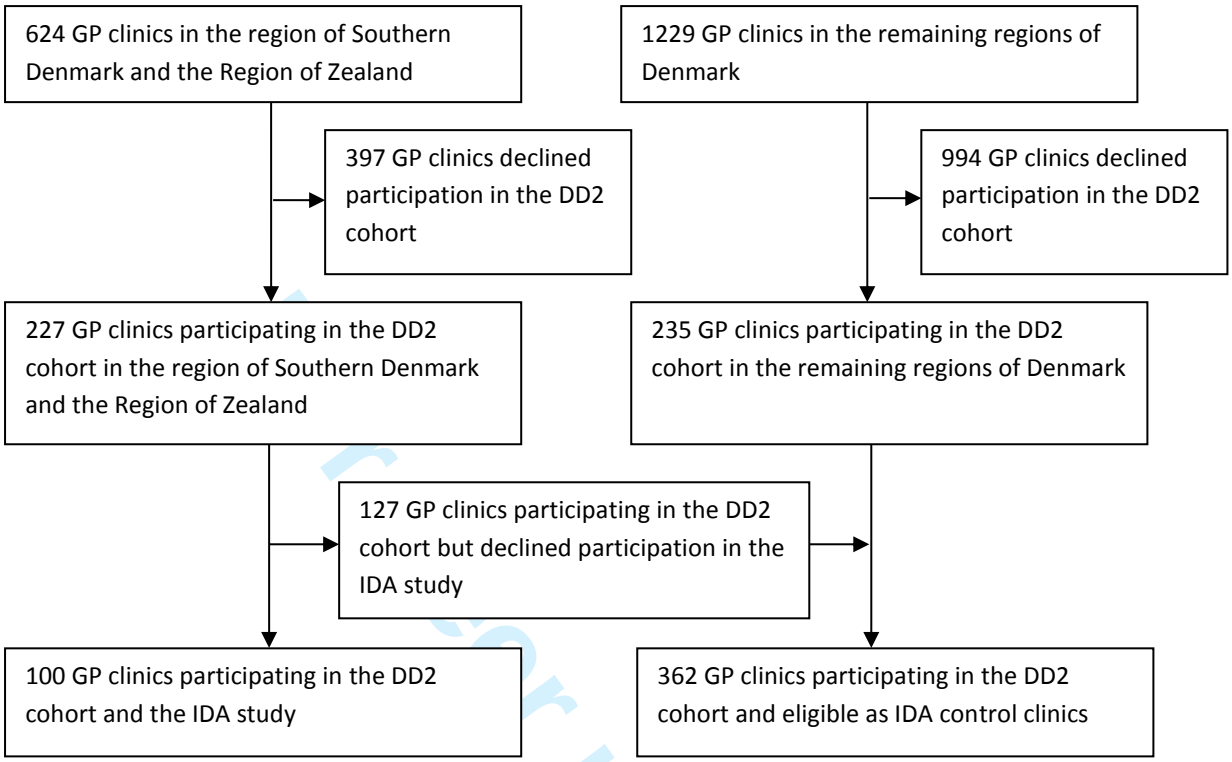
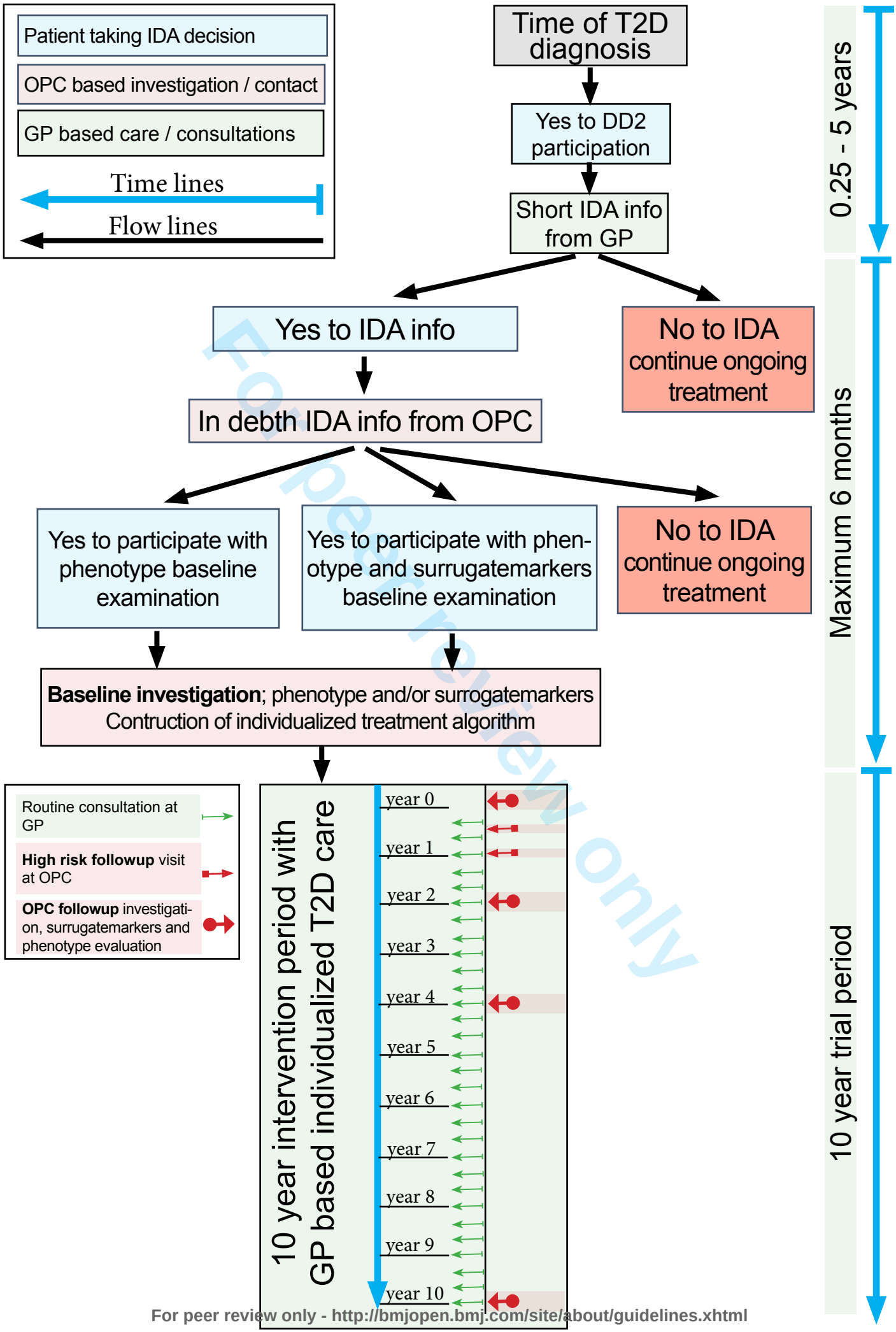


Figure 2. Recruitment flowchart at GP level





Supplemental material

Protocol for the Individualized multifactorial treatment of new clinically diagnosed type 2 diabetes in general practice (IDA)

– A prospective controlled multicenter open-label intervention study

Motivation for the proposed glucose-lowering treatment of specific pathophysiological phenotypes

Ideally, treatment should target the pathophysiological abnormalities. As patients with insulinopenic T2D have beta cell failure, basal insulin and meal-time insulin are recommended. Beta cell failure has been linked to poor response to GLP-analogs [1]. Patients with classical and hyperinsulinemic T2D have high or very high insulin resistance and appear to have increased cardiovascular morbidity at diagnosis,[2] compared to patients with insulinopenic T2D with low insulin resistance. The primary focus in these two groups is thus to target insulin resistance. As hyperinsulinemic patients have severe insulin resistance, glitazones are also recommended for this group. Insulin is introduced earlier in the algorithm for classical T2D, as patients in this group also exhibit a degree of beta cell insufficiency. Metformin,[3], GLP-1 analogs,[4-6] glitazones,[7] and SGLT2-inhibitors,[8 9] are known to decrease insulin resistance. GLP-1 analogues also increase insulin secretion, restore first- and second-phase insulin response, and reduce glucagon secretion and body weight. A meta-analysis of randomized trials of pioglitazone reported a reduced incidence of death, myocardial infarction, and stroke compared to other medications [10]. This finding is supported by favorable effects on cardiovascular surrogate markers [7]. However, the incidence of heart failure was increased by pioglitazone treatment [10].

Evidence is accumulating that SGLT-2 inhibitors decrease the risk of major adverse cardiovascular events, cardiovascular death, heart failure, and death from any cause [11]. SGLT-2 inhibitors also induce weight

reduction. Sodium retention is decreased by GLP-1 analogs and SGLT-2 inhibitors, and increased by pioglitazone. The rationale for introducing pioglitazone after GLP-1 analogs and SGLT-2 inhibitors is to minimize pioglitazone-induced sodium and fluid retention, thereby preventing heart failure in susceptible patients. Bariatric surgery has been shown to reduce mortality, cardiovascular morbidity, and cancer incidence compared to usual care [12-14], and analyses restricted to diabetic patients have had the same results [15]. Diabetes remission rates also remained high after 10 years [12]. The Swedish Obese Subjects (SOS) study found that fasting insulin levels predicted a successful surgical outcome, in terms of mortality and CVD [12]. This supports bariatric surgery as a recommendation for patients with hyperinsulinemic T2D.

The degree of evidence varies for managing specific forms of diabetes. As patients with secondary diabetes have a primary beta cell defect, basal and meal-time insulin are recommended [16]. Patients with latent autoimmune diabetes of the adult (LADA) have diabetes-related antibodies, as seen in type 1 diabetes, but initially present as a T2D phenotype. Over time patients with LADA develop beta cell insufficiency, and therefore basal and meal-time insulin are recommended. A review concluded that insulin therapy preserves beta cell function better than sulphonylureas, although relevant studies on treatment of LADA are scarce [17]. Since many patients with LADA have a type 2 diabetes phenotype with adipositas, metformin is also recommended if BMI>25kg/m^2. Maturity-onset diabetes of the young (MODY) encompasses several monogenetic forms of diabetes. Patients with MODY3 and MODY1 have insulin secretion defects that respond to sulphonylureas[18 19]. Patients with MODY2 have a mutation in the glucokinase gene, which alters the set point of glucose control, while glucose regulation is intact [20 21]. Patients with MODY 2 rarely develop complications and the preferred intervention is diet.

Administration of glucocorticosteroids has the potential to induce diabetes onset and to exacerbate existing type 2 diabetes. It has been reported that prednisolone in particular enhances postprandial plasma glucose values in patients without known diabetes, with unchanged glucose levels at night and in the morning [22-24]. The same results have been reported for patients with type 2 diabetes, impaired glucose

tolerance and normal glucose tolerance,[25-27]. Glucocorticoids impair both IS and BCF [28]. Evidence for optimal treatment of steroid-induced diabetes is sparse and based on case reports. Accordingly, there is little consensus regarding treatment. Insulin isophane (NPH) has been advocated [29], as well as prandial insulin [28]. In patients with metabolic syndrome or T2D, it has been found that sitagliptin did not improve GC-induced postprandial glucose excursions. [30 31]. Nateglinid [23 27] and glitazones have shown some benefit [32 33] and metformin has been found to improve postprandial glucose values from well above 11 to below 7.5 mmol/l in one patient[31]. Intravenous administration of exenatide has been observed to improve postprandial glucose values [34], but only when administered at breakfast and lunch [35]. In cases treated with exenatide, addition of SU was needed to achieve glycemic control. A comparative study of NPH insulin and insulin glargine with bolus insulin found that glucose control could be achieved, with no differences between agents [36].

Motivation for the proposed individual lifestyle intervention

Web- and smartphone-based applications are a possible means for effective and time-saving patient counseling. However, they can result in low compliance over time and thus may be unfeasible as stand-alone lifestyle interventions. A Danish internet platform called Liva has been developed during the past decade by a team of dieticians, computer programmers, and physicians as a commercial weight management program. Its guiding principle is to improve the cost-effectiveness of established best practice for dietician-supported weight management by using an Internet platform to facilitate interactive communication between dieticians and users, as well as by peer-to-peer support through the online community. The program was developed iteratively through trial and error from an initial prototype and is now a well-established commercial product used by 10,000 predominantly healthy overweight or moderately obese persons. The effect of online dietician counseling based on this system was examined in a prospective non-controlled pilot study in obese subjects, and an average weight loss of 7.0 kg (95% CI: 4.6 to 9.3 kg) was observed after 20 months,[37].

In Denmark, diet recommendations for the general population and for patients with T2D are 45%-60E% carbohydrates, 10%-20E% proteins, and 25%-40E% fat[38]. It is being debated whether a diet with reduced carbohydrates (40E% fat, 40E% carbohydrates, and 20E% proteins) and an increased amount of unsaturated fat favors glycemic control in patients with T2D compared to current recommendations [39 40]. Several studies support the beneficial effects of the reduced carbohydrate diet on glycemic control for patients with T2D [41].

Poor physical fitness is one of the most important independent predictors of disease progression, morbidity, and mortality for patients with T2D [42 43]. It has been found that supervised exercise increases fitness,[44]. With the increasing prevalence and incidence of T2D, fully supervised training programs for all T2D patients would be very costly and thus unrealistic. We recently tested the feasibility of implementing unsupervised interval walking training (IWT), compared with continuous walking training, among patients with T2D in a four-month randomized controlled trial [45]. We found that IWT, but not continuous walking, had remarkably beneficial effects on physical fitness level and glycemic control. Moreover, this was achieved with a compliance rate of ~90% [45] and high long-term adherence [46]. We later tested the unsupervised IWT modality for 17 months in a setting with a compliance rate of >60%[47]. On this basis, we believe that the IWT exercise modality can be implemented as unsupervised exercise in a real-life setting. To permit large-scale implementation, guide correct training intensity, and improve feasibility for patients, we developed a smartphone application (InterWalk) that can be downloaded free of charge from App Store.

Determination of covariate balance in propensity score matching

The usefulness of the propensity score models can be tested by how well covariates of the intervention and control patients match. The standardized difference should be used to compare covariates:

$$d = \frac{\overline{X}_{intervention} - \overline{X}_{control}}{\sqrt{\frac{s^2_{intervention} - s^2_{control}}{2}}}$$

$$d = \frac{\hat{p}_{intervention} - \hat{p}_{control}}{\sqrt{\frac{\hat{p}_{intervention}(1-\hat{p}_{intervention}) + \hat{p}_{control}(1-\hat{p}_{control})}{2}}}$$

$\bar{x}$ denotes the mean of a continuous covariate. S is the variance. $\hat{p}$ denotes the prevalence of dichotomous covariates. With 1:k matching, the weighted mean should be used. If n control patients are matched per intervention patient, the weight should be 1/n. A difference below 0.1 is considered acceptable and should be achieved for all covariates [48]. The variance ratio should also be estimated as VR= $\frac{s^2_{intervention}}{s^2_{control}}$. Ratios between 0.5 and 2.0 are considered acceptable [49]. If the model does not conform to this criterion, a new model with inclusion of interaction terms and/or higher-order terms will be fitted. A quantile-quantile plot (or similar approach) for each variable (interactions can also be evaluated) should be used to compare the distribution in the intervention and control groups [50].

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Protocol for the specialist supervised Individualized multifactorial treatment of new clinically diagnosed type 2 diabetes in general practice (IDA) – A prospective controlled multicenter open-label intervention study

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Protocol for the specialist supervised Individualized multifactorial treatment of new clinically diagnosed type 2 diabetes in general practice (IDA)

– A prospective controlled multicenter open-label intervention study

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ABSTRACT

Introduction. We present the protocol for a multifactorial intervention study designed to test whether individualized treatment, based on pathophysiological phenotyping and individualized treatment goals, improves type 2 diabetes (T2D) outcomes.

Methods and analysis. We will conduct a prospective controlled multicentre open-label intervention study, drawing on the longitudinal cohort of the Danish Centre for Strategic Research in Type 2 Diabetes (DD2). New clinically diagnosed T2D patients in the intervention group will be assigned to receive individualized treatment by their general practitioner. Intervention patients will be compared with a matched control cohort of DD2 patients receiving routine clinical care. Among intervention patients, we will first do pathophysiological phenotyping to classify patients into WHO-defined T2D or other specific types of diabetes (monogenic diabetes, secondary diabetes, etc.). WHO-defined T2D patients will then be further sub-characterized by their beta cell function (BCF) and insulin sensitivity (IS), using the revised homeostatic assessment model, as having either insulinopenic T2D (high IS and low BCF), classical T2D (low IS and low BCF), or hyperinsulinemic T2D (low IS and high BCF). For each sub-type a specific treatment algorithm will target the primary pathophysiological defect. Similarly, antihypertensive treatment will be targeted at the specific underlying pathophysiology, characterized by impedance cardiography (relative importance of vascular resistance, intravascular volume, and cardiac inotropy). All treatment goals will be based on individual patient assessment of expected positive versus adverse effects. Web-based and face-to-face individualized lifestyle intervention will also be implemented to empower patients to make a sustainable improvement in daily physical activity and to change to a low-carbohydrate diet.

Ethics and dissemination. The study will use well-known pharmacological agents according to their labels; patient safety is therefore considered high. Study results will be published in international peer-reviewed journals. The study is registered at ClinicalTrials.gov, number NCT02015130.

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STRENGHTS AND LIMITATIONS

Strenghts

- The IDA study is a nationwide intervention study in primary care, based on a close cooperation between hospital-based diabetes specialists and general practitioners
- The study includes patients who are newly diagnosed with T2D and enrolled consecutively without selection
- Endocrinological assessment of pathophysiological phenotypes will form the basis for individual treatment algorithms, made readily available to primary health care providers.
- The study will clarify if an individualized approach to the pharmacological and lifestyle treatment of T2D with individualized treatment goals is associated with a range of improved hard outcomes in everyday clinical practice, including micro- and macrovascular complications and death

Limitations

- The study is not randomized, and potential differences in prognostic factors between intervention and control patients need to be addressed by rigorous statistical methods
- Existing high-quality healthcare registries will be used for assessment of outcomes, rather than primary adjudication of end-points

INTRODUCTION

The importance of individualized glycemic control

Although current advances in the T2D treatment have reduced mortality [1] and possibly complications [2] among T2D patients, they still suffer excess mortality compared to people without diabetes [3]. Poor glycemic control has been linked to cardiovascular morbidity, even below the threshold for diabetes [4], although increased mortality is also seen in the lowest 10th percentile of HbA1c values [5]. This has led to

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several trials testing intensive glucose-lowering against moderate glucose-lowering strategies [6-8]. Their results have been inconclusive, and a meta-analysis of trials of intensive glucose-lowering found no effect on mortality (RR 1.04, 0.91-1.19) or cardiovascular mortality (RR 1.11, 0.86-1.43). A significant effect (risk ratio 0.85, 0.74-0.96) was observed for non-fatal myocardial infarction, although in analyses restricted to high quality studies there was no favorable effect for any myocardial infarction (RR 1.34, 0.77-2.35). In addition, a potential effect was observed for new or worsening retinopathy (RR 0.85, 0.71-1.03) [9 10]. On the other hand, intensive glucose control was associated with a significant increase in severe hypoglycemic events (RR 2.33, 1.62-3.36) [9] The analyzed trials are heterogeneous with respect to diabetes duration among included patients, and achieved HbA1c. In the UKPDS study, intensive glucose lowering to an Hba1c of 7.0% in newly diagnosed T2D was associated with reduced all-cause mortality [11-13], and this has recently been confirmed in an observational study design[14]. Intensive glucose lowering of HbA1c to 6.4% in the ACCORD trial among patients with longer duration of diabetes was associated with an increased risk of all-cause and cardiovascular mortality [6 15]. Post-hoc analyses of the ADVANCE study, which sought to determine the effect on cardiovascular disease of intensive glucose-lowering compared to standard glucose lowering treatment, have shown that patients with severe hypoglycemic events have a higher incidence of micro- and macrovascular events, as well as mortality [16]. Together, these results indicate the necessity for an individualized approach, with differentiated goals for glycemic control. A tight glycemic goal of 48 mmol/mol seems relevant for many patients with newly diagnosed T2D, while patients with former CVD, neuropathy, or high risk of hypoglycemic events arguably could aim for an Hba1c below 58 mmol/mol [17]. Frail patients should aim for relief of hyperglycemic symptoms and treatment should confer a very low hypoglycemic risk [17].

Nonvascular outcomes in T2D become increasingly important these years. The incidence of cancer overall and of several specific cancers is substantially increased in patients with T2D compared to persons without diabetes [18 19], and also mortality from cancer is increased [20]. Whether specific glucose lowering therapies are associated with increased or reduced risk of cancer remains uncertain. A meta-analysis has

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reported a possibly reduced cancer risk with metformin and thiazolidinediones therapy, and an increased risk with insulin, sulfonylurea and alpha glucosidase inhibitor use. When the meta-analysis was restricted to RCTs these associations could not confirmed, with the limitation that most RCTs are too short to properly elucidate cancer risk and have heterogeneous comparators [21]. These uncertainties highlight the need for long-term evaluation of therapy not only with regard to micro- and macrovascular disease but also with respect to cancer risk.

Improved glycemic control through better pathophysiological phenotyping

Diabetes is classified into type 1 diabetes, T2D, other specific types of diabetes, and gestational diabetes [22]. It has become increasingly clear that diabetes is a more heterogeneous disease [23]. Data from the Danish Centre for Strategic Research in Type 2 Diabetes (DD2) show that in clinical practice patients with other specific types of diabetes than T2D (for example, glucocorticoid-induced, LADA or secondary diabetes) are often misclassified as classical WHO-defined T2D patients. As the pathophysiology of other specific types of diabetes is potentially different from classical WHO-defined T2D [24] poor glycemic control could be a consequence if the given treatment does not address the underlying pathophysiological defect. Moreover, DD2 data also show that the classical WHO-defined T2D population is heterogeneous and may be further classified according to pathophysiological phenotypes, with potential implications for appropriate glucose-lowering treatment [25]. In addition ethnic differences in the pathophysiology of T2D have been reported [26 27] underlining the importance of both inter- and intra-ethnical heterogeneity in T2D.

The importance of individualized blood pressure control

Elevated blood pressure in patients with T2D is associated with cardiovascular death, starting with a systolic blood pressure of 120 mmHg [28]. A recent meta-analysis concluded that when systolic office blood pressure was below 140 mmHg, further reduction in blood pressure was associated with increased risk of cardiovascular death in patients with diabetes [29]. However, even under optimal conditions, blood

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pressure control is very difficult to achieve, with only 50% of patients reaching a systolic blood pressure below 140 mmHg [30]. Impedance cardiography has been shown to increase the proportion of patients who achieve blood pressure control [31]. A recent study in a specialized hypertension clinic could not replicate this finding, although the incidence of adverse events was significantly reduced in patients in the impedance group [32]. Impedance cardiography offers an assessment of cardiac contractility, vascular resistance, and intravascular volume. In the IDA study, these estimates will be used to guide selection of anti-hypertensive treatment in order to obtain better blood pressure control and to reduce side-effects.

The importance of individualized lifestyle changes

Lifestyle changes are the first-choice treatment for patients with newly diagnosed T2D. However, such changes are often difficult to implement and also costly, if they need to be supervised. Promoting individualized lifestyle changes will be an important part of this study. Our aim is to provide evidence-based lifestyle interventions that are feasible to implement on an everyday basis. We hope to empower patients to implement changes in their everyday life via face-to-face consultations and novel individualized supportive E-health solutions. We plan to identify and describe patients who will benefit clinically from the E-health solutions being offered and to use this knowledge for large-scale implementation of individualized E-health technology in daily clinical practice.

The importance of multifactorial management of T2D

The Steno 2 study underlined the importance of multifactorial intervention in longer-standing T2D with a marked and durable reduction in morbidity and mortality associated with multifactorial intervention [1]. A multifactorial approach is also emphasized in the current diabetes guidelines [17 33]. In the current study we therefore aim to develop specific individualized approaches to the various components of a multifactorial intervention.

The importance of diabetes management in general practice

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Primary health care providers have an integrated knowledge of the medical history, social status, and family relationships of their patients, together with a general knowledge of treatment. “The Individualized treatment of newly clinical diagnosed T2D in general practice study” (IDA) is designed to integrate specialist knowledge and examinations into the treatment of patients in primary care. Endocrinological assessment of pathophysiological phenotypes will form the basis for individual treatment algorithms, made readily available to primary health care providers.

HYPOTHESIS

We hypothesize that individualized treatment based on pathophysiological traits and a new guidance strategy will improve glycemic and blood pressure regulation and reduce complications in clinically diagnosed T2D patients, compared with outcomes under current guidelines. We hypothesize that individualized treatment will reduce side-effects and polypharmacy, thereby improving patient compliance and quality of life. Furthermore, we hypothesize that an individually tailored approach has the potential to improve the cost-benefit ratio of T2D treatment.

AIM

The study’s aim is to investigate the effect of a new treatment concept for patients with T2D based on personalized treatment in general practice supervised by specialists. Treatment goals, lifestyle interventions, and pharmacological treatment will be individualized. Medication choices will be based on pathophysiological measurements of possible underlying causes of hyperglycaemia and hypertension in individual patients.

OBJECTIVES

The primary objective of the study is to assess the effect of individualized, multifactorial, interactive, and supervised treatment in patients with T2D, compared to treatment based on contemporary guidelines. The composite clinical outcome measure will encompass all-cause mortality, micro- and macrovascular

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complications, cancer, and hypoglycemia. Secondary objectives are to assess effects on individual clinical outcomes, socioeconomic costs and quality of life.

METHODS AND ANALYSIS

Setting and design

The study is designed as a prospective controlled multicenter open-label study of a controlled intervention, in the longitudinal DD2 cohort. Newly diagnosed T2D patients are enrolled prospectively in the population-based DD2 cohort. At baseline, the DD2 project collects interview data and biobanks blood and urine samples [34 35]. Following enrolment, each participant is followed over time using data in nationwide registries [36]. The registries have documented high validity [37-39]. The collected data in the study is summarized in table 1. This study is one of several planned studies drawing on the cohort [40].

The study setting will be community-based. Patients in the intervention group will be recruited and treated by their general practitioners (GPs). Patients in the control group will be passive study participants, followed longitudinally using information from the DD2 cohort and biobank [41] and linked longitudinal to national registries. The biobank contains whole blood, plasma, DNA and urine samples. Patients in the intervention group will be recruited over 3 years, with clinical examinations at baseline and after 2, 4 and 10 years. The project timeline is shown in Figure 1.

The project builds on the concept of shared care, where specialist knowledge is expanded into the primary care sector. For GPs participating in the study, specialist input regarding the patients phenotype and the recommended individualized treatment hereof will be delivered electronically to each patient's electronic health record (EHR) at initiation and regularly during the study. Specialist counselling is also available by phone during the day.

Patients and Recruitment

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A flowchart of GPs participating in DD2 and IDA is provided in Figure 2. Patients in the intervention group will be recruited from GPs in the region of southern Denmark and the region of Zealand participating in both the DD2 cohort and the IDA study. Patients in the control group will be recruited from GPs participating in the DD2 cohort but not in the IDA study. The selection process for patients in the two groups will be different and adjustment for differences in prognostic factors at baseline is therefore warranted as described in the statistical section.

Intervention patients

A flowchart of recruitment is provided in Figure 3A. Participating IDA GPs will be responsible for the initial patient contact, including collection of brief general patient information. If a DD2 patient is interested in the study, the GP automatically will register the patient in the DD2 website, triggering contact by a study nurse who will give the patient detailed study information. This will occur either by phone or during an initial informational meeting. Collection of in-depth patient information, informed consent, and additional screening will take place at central study hospitals prior to the baseline examination.

The following patient inclusion criteria will be used:

1. Member of the DD2 cohort [42]
2. Patient at a GP participating in the IDA study
3. Not diagnosed with Type 1 Diabetes, defined as age <30 years at DD2 enrollment, fasting C-peptide<300pM, and Gad65-ab>20IU/ml (see below)
4. Life expectancy above 2 years
5. No participation in other clinical trials
6. Willing to provide written informed consent

Control patients

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Patients for the control group will be recruited from DD2 clinics throughout Denmark not participating in the IDA study (Figure 2). Availability of valid biobanked samples for measuring GAD-ab, P-glucose, and C-peptide will be required to join the control group. As the control group will be created within DD2, neither GP nor patient will be informed, ensuring that the control group is truly blinded.

Patient examination in the intervention group

Screening will take place at the following four central study sites: Odense University Hospital, Hospital of Southwest Denmark, Næstved Lægecenter, and Holbæk Hospital. A written informed consent will be signed at the baseline visit prior to initiating examination of study participants.

Phenotype evaluation will be performed at the central sites at baseline and after 24 and 48 months. Medical history, medication use, and measures used in the phenotype evaluation will be obtained from the patient. Fasting plasma glucose, GAD65-antibody, and fasting C-peptide will be ascertained from the DD2 database. Repeat measures of cardiac impedance and unobserved automated blood pressure will be taken at the central sites at the following time points, determined by prior blood pressure values:

1) BP≤135/85: impedance measurement repeated after 24 months,
2) 135/85<BP≤145/95: impedance measurement repeated after 12 and 24 months,
3) BP>145/95: impedance measurement repeated after 6, 12 and 24 months.

The results of the phenotype evaluation for each specific patient will be assessed at Odense University Hospital and the patient specific protocol recommendations sent to the patient's general practitioner via the electronic health record.

Treatment and implementation of the phenotype evaluation will take place at the GP's office every third month or at the discretion of the GP (Figure 3B). The GP will measure HbA1c, the lipid profile, the albumin creatinine-ratio, creatinine, and BMI annually. The GP will report treatment goals and any reasons for protocol deviations annually.

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Daily physical activity

To measure daily physical activity level, a Axivity AX3 accelerometer (Axivity, Newcastle, UK) will be taped on the thigh and on the lower back. The AX3 is a 11g and 23x32.5x7.6 mm weatherproof accelerometer with a 512MB internal memory and clock. Accelerometers will be fixed directly on the skin using waterproof taping. Subjects will be instructed to wear the accelerometers at all times (including water activities and sleep) during a 10-day period and additional tape will be provided to patients at examination. The accelerometer on the back will be placed on the right side, above the upper point of the posterior iliac crest and next to the spine with its positive x-axis pointing downward and its negative z-axis pointing forward. The accelerometer on the thigh will be placed on the medial front of the right thigh, midway between the hip and knee joints, with its positive x-axis pointing downward and its negative z-axis pointing forward [43]. A sampling rate of 50 Hz will be used and data stored in in the original cwa Axivity file format, but also converted into a binary gt3x compatible file format using a custom made add-on to OmGui Axivity software. Accelerometer wear time has recently been reported to be high [44]. Patients will be closely instructed how to re-attach the accelerometer in case it falls off.

Cardiovascular surrogate markers

Patients with clinically diagnosed T2D within 2 years of their baseline examination will be invited to participate in additional evaluation of the following cardiovascular surrogate markers:

1) *24-hour ambulatory blood pressure monitoring (24ABPM)*

   24ABPM will be implemented by means of brachial oscillometric measurements, using the Mobil-O-Graph® system (IEM GmbH, Stolberg, Germany). The device will be set to measure BP every 15 minutes during the day (0700-2300 hours) and every 30 minutes during the night (2300-0700 hours). The patient will be instructed to record when s/he went to bed and got up.

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2) *Skin auto fluorescence (SAF) to evaluate advanced glycosolated end-products*

SAF will be measured using the AGE Reader™ (DiagnOptics Technologies BV, Groningen, the Netherlands). Technical details of this non-invasive device have previously been described in detail,[45].

3) *Low-dose non-contrast CT scan to detect coronary artery calcification*

The atherosclerotic plaque burden in the coronary, carotide, aortic, and femoral arteries will be estimated by measuring calcium during a 64-slice CT scan (Discovery VCT; GE Healthcare, Milwaukee, WI, USA) conducted at Odense University Hospital. The scan will be performed with the following parameters: gantry rotation time 500 ms, 16 · 2.5mm collimation, 120 kV tube voltage, 200 mA tube current and a prospectively EGC-triggered scan acquisition gating at 50% of the R–R interval. Scan data will be acquired during an inspiratory breath hold. The CAC Agatston score is computed by summing the CAC scores of all foci in the epicardial coronary system.

4) *Ultrasound of the carotid arteries to evaluate intima media thickness (IMT) and plaques*

IMT will be measured by B-mode ultrasound (Model IE33, Koninklijke Philips Electronics N.V, Eindhoven, The Netherlands), using a linear array transducer (L11-3 with a frequency up to 11 MHz), with acquisition of multi-insonation angles for subsequent analysis with automated edge detection software according to current guidelines,[46].

5) *ECG for approximation of left ventricular hypertrophy*

ECG will be measured digitally (EC Sense Lexor, Cardiolex AB, Solna, Sweden). The following measures of LVH will be calculated:

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- Cornell voltage-duration product, defined as the sum of voltage of SV3 and RaVL multipled by QRS duration (in women 0.6mV is added to the voltage)
- Sokolow-lyon voltage, defined as the sum of SV1 and R in V5 or V6, depending on which is larger.

6) *Fundus photo to evaluate retinal vascular changes*

Retinal vascular changes will be assessed through retinal imaging. Two methods will be employed to assess diabetic retinopathy and vascular damage:

- Diabetic retinopathy will be graded using the Early Treatment of Diabetic Retinopathy Study (ETDRS) classification,[47]. Grading is performed in 7 standard fields. The assessed characteristics are graded in specific fields and/or multiple fields. The grading encompasses the following characteristics: microaneurysm, hemorrhages, hard exudates, soft exudates, intraretinal microvascular abnormalities, venous abnormalities, new vessels on disc or elsewhere, preretinal hemorrhage, vitreous hemorrhage, scars of prior photocoagulation, and clinically significant macular edema.
- The retinal arteriolar and venular caliber as described by Hubbard *et al*.[48] All venules and arterioles in the area half to one disc diameter from the disc margin of the diameter are measured and an averaged measure is derived. The ratio of the venular and arteriolar diameters also is derived.
- Retinal photos will be taken after dilation of both eyes with 1 drop 10% metaoxedrin and mydriacyl 5mg/ml. After 10 min this will be repeated. After a total of 20 minutes, six pictures will be taken of each eye.

  All photographs will be assessed for retinopathy locally as part of the patients' regular screening. Trained ophthalmologists at the Department of Ophthalmology, Odense University Hospital then will assess retinopathy with the methods described above.

Surrogate marker evaluation will take place at baseline and again at two and four years follow-up.

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Study interventions

Patients in the control group will not receive study-related interventions, but rather will be treated by their GP according to national guidelines. Patients in the intervention group will receive multifactorial individualized treatment as outlined below. The outline of treatment will be subject to revision during the study if substantial new clinical evidence emerges. The suggested individualized treatment in the intervention group is made available to the treating GP, but the actual treatment is chosen at the discretion of the GP together with the patient. The intervention is designed to mimic the actual real life effect of specialist treatment suggestions. Patients who do not follow the proposed algorithms are therefore not discontinued.

Anti-diabetic treatment based on pathophysiological phenotypes

Pathophysiological phenotyping will provide the basis for individually guided treatment. At inclusion patients with "other specific forms of diabetes" will be identified. The remaining classical WHO-defined T2D patients will be characterized according to their insulin sensitivity (IS) and beta cell function (BCF). Of note, the subphenotyping and treatment of WHO-defined T2D patients is constructed for patients of Caucasian inheritance (very few Danish citizens are non-Caucasian) and cannot readily be extrapolated to other ethnicities.

Other specific types of diabetes are defined as follows:

1) Maturity-onset diabetes of the young (MODY). Patients will be screened for 10 monogenic causes of diabetes.
2) Late autoimmune diabetes of the adult (LADA). Defined as GAD65-ab≥20 IU/ml.
3) Secondary diabetes. Defined as low BCF (HOMA2-beta < 115.3%) and a history of pancreatitis or pancreas resection.

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4) Steroid-associated diabetes, defined as use of oral glucocorticosteroids within 3 months of diabetes diagnosis. Genuine-steroid induced diabetes is present when it is known with certainty that diabetes was not present in the 3 months prior to steroid initiation. Patients with known prior T2D or with uncertainty about the timing of diabetes onset and steroid use will be allocated to one of the additional phenotypes described below.

Genuine WHO-defined T2D:

5) Insulinopenic T2D. Defined as low BCF (HOMA2-beta < 115.3%) and high IS (HOMA2-S ≥ 63.5 %)
6) Classical T2D. Defined as low BCF (HOMA2-beta< 115.3%) and low IS (HOMA2-S< 63.5 %)
7) Hyperinsulinemic T2D. Defined as high BCF (HOMA2-beta≥ 115.3%) and low IS (HOMA2-S< 63.5 %)

The classification is hierarchical. The phenotypes have been described previously [25]. BCF and IS will be assessed using the HOMA2 model, calculated based upon fasting C-peptide and fasting plasma glucose. HOMA2-beta is an estimate of the beta-cell function and HOMA2-S is an estimate of the IS. In a healthy population without diabetes or impaired glucose tolerance, median HOMA2-beta was found to be 115.3% and median HOMA2-S was 63.5%. In the study population, values of HOMA2-beta or HOMA2-S above these medians will be defined as “high”, while values below the median will be defined as “low”.

Proposed treatment strategies in the study according to diabetes phenotypes are as follows. The treatment proposed for each phenotype is additive, starting with A. B is added if the treatment goal is not reached, and so on.

1) MODY. (1) Types 1 and 3 MODY should be treated with glimepiride or repaglinid. (2) Type 2 MODY should be treated with diet. Secondarily, basal insulin can be used. (3) Type 5 MODY should be treated with basal insulin. (4) Rare types of MODY should be treated individually according to specialist assessment.

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2) LADA.

   In patients who have IS and BCF equivalent to insulinopenic and classic T2D:

   A) Metformin if BMI>25 kg/m2. B) Basal insulin and meal-time insulin.

   In patients who have IS and BCF equivalent to hyperinsulinemic T2D:

   Treatment equivalent to hyperinsulinemic T2D (see below), with additional information on risk of rapid BCF deterioration and possible absolute need for insulin therapy.

3) Secondary diabetes. Basal and meal-time insulin.

4) Steroid associated diabetes. A) Meal-time insulin. B) Metformin. C) Basal insulin if fasting blood glucose is above 7.0.

5) Insulinopenic T2D. A) Metformin. B) Basal insulin. C) Meal-time insulin.

6) Classical T2D.

   In patients without CVD: A) Metformin. B) GLP-1 analogue*. C) Basal insulin. D) Meal-time insulin.

   In patients with former CVD: A) Metformin. B) SGLT-2 inhibitor. C) GLP-1 analogue*. D) Basal insulin. E) Meal-time insulin.

7) Hyperinsulinemic T2D. In patients with BMI>35 kg/m2, gastric bypass should be considered according to current national criteria and patient preference. Pharmacological treatment:

   In patients without CVD: A) Metformin. B) GLP-1 analogue*. C) Pioglitazone. D) Basal insulin. E) Meal-time insulin.

   In patients with former CVD: A) Metformin. B) SGLT-2 inhibitor. C) GLP-1 analogue*. D) Pioglitazone. E) Basal insulin. F) Meal-time insulin.

Pioglitazone is not recommended for patients with heart failure, prior bladder cancer or known osteoporosis. If marked edema develops discontinuation of pioglitazone must be considered. Women should be informed about the increased risk of fractures with pioglitazone, alongside the reduced cardiovascular risk.

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*DDP-4 inhibitors can be used if the patient does not want a GLP-1 analogue. It is recommended that a DDP-4 inhibitor be discontinued if insulin is initiated.

In patients of Asian inheritance with WHO-defined T2D, incretin-based treatment can be considered as first-line treatment [49]. Type of drug within drug classes, dosing, and titration will be chosen at the discretion of the treating physician. Suggestive algorithms will be available to the physicians.

Treatment of hyperglycemia will proceed according to the following individual goals:

1) Optimal control of HbA1c < 48 mmol/mol;
2) Acceptable control of HbA1c < 58 mmol/mol; or
3) Free of symptoms, with best possible HbA1c achieved within this constraint.

All treatment algorithms will be applied according to these predetermined goals. GPs will be free to choose and reassess the goal applicable to an individual patient. In patients with neuropathy or pre-existing cardiovascular disease, careful goal assessment is needed. If a patient has a severe hypoglycemic event, has repeated measures of blood glucose below 4.0 mmol/l, or is therapy resistant, the goal should be reassessed. For an in-depth discussion of the motivation for the glucose-lowering algorithm we refer to the supplemental material.

Anti-hypertensive treatment

Treatment of hypertension will be guided by measurements of thoracic impedance, which provide estimates of vascular resistance, intravascular volume, and cardiac inotropy. These measurements will be used to guide the pharmacological treatment of arterial hypertension. Principles of drug class choice will be as follows:

1) When hypertension or microalbuminuria are present, patients should be treated with an ace-inhibitor (or a angiotensin-2-antagonist), regardless of the result of the impedance measurement.

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2) High vascular resistance, as the only abnormal impedance measure, should be treated with a calcium-channel antagonist (dihydropyridins) (CCBs) in addition to an ace-inhibitor.
3) High intravascular volume, as the only abnormal impedance measure, should be treated with a thiazide in addition to current anti-hypertensive treatment. If the patient already is receiving a thiazide in maximum dose, an aldosterone receptor antagonist should be added.
4) In cases of high vascular resistance and high intravascular volume (more than double the vascular resistance in relative terms), diuretics (thiazide or secondarily aldosterone receptor antagonist) should be increased, comparable to the maximum dose of one new drug. As a next step, a CCB should be added. Finally, an aldosterone receptor antagonist should be increased to its maximum dose.
5) In cases of high vascular resistance and high intravascular volume (but less than double the vascular resistance in relative terms), an ACE inhibitor or CCB should be added, depending on initial treatment. As a second measure, diuretics (thiazide or, less often, an aldosterone receptor antagonist) should be increased comparable to the maximum dose of one new drug. As a third measure, CCB should be titrated to its maximum dose. Finally, an aldosterone receptor antagonist can be increased to its maximum dose.
6) High inotropy is addressed only when the patient receives an ACE-inhibitor, thiazide, and CCB and the impedance measurement is made while the patient is receiving this treatment. Other abnormalities need to be addressed first. Carvedilol up to 50mg is recommended.

The maximum dose of bendroflumethiazide is considered to be 5.0 mg, that for hydrochlorthiazide is 50 mg, and that for spironolactone is 50 mg. In cases in which the eGFR is below 30 mL/min/1.73m^2, high ceiling diuretics are substituted for thiazides. Non-hypertensive indications for anti-hypertensive medication overrule this algorithm.

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Impedance measurements also are used to downgrade anti-hypertensive treatment, in the following situations:

1) When inotropy is decreased, beta-blockers are terminated, or the dose reduced.
2) When hypovolemia is present, diuretics are terminated or the dose reduced.
3) When inotropy is decreased, vascular resistance is normal, and blood pressure is regulated, CCBs can be reduced or terminated.

For patients with prior cardiovascular disease, chronic kidney disease (eGFR<60 mL/min/1,73 m^2) or albuminuria, the goal of anti-hypertensive treatment will be to achieve a blood pressure <130/80 mmHg on 3 drugs, measured as home blood pressure or with an automated blood pressure device. For other patients, the goal is blood pressure<135/80 mmHg on 3 drugs. In cases in which control of blood pressure is not achieved with 3 anti-hypertensive drugs, the patient will be referred to a specialist clinic. Blood pressure below 120/70 mmHg should be avoided, if necessary by means of down-titration, unless other considerations are present.

Hypertension at study inclusion will be defined by presence of anti-hypertensive treatment or a blood pressure measurement above or equal to 135/80 mmhg in the office under standardized conditions using an automated blood pressure device (Mobilograf).

Treatment of dyslipidemia

Treatment with atorvastatin or simvastatin 40 mg will be recommended for all patients, regardless of LDL-C. If the treatment goal is not met, atorvastatin 80 mg or rosuvastatin 40 mg will be recommended. Combining lipid-lowering drugs will not be recommended. The treatment goal will be LDL cholesterol ≤2.5mM and LDL cholesterol ≤2.0mM in patients with established cardiovascular disease.

Termination of inefficient medication

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The effect of a specific anti-diabetic, antihypertensive, or cholesterol-lowering treatment will be measured.

The following efficacy requirements after titration to the full tolerable dose will need to be met:

1) Decline in Hba1c exceeding 0.5 % within 3 months.
2) Decline in systolic blood pressure exceeding 5 mmHg within 1 month.
3) Decline in LDL-cholesterol exceeding 0.5 mM within 1 month.

If the target is not met, the specific treatment should be terminated and replaced by another drug according to the algorithm. The missing effect on blood pressure should be validated by home blood pressure measurements according to national guidelines. For anti-hypertensive medication, another drug within the same class can be tried.

Lifestyle interventions

Supportive individualized M-health initiatives and face-to-face consultations for promoting changes in lifestyle will be used in this study. The aim is to empower patients to achieve sustainable reductions in carbohydrate intake and increase the daily physical activity level.

In the current study, we will integrate dietician-supported self-management by using a commercially Internet platform (Liva) to facilitate interactive communication between dieticians and users, as well as by peer-to-peer support. The platform will be further developed to support individualized education, goal setting and evaluation of diet and exercise behavior as described below. In addition, interactive communication between patient and a personal healthcare professional will allow for asynchronous contact when needed, in the form of video, text, or spoken messages. The advanced interactive platforms will be supported further by an individualized number of face-to-face consultations between the patient and the personal healthcare professional, with whom the patient will be acquainted from the interactive platform.

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The current study aims to empower patients to decrease the amount of carbohydrates in their diet (40E% fat, 40E% carbohydrates, and 20E% proteins), while keeping energy intake unchanged or slightly decreased in cases in which the patient seeks weight reduction. We will support individualized changes towards a sustainable increased number of low-carb meals each week. To support these changes, we have designed an Internet and smartphone platform (www.dd2mad.dk) that easily allows individuals to plan, purchase groceries, and cook low-carb meals for all daily meals, including snacks. A dietician developed the recipes, and the macro-nutritional composition of each recipe has been calculated using "DANKOST" software (Dankost Aps, Copenhagen, DK). The platform is updated monthly with new recipes and will be developed further using a user-driven iterative process. We will implement this platform in the modified Liva.

We aim to empower patients to make a sustainable increase in physical activity level by implementing interval walking. To enable the patients to engage in and maintain correct individualized interval walking we have developed a smartphone application (InterWalk). The application is designed to individually guide duration and intensity of the training in real time based on a small test at the first use of the application. During use, the app automatically monitors exercise intensity, training duration, and walking distance. Following each training session, the app sends the data to a central server [50]. The training data will be available for the patient and the healthcare professionals making it possible to provide evidence-based training feedback to patients, using physical fitness data [51], training duration, and compliance from the App [50]. The InterWalk App will be implemented in the Liva platform. For a discussion of the motivation of the lifestyle intervention see the supplemental material.

Outcomes

The study's primary outcome measure is time to a composite outcome of all-cause mortality, non-fatal myocardial infarction, coronary revascularization, cardiac arrest with resuscitation, hospitalization for heart failure, non-fatal stroke, development or progression of nephropathy or retinopathy (see below), severe hypoglycemia leading to hospitalization, and development of any cancer (except basocellular carcinoma) .

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Development or progression of nephropathy is defined as renal failure (defined by the need for chronic dialysis), development of macroalbuminuria, or doubling of baseline s-creatinine to a level above 200uM. Development of retinopathy is defined as proliferative retinopathy or macular edema that requires laser therapy, injection of vascular endothelial growth factor inhibitors or vitrectomy, or diabetes-related blindness (Snellen visual acuity below 0.1). Information on deaths will be obtained from the Civil Registration System. Individual diagnoses, operations, and procedure codes will be obtained from the Danish National Patient Registry (See Table 2). S-creatinine values and albumin-creatinine-ratios will be obtained through the Danish Diabetes Database for Adults.

Secondary outcome measures are all-cause mortality, socioeconomic costs, and quality of life. Quality of life will be assessed with SF-12 and Q-5 questionnaires at study inclusion and after 2 and 4 years.

Tertiary outcome measures are the individual endpoints in the composite endpoint. Other endpoints are

1) time to any macrovascular endpoint (as defined in the primary endpoint)
2) time to any microvascular endpoint (as defined in the primary endpoint)
3) time to fatal acute myocardial infarction
4) time to fatal stroke
5) time to lower-limb amputation
6) time to other revascularization procedures and peripheral thrombosis (not cardiac or cerebrovascular events)
7) overall hospitalizations per 1000 patient-years
8) treatment adherence, defined as reimbursement of prescriptions, compared to intended treatment dose: Total yearly reimbursed doses vs. intended yearly doses.
9) time trends of HbA1c, blood pressure, and LDL cholesterol
10) individual time trends of daily physical activity in intervention patients
11) proportions of patients in the interventions group reaching their goal of HbA1c and blood pressure

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Cause of death will be obtained from the Danish Cause of Death Register. Reimbursement of prescriptions will be ascertained through the Danish National Prescription Registry. Intended treatment dose will be obtained through the electronic medicine chart "FMK".

Power calculations

The power calculation was performed using Lakatos normal approximation for a log-rank test of two survival curves. The estimated sample size of 1123 patients will have 80% power to detect a reduction of 20% of the incidence rate of the primary endpoint, with a type 1 error of 5%, during 10 years of follow-up. A composite yearly event rate of 5% is estimated, based on estimated incidence rates of 2.5% per year of macro- and microvascular complications, 1.5% per year for cancer, and approximately 1% for overall mortality. The hypoglycemic event rate is expected to be less than 0.4%. Due to the database approach, loss to follow-up should be minimal.

Statistical analysis

The advantage of our pragmatic study approach is that our results will reflect effectiveness, harms and costs of individualized treatment in daily practice in primary care, improving generalizability compared to single-exposure RCTs typically conducted among heavily selected patient and clinic populations. On the other hand, GP practices and their patients are self-selected to participating in the IDA intervention in our study, and will be non-blinded to receiving this treatment. The main methodological challenge for our proposed study will therefore be to address possible confounding caused by imbalance of prognostic factors in participants versus controls. We will use appropriate statistical methods for dealing with confounding, including regression analyses and propensity score matching.

Confounders

Covariates expected to be confounders will be selected according to available evidence and knowledge, and will include the following:

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1) *General variables:* Age, gender, diabetes onset, DD2 enrollment year, time from DD2 enrollment to IDA study entry, GP and place of residence (municipality)
2) *Lifestyle variables:* Smoking, alcohol consumption, physical exercise (self-reported)
3) *Comorbidity:* Each of the individual strata of the Charlson Comorbidity Index, except diabetes, hospitalization for hypoglycemia, chronic dialysis, laser treatment of retinopathy/maculopathy, vitrectomy, chronic heart disease, angina pectoris, any revascularization procedure, lower-extremity amputation, atrial fibrillation and history of psychiatric disease (8 covariates defined by ICD-10: DF1 to DF8)
4) *Socioeconomic variables:* Education, employment, income, social support
5) *Clinical variables:* Blood pressure, BMI, waist circumference, LDL-C, HDL-C, triglyceride level, creatinine level, urine albumin creatinine ratio, diabetes phenotype
6) *Medication use:* Aspirin, statins, anti-coagulating drugs, thiazides, ACE-inhibitors or angiotensin 2 antagonists, calcium channel antagonists, beta-blockers, potassium-sparing diuretics, metformin, sulfonylurea, DD4-inhibitors, GLP-1 analogues, SGLT-2 inhibitors, insulin, oral corticosteroids, and number of redeemed drugs (including the above drugs)

Ascertainment of confounder variables will be through the DD2 cohort and registries. Comorbidity is defined as all diagnoses registered from 1977 until enrollment. Socioeconomic variables are defined as the values recorded in the enrollment year. Medication use is defined as redeemed prescriptions 1 year prior to enrollment. Clinical variables are defined by the value measured closest to enrollment, no more than 1 year prior to enrollment and 1 month after enrollment.

Cox regression analysis

Follow up will extend for 10 years from the date of IDA intervention start until first of any of the individual composite outcome events, emigration out of Denmark, or end of study 1.January 2028, whichever comes

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first. For patients in the control group the entry date will be the date of DD2 enrollment or date of the overall IDA study initiation 1.January 2015, whichever comes last. We will construct survival curves for intervention and control patients and compute cumulative incidence rates. We then compute incidence rate ratios (IRRs) with 95% confidence intervals (CIs) for intervention patients compared with controls using Cox regression analysis and controlling for confounders described above. Stratified analyses will be performed by gender, age below/above 60 years, eGFR below/above 60, former CVD, and diabetes phenotype with test for interaction.,.

Propensity score analysis

In a second analysis, we will use propensity score matching. For this analysis, we will compute the probability of each DD2 cohort non-IDA-intervention patient being included in the IDA intervention arm in a logistic regression analysis, conditioned on the patient's covariate profile. Next, we will match each intervention patient to a DD2 control patient with the closest propensity score in a 1:3 fashion and eliminate the remaining controls. The matching will be performed in a random sequential order. After determining that the covariates are balanced, between the two treatment groups (see supplemental material), we will conduct a matched Cox regression analysis without further adjustment. If any covariate is not balanced a model with adjustment for non-balanced covariates will be made. The assumption of proportional hazards in the Cox models will be assessed graphically.

ETHICS AND DISSEMINATION

The study will use well-known pharmalogical agents and bariatric interventions. Thus the safety of the patients is considered high. Patients in the intervention group will provide written informed consent before participation. The study will be conducted in compliance with the principles set forth in the Declaration of Helsinki and the Good Clinical Practice (GCP) Guidelines. The study has been approved by the Regional

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Committee on Medical Health Ethics (Region of Southern Denmark S-20120186), the Danish Data Protection Agency, and the Danish Health and Medicines Authority (journal nr. 2012120204).

All subjects will be identified by an unambiguous subject code that can be linked to the civil registration number. The subject code will be used as a pseudo-anonymization code throughout the study. Handwritten source data (CRFs) or hard-copy source data will be securely safeguarded against unauthorized access and kept under lock, with access only by authorized persons. Electronically reported source data will conform to good clinical practice standards by using the RedCap data collection system and the DD2-established data collection system. Both systems have a high level of security and use data verification and detailed logging during reporting.

Most study data will be stored in OPEN – a custom-designed study database secured against unauthorized access. OPEN is a research service provided by the University of Southern Denmark that enables researchers to store research data in accordance with national legislation and requirements for data logging, password security, and backup.

Study results will be made public via articles in national and international peer-reviewed journals, which will be accessible at www.dd2.nu. Positive, negative, and inconclusive results will be published according to the Vancouver Principles. The results will be disseminated through www.clinicaltrials.com and the Danish Diabetes Association.

PERSPECTIVES

IDA is one of the first studies to formalize a specific implementation of individualized medicine in treating T2D. The ultimate goal is to improve quality of life and reduce complications in T2D patients – in a manner requiring less medication and fewer resources over a 10 year period.

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Competing interests statement

JEH is a member of the MSD and Boehringer National Advisory board. HBN has received personal lectures fees from Novo Nordisk, outside the submitted work. MHO has received a clinical research grant from the Novo Nordisk Foundation. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of those studies have any relation to the present study. All other authors declare no competing interests.

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Authors' contributions

The study concept was developed by HBN and JEH. HBN, JEH, MHO, JVS, JSN, TBO, RWT and SF designed the study. Principal Manager of the DD2 study is JSN. JVS drafted the article and JSN, RWT, HBN and MHO revised the draft. All authors participated in the critical revision of the intellectual content of the report.

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Table 1. Data sources.

Variables	Source	Intervention	Control
Baseline biochemical measurements from whole blood, plasma and urine (eg. C-peptide and GAD-ab)	DD2 biobank	Yes	Yes
DNA samples	DD2 biobank	Yes	Yes
Baseline clinical variables (smoking, physical exercise, alcohol consumption)	DD2 interview	Yes	Yes
Longitudinal clinical biochemical measurements (HbA1c, Lipids, s-creatinine, U-ACR)	The Danish Laboratory Registry	Yes	Yes
Longitudinal clinical measures (BMI, waist, blood pressure, smoking)	Danish Diabetes Database for Adults	Yes	Yes
Medical history at baseline (Hospital contact history)	the Danish National Patient Register	Yes	Yes
Medical events during the study (hospital contacts)	the Danish National Patient Register	Yes	Yes
Medication prior to baseline	the Danish National Prescription Registry	Yes	Yes
Medication during the study	the Danish National Prescription Registry	Yes	Yes
Intended medication	National electronic medicine chart "FMK"	Yes	Yes
Socioeconomic variables	Statistics Denmark	Yes	Yes
Quality of life at baseline and longitudinally	DD2	Yes	Yes
Cardiovascular surrogate markers obtained at IDA examinations	Study measurements	Yes	No
Daily physical activity at IDA examinations	Study measurements	Yes	No
Patient-reported medical history and medication use	Study interview	Yes	No
Cardiac impedance	Study measurement	Yes	No
Blood pressure and HbA1c goal	DD2	Yes	Not relevant

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Table 2. Endpoint definitions.

ICD-10 codes for diagnoses and operation codes were obtained from the Danish National Patient Registry, as follows:

Non-fatal myocardial infarction	I21-23, T822A, T823 (without death within 30 days)
Coronary revascularization	KFNG, KFNA, KFNB, KFNC, KFND, KFNE, KFNF, KFNH, KFNW, KFLF
Cardiac arrest with resuscitation	I46
Hospitalization for heart failure	I50, I11.0, I13.0+2 (only as a-diagnosis)
Non-fatal stroke (including cerebral hemorrhage)	I61, I63, I64, KAAL10, KAAL11 (without death within 30 days)
Development of nephropathy	BJFD2 (chronic dialysis) or UACR>300g/mg or Doubling of creatinine (if creatinine >=200uM)
Development of retinopathy	KCKC10, KCKC15 (Laser therapy) or DH360K AND KCKD05B KCKD65 (vitrectomy) or H540+1+4 (blindness)
Severe hypoglycemia leading to hospitalization	E15, E160-2, T383A
Cancer (except basocellular carcinoma)	C00-99 (except when ZM809xx are added)
Amputation of the lower limbs:	KNEQ, KNFQ, KNGQ, KNHQ
Revascularization procedures and peripheral thrombosis (not cardiovascular or cerebrovascular disease)	I74, N280, K550-1, K558-9, H340-2 KPBE+F+H+N+P+Q, KPBW, KPGH10. KPGE+F+H+N+P+Q, KPGW99, KPGW20, KPEE+F+H+N+P+Q+W, KPFE+H+N+P+Q+W, KPGH20+21+22+23+30+31+40+99, KPDU74+82+83+84, KPEU74+82+83+84, KPFU74+82+83+84, KPAE+F+H+N+P+Q, KPAW99, KPAU74, KPCE+F+H+N+P+Q, KPCW99, KPCW20, KPCU74+82+83+84, KPGU74+83+84+99, KPGW, KPWG
Fatal acute myocardial infarction	I21-23, T822A, T823, R96-99 with death within 30 days
Fatal stroke	I61, I63, I64 with death within 30 days

Figure 1. Study timeline.

Figure 2. Recruitment flowchart at GP level

Figure 3. Recruitment (A) and GP contacts in the intervention group (B)

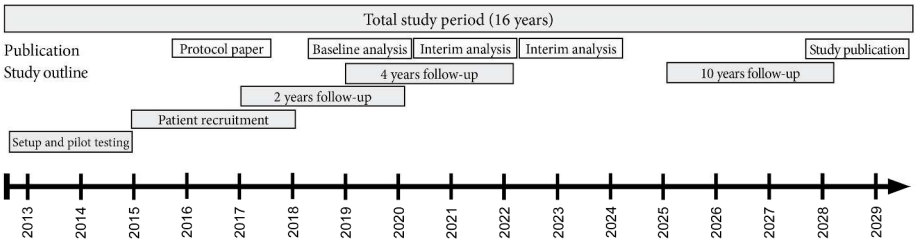

Figure 1. Study timeline

297x210mm (300 x 300 DPI)

Figure 2. Recruitment flowchart at GP level

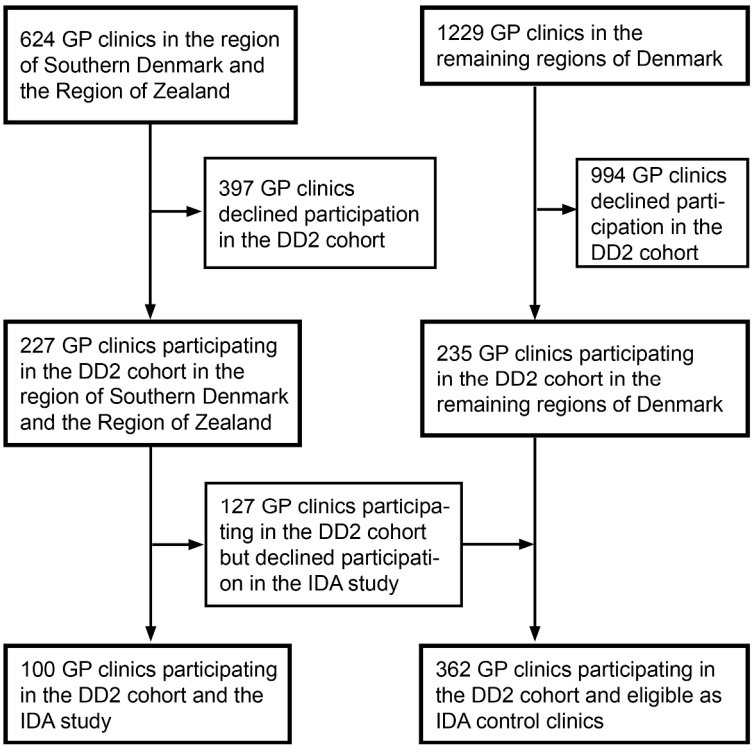

Figure 2. Recruitment flowchart at GP level

210x297mm (300 x 300 DPI)

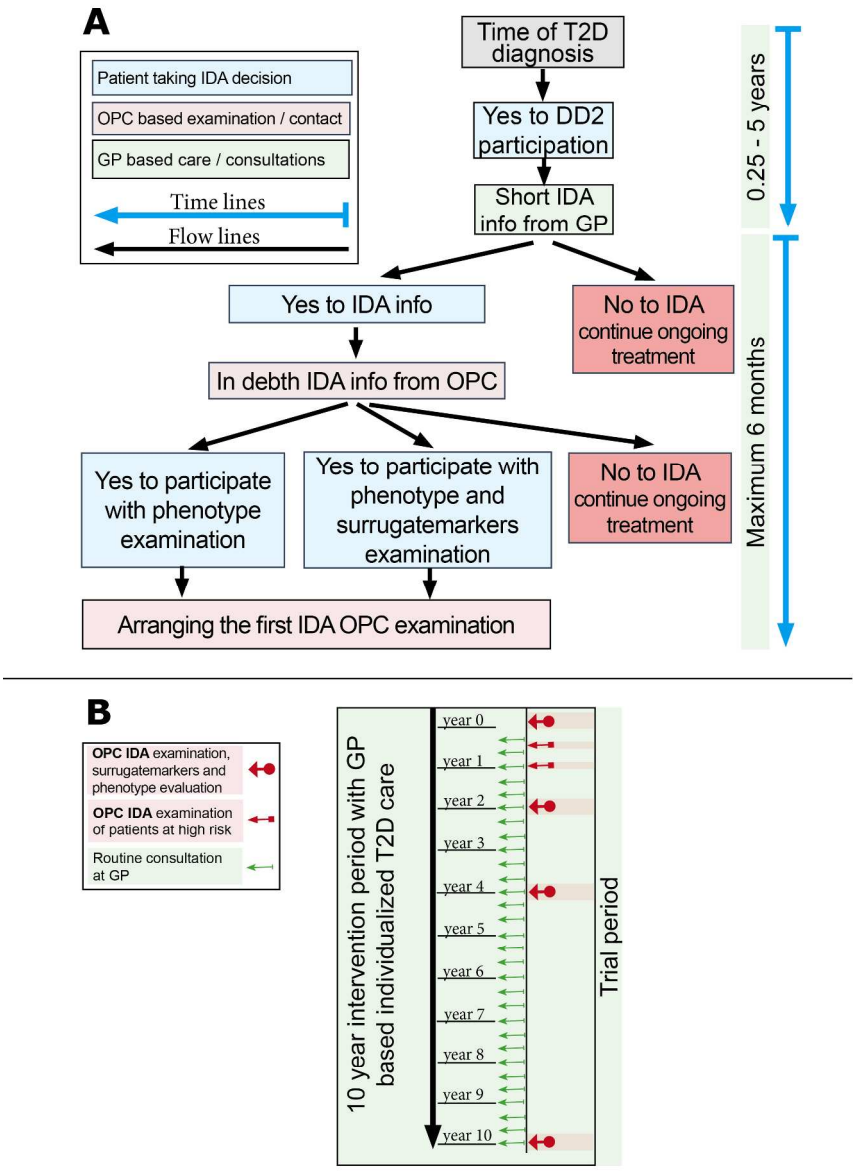

Figure 3. Recruitment (A) and GP contacts in the intervention group (B)

210x297mm (300 x 300 DPI)

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Supplemental material

Protocol for the Individualized multifactorial treatment of new clinically diagnosed type 2 diabetes in general practice (IDA)

– A prospective controlled multicenter open-label intervention study

Motivation for the proposed glucose-lowering treatment of specific pathophysiological phenotypes

Ideally, treatment should target the pathophysiological abnormalities. As patients with insulinopenic T2D have beta cell failure, basal insulin and meal-time insulin are recommended. Beta cell failure has been linked to poor response to GLP-analogs[1]. Patients with classical and hyperinsulinemic T2D have high or very high insulin resistance and appear to have increased cardiovascular morbidity at diagnosis[2] compared to patients with insulinopenic T2D with low insulin resistance. The primary focus in these two groups is thus to target insulin resistance. As hyperinsulinemic patients have severe insulin resistance, glitazones are also recommended for this group. Insulin is introduced earlier in the algorithm for classical T2D, as patients in this group also exhibit a degree of beta cell insufficiency. Metformin[3], GLP-1 analogs[4-6], glitazones[7] and SGLT2-inhibitors[8 9] are known to decrease insulin resistance. GLP-1 analogues also increase insulin secretion, restore first- and second-phase insulin response, and reduce glucagon secretion and body weight. A meta-analysis of randomized trials of pioglitazone reported a reduced incidence of death, myocardial infarction, and stroke compared to other medications[10 11]. This finding is supported by favorable effects on cardiovascular surrogate markers[7]. However, the incidence of heart failure was increased by pioglitazone treatment[10 11], and pioglitazone also increase the risk of fractures in women[12]. Pioglitazone has been linked to bladder cancer[13], but a recent multipopulation analysis, focusing on statistical procedures minimizing allocation bias found no such association[14]. In addition

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recent long-term study, including a case-control design, was not able to link bladder cancer to use of pioglitazone[15]. GLP-1 analogs are chosen over dipeptidyl peptidase-4 (DDP-4) inhibitors as GLP-1 analogs reduce weight and cardiovascular disease and mortality[16], while DDP-4 inhibitors have no proven effect on weight or macro- and microvascular complications[17]. An increased risk of heart failure might also be present[17 18]. Moreover DDP-4 inhibitors do not seem to reduce insulin resistance[19]. For these reasons we only recommend DDP-4 inhibitors in patients who do not want to use GLP-1 analogs. In case insulin becomes relevant we recommend the DDP-4 inhibitor to be discontinued in order to reduce medication which has no proven effect on clinical endpoints. In patients of Asian inheritance incretin-based therapy has been shown to be more effective and is therefore first-line treatment in Asia[20]. Evidence is accumulating that SGLT-2 inhibitors decrease the risk of major adverse cardiovascular events, cardiovascular death, heart failure, and death from any cause [21-23]. SGLT-2 inhibitors also induce weight reduction. The primary population, in the dominating studies, has been patients with prior cardiovascular disease and therefore we only recommend SGLT-2 inhibitors in this subpopulation. Sodium retention is decreased by GLP-1 analogs and SGLT-2 inhibitors, and increased by pioglitazone. The rationale for introducing pioglitazone after GLP-1 analogs and SGLT-2 inhibitors is to minimize pioglitazone-induced sodium and fluid retention, thereby preventing heart failure in susceptible patients. Bariatric surgery has been shown to reduce mortality, cardiovascular morbidity, and cancer incidence compared to usual care [24-26], and analyses restricted to diabetic patients have had the same results [27]. Diabetes remission rates also remained high after 10 years [24]. The Swedish Obese Subjects (SOS) study found that fasting insulin levels predicted a successful surgical outcome, in terms of mortality and CVD [24]. This supports bariatric surgery as a recommendation for patients with hyperinsulinemic T2D.

The degree of evidence varies for managing specific forms of diabetes. As patients with secondary diabetes have a primary beta cell defect, basal and meal-time insulin are recommended [28]. Patients with latent autoimmune diabetes of the adult (LADA) have diabetes-related antibodies, as seen in type 1 diabetes, but initially present as a T2D phenotype. Over time patients with LADA develop beta cell insufficiency, and

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therefore basal and meal-time insulin are recommended. A review concluded that insulin therapy preserves beta cell function better than sulphonylureas, although relevant studies on treatment of LADA are scarce [29]. Since many patients with LADA have a type 2 diabetes phenotype with adipositas, metformin is also recommended if BMI>25kg/m^2. Maturity-onset diabetes of the young (MODY) encompasses several monogenetic forms of diabetes. Patients with MODY3 and MODY1 have insulin secretion defects that respond to sulphonylureas[30 31]. Patients with MODY2 have a mutation in the glucokinase gene, which alters the set point of glucose control, while glucose regulation is intact [32 33]. Patients with MODY 2 rarely develop complications and the preferred intervention is diet.

Administration of glucocorticosteroids has the potential to induce diabetes onset and to exacerbate existing type 2 diabetes. It has been reported that prednisolone in particular enhances postprandial plasma glucose values in patients without known diabetes, with unchanged glucose levels at night and in the morning [34-36]. The same results have been reported for patients with type 2 diabetes, impaired glucose tolerance and normal glucose tolerance,[37-39]. Glucocorticoids impair both IS and BCF [40]. Evidence for optimal treatment of steroid-induced diabetes is sparse and based on case reports. Accordingly, there is little consensus regarding treatment. Insulin isophane (NPH) has been advocated [41], as well as prandial insulin [40]. In patients with metabolic syndrome or T2D, it has been found that sitagliptin did not improve GC-induced postprandial glucose excursions. [42 43]. Nateglinid [35 39] and glitazones have shown some benefit [44 45] and metformin has been found to improve postprandial glucose values from well above 11 to below 7.5 mmol/l in one patient[43]. Intravenous administration of exenatide has been observed to improve postprandial glucose values [46], but only when administered at breakfast and lunch [47]. In cases treated with exenatide, addition of SU was needed to achieve glycemic control. A comparative study of NPH insulin and insulin glargine with bolus insulin found that glucose control could be achieved, with no differences between agents [48].

Motivation for the proposed individual lifestyle intervention

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Web- and smartphone-based applications are a possible means for effective and time-saving patient counseling. However, they can result in low compliance over time and thus may be unfeasible as stand-alone lifestyle interventions. A Danish internet platform called Liva has been developed during the past decade by a team of dieticians, computer programmers, and physicians as a commercial weight management program. Its guiding principle is to improve the cost-effectiveness of established best practice for dietician-supported weight management by using an Internet platform to facilitate interactive communication between dieticians and users, as well as by peer-to-peer support through the online community. The program was developed iteratively through trial and error from an initial prototype and is now a well-established commercial product used by 10,000 predominantly healthy overweight or moderately obese persons. The effect of online dietician counseling based on this system was examined in a prospective non-controlled pilot study in obese subjects, and an average weight loss of 7.0 kg (95% CI: 4.6 to 9.3 kg) was observed after 20 months,[49].

In Denmark, diet recommendations for the general population and for patients with T2D are 45%-60E% carbohydrates, 10%-20E% proteins, and 25%-40E% fat[50]. It is being debated whether a diet with reduced carbohydrates (40E% fat, 40E% carbohydrates, and 20E% proteins) and an increased amount of unsaturated fat favors glycemic control in patients with T2D compared to current recommendations [51 52]. Several studies support the beneficial effects of the reduced carbohydrate diet on glycemic control for patients with T2D [53].

Poor physical fitness is one of the most important independent predictors of disease progression, morbidity, and mortality for patients with T2D [54 55]. It has been found that supervised exercise increases fitness,[56]. With the increasing prevalence and incidence of T2D, fully supervised training programs for all T2D patients would be very costly and thus unrealistic. We recently tested the feasibility of implementing unsupervised interval walking training (IWT), compared with continuous walking training, among patients with T2D in a four-month randomized controlled trial [57]. We found that IWT, but not continuous walking,

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had remarkably beneficial effects on physical fitness level and glycemic control. Moreover, this was achieved with a compliance rate of ~90% [57] and high long-term adherence [58]. We later tested the unsupervised IWT modality for 17 months in a setting with a compliance rate of >60%[59]. On this basis, we believe that the IWT exercise modality can be implemented as unsupervised exercise in a real-life setting. To permit large-scale implementation, guide correct training intensity, and improve feasibility for patients, we developed a smartphone application (InterWalk) that can be downloaded free of charge from App Store.

Motivation for the proposed lipid-lowering treatment

Statin treatment reduce cardiovascular disease and mortality in type 2 diabetes, with no difference in effect between phenotypes and with no clear lower LDL-C boundary of effect[60]. Intensive statin treatment compared to moderate statin treatment in type 2 diabetes patients with prior cardiovascular disease reduce a combined cardiovascular endpoint[61]. Addition of ezetimibe to statins are not extensively investigated and addition to high dose statin dose is not evaluated[62]. PCSK9 inhibitors do provide additional lowering of LDL-C when added to other lipid lowering medication and might also reduce any CVD[63]. Further studies is needed to establish the effect on cardiovascular disease. The effect in patients with diabetes seem to be equal or better than in patients without diabetes. As the evidence on cardiovascular endpoints for combination of lipid-lowering drugs is low we advocate treatment with statins in monotherapy.

Determination of covariate balance in propensity score matching

The usefulness of the propensity score models can be tested by how well covariates of the intervention and control patients match. The standardized difference should be used to compare covariates:

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$$d = \frac{\overline{X}_{intervention} - \overline{X}_{control}}{\sqrt{\frac{s^2_{intervention} - s^2_{control}}{2}}}$$

$$d = \frac{\hat{p}_{intervention} - \hat{p}_{control}}{\sqrt{\frac{\hat{p}_{intervention}(1 - \hat{p}_{intervention}) + \hat{p}_{control}(1 - \hat{p}_{control})}{2}}}$$

$\bar{x}$ denotes the mean of a continuous covariate. S is the variance. $\hat{p}$ denotes the prevalence of dichotomous covariates. With 1:k matching, the weighted mean should be used. If n control patients are matched per intervention patient, the weight should be 1/n. A difference below 0.1 is considered acceptable and should be achieved for all covariates [64]. The variance ratio should also be estimated as VR= $\frac{S^2_{intervention}}{S^2_{control}}$. Ratios between 0.5 and 2.0 are considered acceptable [65]. If the model does not conform to this criterion, a new model with inclusion of interaction terms and/or higher-order terms will be fitted. A quantile-quantile plot (or similar approach) for each variable (interactions can also be evaluated) should be used to compare the distribution in the intervention and control groups [66].

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