A protocol for THE STENO INTEN-CT TRIAL
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Screening and intervention for subclinical coronary artery disease in patients with type 2 diabetes:

Rationale and design of THE STENO INTEN-CT TRIAL

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ABSTRACT

Introduction

Cardiovascular disease (CVD) risk remains high in patients with type 2 diabetes (T2DM) but is unevenly distributed in the patient group. Current risk stratification strategies are far from optimal leading to both under- and overtreatment of patients. The Steno INTEN-CT trial aims to evaluate a combined strategy of improved CVD risk stratification by use of cardiac CT (coronary artery calcification, CAC) and tailoring of multifactorial CVD treatment based on CAC score. We hypothesize that i) intensified medical treatment will lower CVD event rates in high-risk patients (CAC $\geq$ 100), and ii) less intensive multifactorial treatment is safe in very low-risk patients (CAC = 0).

Methods and analysis

The Steno INTEN-CT trial is an investigator-initiated pragmatic open-label event-driven randomized controlled trial including patients with T2DM without known CVD. All participants (expected n = 7300) will be invited for a non-contrast coronary CT scan. After the scan, participants will be randomized to either standard treatment (blinded for CAC results) or CAC-based treatment. Participants in CAC-based treatment and their general practitioner will receive information on CAC and a recommendation of multifactorial treatment. High-risk participants in the interventional arm will be invited for one or more initial study visits in order to intensify treatment with a combination of sodium glucose co-transporter 2 inhibitors, glucagon-like peptide 1 agonists, high-dose lipid-lowering, antihypertensive, and antithrombotic treatment. Very low risk patients in the interventional arm will be recommended less intensive treatment targets. After initial study-related activities, all participants will continue treatment together with their general practitioner. The first outcome in the primary hierarchical analysis (the rate of the combined CVD endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for heart failure) will be monitored through national health registries. The trial is event-driven, but a median follow-up of 5 years is expected. Key secondary outcomes include patient reported outcomes and health economics.

Ethics and dissemination

The protocol is approved by the Research Ethics Committee and the Danish Medicines Agency (EU CT number: 2022-500143-21-01) and the Danish Data Protection Agency. The results of the study – positive, negative or neutral - will be published in peer-reviewed journals and through www.clinicaltrials.org (NCT05700877).

Strengths and limitations

- The Steno INTEN-CT trial address an urgent need to optimize primary CVD prevention strategies in T2DM. The trial will provide robust evidence to whether a combined CVD screening and treatment strategy may be beneficial compared to current clinical practice in terms of CVD prophylaxis, patient reported outcomes and cost-effectiveness.

- Pragmatic design choices have been made in order to evaluate the potential implementation of a combined CVD screening and intervention strategy in a “real world” usual care setting.

- The study is ongoing in all five regions of Denmark in both urban and rural/remote areas to ensure broad inclusion of patients with diabetes type 2. Thus, we expect that the study results will be generalizable to the Danish population. The results may be less generalizable to populations with differing healthcare systems.

- We have used pilot studies and updated registry data in the design phase to ensure a proper dimension of the sample size and study period, and we believe that the inclusion of 7300 participants and the event driven study period (expected median 5-year follow-up) will be sufficient to answer our research question.

- The study is a national project that has brought new scientific and clinical bonds between cardiology, endocrinology and general practitioners of the 13 hospitals involved in Denmark.

KEY WORDS

Type 2 Diabetes Mellitus, Cardiovascular Disease, Diabetes Complications, Pragmatic Clinical Trial,

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) confers an elevated risk of cardiovascular disease (CVD) [1]. The risk is, however unevenly distributed within the group of T2DM patients and current methods to estimate CVD risk are highly inaccurate[2-4]. Recently, the Score2-DM has shown better accuracy than previous models ([5]), however SCORE2-DM is still based on the same traditional risk factors (age, sex, smoking, systolic blood pressure, total and LDL cholesterol) and diabetes-specific factors (age at diabetes diagnosis, HbA1c and eGFR) as previous models. Inaccurate risk prediction challenges the clinical decision of primary CVD prophylaxis in T2DM as one approach does not fit all. Primary CVD prophylaxis is further complicated by the emergence of two drug classes (sodium glucose co-transporter 2 inhibitors [SGLT2i], and glucagon-like peptide 1 agonists [GLP1ra]), each with proven cardiovascular protection in patients with T2DM and manifest CVD and, to a lesser degree, patients with T2DM with presence of cardiovascular risk factors [6-12].

We present the design and rationale for the randomized Steno INTEN-CT trial. The trial aims to evaluate a CVD prevention strategy with coronary calcification score (CAC) as a decisive tool to risk stratify patients with T2DM and based on this information to intensify or de-intensify multifactorial treatment.

HYPOTHESIS AND AIMS

The overall research objective is to evaluate the possible cardiovascular **benefit** of a multifactorial treatment strategy based on a CAC score.

Our two co-primary aims are

- Co-primary aim 1: to compare the effect of intensified multifactorial treatment versus standard treatment on rates of a composite cardiovascular endpoint (cardiovascular mortality, non-fatal stroke, non-fatal myocardial infarction and hospitalization for heart failure) in patients identified with high cardiovascular risk as indicated by a CAC score ≥100. We hypothesize that intensified multifactorial treatment is superior to standard treatment in patients with CAC score ≥100.

- Co-primary aim 2: to compare the effect of de-intensified multifactorial treatment versus standard treatment on rates of the same composite cardiovascular endpoint in patients identified with low cardiovascular risk as indicated by a CAC score of zero. We hypothesize that downgraded multifactorial treatment is non-inferior to standard treatment in patients with CAC score of zero.

Secondarily, we aim to

- Compare the effect of intensified multifactorial treatment versus standard treatment on rates of the same composite cardiovascular endpoint in the complete study population.
- Compare patient-reported outcomes in the CAC-based treatment group and the control group.
- compare costs and outcomes between the two groups after study completion.
- compare age- and sex differences in cardiovascular outcomes between the two study arms.
- quantify and compare the diagnostic tests and therapeutic invasive interventions between the intervention groups and control groups during the study period.
- evaluate the adherence and efficacy of the therapeutic interventions in the intervention groups and the control groups during the study period.
- evaluate the association of CAC score and coronary CT angiography derived measures of coronary atherosclerosis burden, respectively, and CVD prognosis and treatment effects in patients with T2DM.
- explore the association between CAC score, biochemical markers of inflammation and atherosclerosis in relation to CVD prognosis in patients with T2DM.

METHODS

Design

The Steno INTEN-CT study is an investigator-initiated, pragmatic, open-label event-driven, randomized controlled trial. The design of the study is depicted in Figure 1.

Participants

We will include men and women with T2DM in Denmark.

Inclusion criteria:

- New or former diagnosis of T2DM according to WHO[13].
- Age between 55-69 years (men) and 60-74 years (women).

Exclusion criteria:

- Previous history of CVD (previous myocardial infarction or coronary intervention [Percutaneous coronary intervention or by-pass]), heart failure with last observed systolic dysfunction (ejection fraction < 40%), stroke or peripheral artery disease (ABI<0.9 and symptoms or surgical intervention) as documented by the patient or the patient medical record).
- Contraindications or allergies to both dapagliflozin and semaglutide.
- Signs of critical cardiac disease at screening: >50% stenosis of left main coronary artery (CT contrast enhanced angiography) or left ventricular ejection fraction below 40% (echocardiography). If a CT angiography is not available, a CAC>1000 on the non-contrast cardiac CT will be considered equal to critical cardiac disease. Other signs of critical CVDs are defined as findings for which further control or treatment may have a significant impact on participant prognosis.
- Expected life duration < 1 year for any reason.

Recruitment

Men and women with T2DM and no registration of CVD are identified by linking personal identification numbers to national health registries. On this basis, potential participants will receive an invitation to participate in the study through “e-boks” – a secure platform used by authorities and other public institutions (e.g. hospitals) to communicate with Danish citizens. In

order to secure a broad inclusion, written information, a graphical presentation of the study and a link to a webpage with a short information video is included in the invitation. Furthermore, participants without “e-boks” are sent a physical letter instead. Potential participants can schedule a screening visit in which they will receive oral information about the study by trained study personal. They may then choose to 1) decline, 2) to ask for time for consideration or 3) sign a consent form.

Study program

After written informed consent has been given, all participants will be examined with trial examinations: anthropometric measures, blood pressure a blood sample, and a non-contrast cardiac CT scan. Based on predefined standard operating procedures, study personal performing cardiac imaging will forward image files to a central imaging core lab without performing any analysis at the local study site. Trial participants will be sent home and within 1-2 weeks they will receive information about randomization and intervention in their e-boks.

The core lab receives raw image files from study sites and performs image analysis including estimation of CAC based on the non-contrast cardiac CT scan. Image quality will be evaluated on a 5-point scale at the time of study site initiation and consecutively through the study, and in case of suboptimal image quality, core lab will contact the study site in order to improve image acquisition. After the image work-up is completed, a message will be sent to a central secretariat that the participant has either signs of subclinical severe heart disease (exclusion criteria, and the participant will be referred to a clinical specialist in cardiology) or that the patient is ready for randomization. Participants are randomized to either i) continue standard diabetes treatment blinded to CAC results or ii) receive CAC-based treatment. The result is sent to both the participant and the participant’s general practitioner (primary care physician).

Depending on availability on the local study site, a contrast-enhanced coronary CT angiography and an echocardiography can be added, but these optional scan modalities will not impact the protocolized intervention unless signs of critical cardiac disease are detected.

Standard treatment

Participants randomized to standard treatment and their general practitioner are not informed about the CAC-score, but they are encouraged to follow contemporary diabetes guidelines. Thus, participants in standard treatment will visit their general practitioner as part of their usual diabetes control program and, if necessary, adjust treatment. Participants in the standard treatment arm will not be offered a study visit. As per usual care, patients can be referred to a diabetes outpatient clinic, if there is a clinical indication as judged by their general practitioner.

CAC-based treatment

Participants randomized to CAC-based treatment and their general practitioners will be informed about the CAC-score category and the CAC-based multifactorial treatment. Participants are classified into one of four risk categories: i) Very low risk (CAC=0), ii) low risk (CAC=1-99), iii) high risk (CAC=100-399), and iv) very high risk (CAC>399). The CAC-based multifactorial treatment algorithm is shown in Table 1.

High-risk and very high-risk participants are invited for a study visit at the study site and offered intensified multifactorial medical treatment. They will initiate combined treatment with a sodium glucose co-transporter 2 inhibitor (dapagliflozin 10 mg once daily), and glucagon-like peptide 1 agonists (subcutaneous semaglutide 0,25/0,5/1mg once weekly). This part of the intervention will be conducted as a single group, open label phase 4b drug trial, and the two drugs are formally investigational medicinal products. Both drugs will be delivered without compensation throughout the study, however it will be delivered in normal commercial packaging and in a fashion mimicking a normal pharmacy outlet. Furthermore, high-dose lipid-lowering, antihypertensive and antithrombotic treatment are initiated. Adjustments can be made at the discretion of study investigator (see Table 1 for treatment targets and differences between high- and very high-risk groups). After adjustments have been made during one or more study visits at the study site, participants will be discharged to their general practitioner who are encouraged to continue the medical intervention for the remaining follow-up period and continue the usual screening for

other diabetes complications (e.g. microvascular complications), and if needed, prophylactic diabetes treatment should be intensified.

Very low-risk (CAC = 0) participants will receive recommendations on less intensive medical treatment, and they are encouraged to visit their general practitioner to discuss medical adjustments (Table 1). The decision to follow the study recommendations is made by the patient and general practitioner.

Low risk participants (CAC = 1-99) are not included in the intervention study and will not receive specific recommendations other than to follow contemporary guidelines for risk stratification and treatment in collaboration with their general practitioner.

Lifestyle intervention programs are generally offered to all patients with T2DM as part of standard treatment and no further study-related lifestyle intervention is offered in this trial.

Outcomes

Outcomes are registered through linked national health registries and patient reported outcomes (questionnaire).

Register-based outcomes

In the primary hierarchical analyses (see "Statistics"), the first primary outcome is the rate of a first-time composite cardiovascular endpoint: Cardiovascular mortality, non-fatal stroke, non-fatal myocardial infarction, and hospitalization for heart failure.

Other outcomes include:

- All-cause mortality
- First-time individual components of the composite cardiovascular endpoint
    - Cardiovascular mortality
    - Non-fatal stroke
    - Non-fatal myocardial infarction
    - Hospitalization for heart failure

- Recurrent events of non-fatal stroke, nonfatal myocardial infarction and hospitalization for heart failure.
- Safety and harms: severe bleedings, sepsis, ketoacidosis, pancreatitis, hypoglycemia, retinopathy.

An Outcome Committee blinded for randomization, monitor and adjudicates all events by look-up in electronic patient files. A separate and blinded member of the Outcome Committee monitor when 293 primary events have occurred in the high-risk control group.

Patient reported outcomes:

The EQ-5D-5L, PHQ-9- and GAD-7 questionnaires will be used to evaluate quality of life and mental well-being of participants during the study and to estimate quality-adjusted life year (QALY) in combination with the economic evaluation of the study.

The questionnaires will be sent to all participants at baseline (before randomization) and then every second year during follow-up and as part of an End of Study questionnaire. High-risk and very high-risk participants in the CAC-based arm will also receive the questionnaires at the first study visit after randomization and three months after randomization.

Health economic evaluation

We perform a health economic evaluation of the trial following the lines of Drummond et al[14] and adhering to the reporting standards described in the CHEERS good practice guide from published by ISPOR[15]. The health economic evaluation consists of a cost effectiveness study (CEA) and a cost utility analysis (CUA). In the CEA, the incremental cost effectiveness ratio (ICER) will be the ratio between the incremental cost and the primary outcome as measured in the clinical effect analysis. In the CUA the incremental cost will be related to the increase in quality adjusted life years (QALYs). The QALYs will be calculated based on the EQ-5D-5L questionnaire and the Danish QALYs weights [16]. The incremental cost will follow the rigorous approach described in the references above by identifying the relevant cost components, measuring the cost in the relevant units and finally pricing the costs with the appropriate rates.

Costing will as far as possible be based on register data supplemented by observations, interviews and clinical time schedules.

We choose the follow up time in the trial as the follow up time in the health economic evaluation but propose to do a health economic model (Markov model) to evaluate the long-term health economics consequences after the end of study.

Statistics

We have based our sample size calculations on our previous screening studies (DANCAVAS[17], and pilot studies to Steno INTEN-CT[18]) and expect the following distribution of patients in risk categories: Very low-risk (CAC=0): 17%, Low-risk (CAC1-99): 33%, High-risk (CAC ≥ 100): 50%.

Based on data from Danish registries[19], we assume an expected five-year event rate of the composite of cardiovascular endpoint of 1 % in the very-low-risk group and of 17% in the combined high- and very high-risk group.

Co-primary aim 1: for the **primary analysis in the combined high- and very high-risk groups**, we expect a benefit of 20% in the CAC-based treatment group compared to high-risk patients in the standard treatment group. With a power of 80%, and a probability of type I error of 0.05, the estimated sample size is 3482 patients (1,741 in the intervention group and 1,741 in the control group).

Co-primary aim 2: for the primary analysis in the very low-risk groups, we will perform a non-inferiority analysis on the primary outcome. The sample size calculation is based on the exact confidence interval for the risk difference [20]. Assuming a composite event rate of 1% within 5-year in each group, a significance level of 2,5%, and evaluating non-inferiority with a margin of 2% using a one-sided statistical test then 1078 patients (539 patients in each group) are needed to ensure 80% power.

With the above-mentioned expected distribution of low- and high-risk patients, and an expected dropout of 5%, we need to include a total of 7,300 patients in order to identify a sufficient number of patients for the two co-primary analyses. Inclusion will continue until all 3482 high-risk patients

are in the study. We expect inclusion to take 2 years and therefore the study is estimated to run for four more years after inclusion has ended.

All patients will be analyzed according to intention-to-treat principles, i.e. according to planned treatment in all randomized patients. In the primary analysis in the high- and very high-risk groups, a Cox proportional hazards model will be used to compare hazard rates. Kaplan-Meyer curves will be provided for the cumulative proportions of events by randomization group.

The primary analysis will follow a hierarchical approach in which patient-reported outcomes, all-cause mortality and individual events of the primary composite outcome will be tested consecutively. The primary analysis stops if a test exceeds a two-sided p-value above 0.05 and further analysis will be considered hypothesis generating. The following order will be used:

- All-cause mortality
- Non-fatal stroke
- Non-fatal myocardial infarction
- Hospitalization for heart failure
- CVD mortality
- Recurrent of the combined outcome of nonfatal MI and non-fatal stroke

In the co-primary analysis of the very low-risk groups, non-inferiority of the primary outcome will be examined by evaluating whether the upper bound of the 95% confidence interval of the risk difference is below the non-inferiority margin. Similar to the high-risk analysis, combined and individual outcomes will be tested as part of a primary analysis using the same hierarchical approach as in the high- and very high-risk groups.

Detailed statistical analysis plans are provided in supplementary.

Ethics and dissemination

The trial is to be conducted in full compliance with the International Conference on Harmonization Good Clinical Practice guidelines and the articles of the Declaration of Helsinki. The protocol is approved by the Research Ethics Committee and the Danish Medicines Agency (EU CT number: 2022-500143-21-01) and the Danish Data Protection Agency. Important stakeholders representing

the primary and secondary health care sector in Denmark have approved the study (Danish Regions and the Danish College of General Practitioners).

The safety of the participants is considered high. The participants will undergo a heart CT-scan, and at selected sites an echocardiography. In the presence of critical coronary artery disease (Left main stenosis > 50%) or signs of systolic dysfunction (ejection fraction <40%), we will exclude and unblind the patient and offer further investigations and/or treatment. We use a CT reconstruction technic in which minimal parts outside of the heart will be visible in the CT images; thus, image-based findings unrelated to the heart will not be a part of the screening and this will be stated in the participant information.

High- and very high-risk participants in the CAC-based treatment arm will be enrolled in a low intervention phase 4b drug trial with dapagliflozin and semaglutide. Open label study drugs are used within their approved area of indication, and this means that safety monitoring is balanced in order not to pose an unreasonable extra burden to participants and study personal during follow-up (e.g. safety visits and safety phone calls). Safety monitoring consists of adverse event registration during the initial adjustment period at the study site.

Electronically reported source data will conform to good clinical practice standards by using the REDCap® data collection. Data will be stored in OPEN, a custom-designed study database secured against unauthorized access provided by the University of Southern Denmark. OPEN enables researchers to store research data in accordance with national legislation and requirements for data logging, password security and backup system. After termination of the study, the research data will be stored in a research biobank which will be made accessible to researchers outside of the research group on the condition that data access and use comply with national legislation.

The results of the study – positive, negative or neutral - will be published in peer-reviewed journals and through www. clinicaltrials.org.

Patient and public involvement

During the design phase of the study, meetings between the researchers and patient representatives was held (organized by the Danish Diabetes Association and Steno Diabetes Center Aarhus, respectively) . The meetings aimed to evaluate the study's objectives, recruitment process, and overall conduct. Based on these meetings and previous interview studies[21], we made specific changes to the study design, e.g. prioritized patient reported outcomes as part of the primary analysis, re-evaluated the recruitment process, changed/modified the wording/illustrations of recruitment materials etc.). We are currently sharing updates on the ongoing study through local news media near participating centers. Results will be published in scientific journals but also disseminated through the Danish Diabetes Association, the Danish Heart Foundation and pushed to national media.

DISCUSSION

The Steno INTEN-CT trial is initiated by a consortium of endocrinologists, cardiologists, general practitioners and health economists with the aim to improve the treatment and quality of life of patients with T2DM without known CVD. Central design choices of the trial will be discussed below.

Pragmatic randomized controlled trial design

The research question of the Steno INTEN-CT concerns the effectiveness of a combined strategy of screening and intervention in a format that may be introduced to clinical practice if proven superior to a “real world” usual care setting. Thus, pragmatic design choices have been made to support this[22]:

- Broad in/exclusion criteria of the study population.
- Open label study medication in commercial packaging.
- Register-based follow-up on safety and outcomes.
- An intervention group that receives a clearly defined treatment strategy on top of standard clinical care.
- A blinded comparator group that follows standard clinical care with minimal study related procedures.

Cardiovascular risk and risk stratification

Until recently, T2DM has been considered a "CVD equivalent", implying that all T2DM patients have an elevated risk of future CVD comparable to non-diabetic patients with manifest CVD [23,24]. However, mounting evidence suggests that T2DM is a heterogeneous disease and, importantly, patients harbor a highly uneven risk of future CVD[25,26]. Conventional clinical risk factors (hyperglycemia, hyperlipidemia, smoking, and hypertension) and risk models with these factors incorporated do not reliably estimate CVD risk in T2DM[2-4,27], although the recent SCORE2 model re-calibrated for T2DM (SCORE2-DM) shows an improvement in performance[5]. Novel CVD biomarkers (e.g., blood, urine, vascular, genetic and environmental markers) have been proposed as means to improve CVD risk prediction, however most markers do not improve prediction to an extent that is clinically meaningful[28] and generally there is a lack of prospective studies evaluating the effect of novel biomarkers on CVD prophylaxis and subsequent CVD outcomes [29].

CAC stands out as a biomarker that shows potential for CVD risk prediction beyond conventional CVD biomarkers and it holds potential as a tool to guide CVD prophylaxis [30]. It is highly specific of underlying subclinical atherosclerotic coronary artery disease [31] and thus reflects pathologic processes that are common for most types of CVD. Cohort studies in asymptomatic diabetes patients, show that CAC improves the prediction of future CVD[32,33] and all-cause mortality[34,35]. In particular, a CAC of 0 (~20% of patients with T2DM) entails a very low risk of CVD regardless of T2DM for at least 5 years [25,35,36]. Conversely, a large number of persons with T2DM suffer from silent, undiagnosed significant coronary artery disease (CAC score above 100) with CVD and all-cause mortality rates 6-10 times higher than T2DM patients without presence of CAC and two-fold higher compared to nondiabetic individuals with similar CAC[32,34,37,38]. In smaller studies, CAC has also shown value in prediction of non-coronary CVD events (incident stroke[39] and heart failure[40]).

In the Steno INTEN-CT trial, four risk categories with CAC thresholds at 0, ≥100 and ≥400 units have been chosen based on the predictive value and precision of CAC, however we acknowledge that CAC has important limitations. Firstly, in the very low-risk group, the predictive value of CAC = 0 seems to be attenuated during long term follow-up[34], and furthermore, a subpopulation of patients with CAC=0 will have presence of non-calcified atherosclerosis and may represent a

"hidden" high-risk population within the very low-risk group (in a Korean study, 10% of asymptomatic patients with CAC = 0 had signs of significant coronary atherosclerosis on CT angiography [41]). Secondly, the threshold for initiation of intensified medical prophylaxis is a compromise between an increased average risk and an acceptable false positive proportion of patients. Diabetes patients with CAC 1-99 face a slightly elevated risk of future CVD events; however, we have chosen not to give specific advice on CVD prophylaxis for this group as the accuracy in this CAC range is only modest[38] and the advice would likely not differ from standard recommendations. With increasing CAC, the false positive rate declines [38], and thus thresholds of CAC $\geq$100 and $\geq$400 were chosen. Finally, presence and extent of CAC is dependent on age and sex, thus sex-specific age intervals were chosen as inclusion criteria.

In the Steno INTEN-CT trial, we will evaluate the above limitations of the CAC score. Importantly, a coronary CT angiography will be obtained in a large subgroup of participants, and this will provide measures of calcified/noncalcified plaque volumes and vulnerable plaque characteristics that may reclassify patients stratified by CAC[42]. Moreover, the authors will pursue the possibility of a re-scan at the time of study completion to evaluate CAC-progression and risk re-classification after expectedly 5 years follow-up.

Primary prophylaxis of CVD in type 2 diabetes

The concept of CVD risk equivalence has also influenced the recommendations for primary CVD prevention in T2DM in which targets for CVD risk factor control (blood glucose, blood pressure, plasma lipids and prophylactic antithrombotic drug use) have been largely the same for all patients (stratifying treatment according to the presence or absence of albuminuria and/or other CVD risk factors). Furthermore, the importance of multifactorial risk factor control was demonstrated in the Steno 2 trial [43] and now universally accepted as an important premise for the treatment of T2DM. Maybe somewhat neglected, the Steno 2 trial was based on T2DM patients with albuminuria, thus representing a high-risk subgroup of T2DM. Since then, several attempts have been made to target CVD risk factors without risk stratification in broad diabetes populations without known CVD, but these studies showed no effect on CVD events [44,45]. Recently, a clinical

trial with 8.5 years of multifactorial intervention found no overall decrease in CVD incidence despite a significant reduction in several CVD risk factors [46].

In addition, the possibility for differentiated CVD prophylaxis in T2DM has increased with the emergence of new drugs. The introduction of sodium glucose co-transporter 2 inhibitors and glucagon-like peptide 1 agonists has gathered particular attention as large cardiovascular outcome trials have shown a reduction in CVD events in patients at high risk of - or - with manifest CVD [6-12]. Importantly, these drugs lower CVD risk independently of HbA1c reductions. However, the clinical position of the drugs in primary CVD prophylaxis is debated and the effect of combining these two drug classes remain unsettled. Lipid-lowering therapy (primarily with statins) is also a cornerstone in primary CVD prohylaxis[47] with increasingly tight LDL cholesterol targets introduced in guidelines recent years[48] but with the strongest evidence of effect among patients with atherosclerotic disease[49]. Likewise, the role of aspirin in primary prophylaxis is debated and currently only recommended on an individual basis[48,50]. Angiotensin converting enzyme inhibitors or angiotensin receptor blockers are recommended in the presence of hypertension and/or albuminuria as the drugs have shown to lower the rate of cardiovascular outcomes in diabetes patients with risk factors or manifest CVD [51,52].

In our previous cardiac screening studies (DANCAVAS[17] and a pilot study to Steno INTEN-CT[18]), we have data on 1,510 patients with diabetes but without prior CVD. Among these, statin treatment was used in comparable fractions of patients with a CAC score of 0 (57%) and CAC score above 100 (68%). Likewise, aspirin was used by 14% patients with a CAC score of 0 and by 37% with a CAC score above 100. In addition, the use of GLP1ra and SGLT2i where similar irrespective of CAC. These results suggest that among Danish patients with T2DM, a significant number of low-risk patients may be treated with unnecessary medication, while others, despite having a high CVD risk, seems to be unprotected against CVD.

Screening and intervention for CVD in type 2 diabetes

The concept of screening for subclinical CVD and stratified treatment in the general population has been evaluated in large screening trials and holds a promise for implementation in a real life

setting [17]. Unfortunately, no such strategy in patients with T2DM have proven effective to date. Five different CVD prevention strategies combining novel risk stratification methods and downstream subgroup treatment algorithms have been evaluated in relatively small randomized controlled trials but (apart from the small 2005 study of Faglia) with neutral results [53-57]. Only the Factor64 study used coronary CT angiography as a screening tool [56]. Overall, these studies were designed to randomize patients to either screening or standard care without screening, leaving the risk status of the control group unknown. Consequently, direct comparisons between high-risk or low-risk patients in the interventional and control arm has not been possible. Furthermore, a general assumption in the above-mentioned screening trials has been that coronary bypass or percutaneous coronary intervention of subclinical coronary atherosclerosis would be the most important part of the intervention and in some studies leaving the medical intervention at the discretion of the clinician[58]. In the Factor64 study, a mix of type 1 and 2 diabetes patients were included, and although an intensified treatment strategy was scheduled for the intervention group, only a modest proportion of participants achieved optimal medical treatment [56]. Moreover, the Factor64 study was performed in the era before sodium glucose co-transporter 2 inhibitors and glucagon-like peptide 1 agonists and finally, it was challenged by low inclusion rates and lower-than-expected event rates [56].

The Steno INTEN-CT trial contrasts from previous T2DM screening-and-intervention trials in several important aspects. Notably, the (blinded) risk status of the control group is attained which allows for comparison between similar risk categories in the interventional arm. Also, the intervention is primarily based on medical optimization including cardioprotective drugs that were not available in previous trials, and the intended sample size of the study will hopefully give firm signals on the effectiveness of the proposed treatment strategy.

PERSPECTIVES

With the widespread availability of coronary CT and the increasingly complicated landscape of medical treatment available for primary CVD prophylaxis, we believe that the Steno INTEN-CT trial

address an urgent need to optimize primary CVD prevention strategies in T2DM. Our ambition is to challenge the contemporary strategies and enable individualized imaging based preventive treatment in T2DM patients without manifest CVD. We hypothesize that the Steno INTEN-CT screening program will be superior to the current guidelines not only in CVD protection but also in terms of patient reported outcomes, and cost-benefit. Thus, the INTEN-CT study meets crucial parts of the WHO criteria for the assessment of a screening examination and will provide robust answers to evaluate the proposed treatment strategy in a clinical setting.

Authors' contributions

KLF wrote the first draft of the manuscript and AD and PLP revised the first subsequent versions. Hereafter, AS, EKF, JS, SR, JLT, PK, KE, MHO, TWH, PR, and PV each critically commented and revised the manuscript. All authors have been involved in the idea and design of the Steno INTEN-CT trial.

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Competing interests statement

The authors declare no conflicts of interests.

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