BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019214
Article Type:	Research
Date Submitted by the Author:	17-Aug-2017
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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Epidemiology, Diabetes and endocrinology, Medical management
Keywords:	Type 2 diabetes, Glycemic control, Outcomes, CVD risk, Multifactorial treatment

Title page

Impact of a short term multifactorial treatment program on clinical outcomes and cardiovascular risk estimates: a retrospective cohort study

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Number of tables: 2

Number of figures: 3

Abstract

Objectives: To investigate the impact of a short term multifactorial treatment program in a real-life setting on clinical outcomes and estimated cardiovascular disease (CVD) risk.

Design: A retrospective observational cohort study, using data from the electronic medical records and national registers.

Setting: Tertiary diabetes center in Denmark.

Participants: Patients with type 2 diabetes (n=4,299) referred to a short term treatment program between Jan 1st 2001 and April 1st 2016.

Outcomes: Primary outcomes were HbA1c, blood pressure and LDL cholesterol and changes in pharmacological treatment. Our secondary outcome was the impact on estimated CVD risk.

Results: The patients achieved a mean ± SD decrease in HbA1c, systolic and diastolic blood pressure (BP), and LDL cholesterol of 1.16±0.04% (12.7±0.4 mmol/mol), 6.3±0.4 mmHg, 2.6±0.2 mmHg and 0.40±0.02 mmol/l, respectively (p<0.0001). The proportion of patients who met the treatment goal for HbA1c (<7% [<53mmol/mol]) increased from 31% to 58% (p <0.0001); for BP (<130/80 mm Hg) from 24% to 34% (p <0.0001), and for LDL cholesterol (<2.5 mmol/l (patients without previous CVD) or <1.8 mmol/l (patients with previous CVD)) from 52% to 65%. Those reaching all three guideline treatment targets increased from 4% to 15% (p<0.0001), and when relaxing the BP target to <140/85 from 8% to 24%. The estimated CVD risk was relatively reduced by 15.2% using the Swedish NDR Risk Engine and 30.9% using the UKPDS risk engine.

Conclusions: Our data support that short term multifactorial treatment of patients with glycemic dysregulation in a specialist outpatient setting is both achievable and effective, and associated with a clinically meaningful improvement in CVD risk.

Strengths and limitations of this study

- Large cohort of dysregulated patients with type 2 diabetes under real-world conditions and strong validity of data with repeated recordings of clinical measurements and access to national registries.
- Selection bias in terms of more motivated and high risk patients being referred to the clinic, and by exclusion of those who did not show up.
- The use risk engines can only give an estimate of the CVD risk and the UKPDS risk engine is based on a population many years prior to ours where treatment guidelines were different.

Keywords: Type 2 diabetes, glycemic control, outcomes, CVD risk and multifactorial treatment

Introduction

Type 2 diabetes is an increasing global health threat. It is estimated that 439 million people will be diagnosed with diabetes by 2030 (1). Type 2 diabetes is associated with an increased risk of microvascular complications such as nephropathy, neuropathy, and retinopathy as well as macrovascular disease, resulting in a decreased life expectancy and substantial personal and societal expenses (2). Ensuring good glycemic control remains the most effective therapeutic measure to reduce the risk of developing microvascular disease (3, 4). Multifactorial treatment with tight control of glycaemia, blood pressure (BP) and lipids, accompanied by acetylsalicylic acid and lifestyle advice, is known to reduce progression of microvascular complications, cardiovascular disease (CVD), and mortality by 50% in patients with type 2 diabetes and microalbuminuria (5-7). Consequently, diabetes guidelines have advocated an intensified treatment approach aiming at addressing and reducing all CVD risk factors in patients with diabetes since several years (8, 9).

For most patients, sufficient glycemic, BP and lipid control can be achieved in a primary care setting but in high risk patients, or in patients with complex treatment regimens, the proportion of patients who achieves metabolic control in primary care decreases (10, 11). In this situation, in most health care systems, high risk patients are referred to specialist clinics for evaluation. A broad risk factor intervention in this subgroup has proven particularly effective in the Steno-2 study (5). However, it remains unknown whether the results seen in the study setting can be achieved in clinical practice.

The overall aim of this study was to describe how the multifactorial intervention methods from the Steno-2 study perform in a larger scale clinical setting. Our primary objective was to describe changes in metabolic outcomes and pharmacological treatment as a result of such

structured short term intervention. Our secondary objective was to evaluate the impact on estimated CVD risk by using two different risk assessment tools: the UKPDS Risk Engine (12), and the 5-year Swedish National Diabetes Registry (NDR) risk model (13).

Methods

Study Population

This study is based on patients referred to Steno Diabetes Center, a tertiary multidisciplinary and highly specialized diabetes center in the Capital Region of Denmark. It serves as one out of three referral centers with a catchment area of over 1.7 million people and provides diabetes care on a permanent basis to about 5.600 patients. During the Steno-2 study, SDC designed a treatment program algorithm specifically for patients with type 2 diabetes and glycemic dysregulation. The primary goal of the program is to improve patient quality of life and reduce mortality by prevention of acute and chronic complications of diabetes. This is done by motivating and encouraging self-management, professional support in behavioral changes, and pharmacological treatment according to national and international guidelines. The SDC Type 2 Clinic (T2C) opened in 2001, providing care for patients referred from general practitioners (GPs) or other hospitals in the region. Patients were referred to the clinic either as newly diagnosed with a need for education and start of treatment, requiring a shift to insulin treatment, having micro- or macrovascular complications, or having glycemic dysregulation in spite of attempts to control the disease by the GP. The program, which is still running, involves a consultation with a nurse, a dietician, and a physician in a structured order with specific assignments and is comparable to the intensive treatment arm of the Steno-2 study (Figure 1). The individual visits are complemented by optional group-based theme sessions with the overall aim of facilitating patient empowerment. The treatment program consist of self-management training with a focus on knowledge, lifestyle behavior

including diet, physical activity and smoking cessation, skills to improve glycemic control such as self-monitoring of blood glucose and skills to prevent and identify complications. Furthermore, there is focus on pharmacological treatment of hyperglycemia, hypertension and dyslipidemia. After approximately eight months, patients were evaluated for referral back to their GP, or to continue at the SDC outpatient clinic. The structure of program has remained unchanged in the study period while e.g. medications used have followed updated treatment guidelines. We defined the baseline and evaluation follow-up visits as the first and last visit to the T2C, respectively. This study is a retrospective observational study with demographics, clinical, and laboratory information extracted from the electronic medical records and laboratory database of SDC. We included all patients who had finalized a treatment program between 1st of January 2001 and 1st of April 2016 (n = 4,489), and to avoid no-shows, once off or very brief consultations we excluded patients with a treatment duration under 30 days (i.e. between the baseline and follow-up visits, n = 190). We ended up with a total of n = 4,299 patients. 16% of the patients were subsequently re-referred to the clinic, but we only included their first treatment program here.

Anthropometric, clinical and biochemical measurements

Laboratory analyses at the baseline visit were encouraged to be fasting and included: glucose, HbA_{1c}, hemoglobin, creatinine, total-cholesterol, high-density lipoprotein-cholesterol (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides (TG), C-peptide and urine albumin. At all in-between visits and at follow-up an HbA_{1c}, BP and weight were measured. All laboratory and anthropometric measurements were recorded using standardized procedures at the SDC accredited laboratory (ISO 15189). Body mass index (BMI) was calculated from weight and height (kg/m^2). A person was considered overweight at BMI $\geq$ 25 kg/m^2, and obese at BMI $\geq$ 30 kg/m^2. For BP and heart rate automated

oscillometric blood pressure recorders were used (AND UA-787plus, A&D medical, California, USA). Smoking status was obtained at every visit.

Diabetes complications and treatment

Micro albuminuria was here defined as a morning urine sample with urine albumin of 30-300 mg/L or urine albumin to creatinine ratio > 30 mg/g to 300 mg/g at the first visit. Macro albuminuria likewise but with a value > 300 mg/L or > 300 mg/g. Peripheral neuropathy was defined by examining vibration sensation with a biothesiometer and using an age-adjusted threshold (14). Information on cardiovascular disease was obtained from The National Patient Register and included diagnosis from 1977 till 2015 and procedures from 1995 till 2015. Prior CVD was defined as one or more of the following: myocardial infarction, heart surgery, ischaemic heart disease, heart insufficiency, atrial fibrillation, vascular surgery, stroke, transitory cerebral ischaemia and amputations using ICD-8 and ICD-10 codes.

Information on medication was obtained by Register of Medicinal Products Statistics, where individual-level data on all prescription drugs sold in Danish community pharmacies since 1994 has been recorded and administered by Statistics Denmark (15). A person was defined as being on a treatment at baseline if they had purchased a prescribed drug less than 180 days before their first visit and at follow-up if they purchased a prescribed drug after their first visit and less than 30 days after their last visit.

Permission to use data from the patient register was obtained from the Danish Data Protection Agency (ref. number: 2007-58-0015) and from the Danish Patient Safety Authority.

Statistical methods

We investigated how many patients reached the recommended targets for HbA1c (A), BP (B) and LDL cholesterol (C) according to national guidelines (16), collectively referred to as

ABC control: HbA1c < 7% (< 53 mmol/mol), BP < 130/80 mm Hg and LDL cholesterol < 2.5 mmol/l (< 100 mg/dl, patients without previous CVD) or < 1.8 mmol/l (< 70 mg/dl, patients with previous CVD). The primary outcomes were changes in blood glucose control (HbA_{1c}), BP and lipids from first visit (baseline) to end of treatment (follow-up evaluation visit). Secondary outcomes were the proportion of patients achieving the recommended targets for A, B or C and all three, ABC. For blood lipids, the T2C program assumed they would not deteriorate if they were on target at baseline and measurements were only repeated in case they were not at target at baseline. Accordingly, for this analysis a last observation carried forward approach was used to impute missing data. To evaluate the effect of changes in metabolic outcomes on the estimated risk of CVD, we calculated CVD risk at baseline and at follow-up using two different risk assessment tools: a Swedish risk model specific for type 2 diabetes (13) and the UKPDS Risk Engine (12) . The Swedish model is based on patients with type 2 diabetes using 12 predictors derived from a large observational sample of patients (n = 24,288) in the Swedish National Diabetes Register (NDR) followed from 2002 to 2007 and estimates the 5-year risk of CVD. The UKPDS Risk Engine is also type 2 diabetes-specific and based on 4,540 patients from the UKPDS trial (1977 to 1991). It includes HbA1c as a continuous variable and calculates the risk of developing a new coronary heart disease (CHD) event. *T* test was used for gender differences. Comparison between baseline and follow-up was made using mixed model for repeated measurements (MMRM) for continuous variables and logistic regression for dichotomous variables. McNemar test was used to compare changes in categorical variables. For risk estimates, exact 95%-confidence intervals (CI) were calculated. SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC) was used for database management and all of the above-mentioned analyses.

Results

Study cohort characteristics

Baseline characteristics of the study cohort are shown in Table 1. The majority of patients were Caucasians, and 19% were diagnosed with diabetes within a year before their referral. There were more males (n = 2,567) than females (n = 1,732) but no difference in treatment duration: median treatment program duration was 8.4 months (IQR: 6.1, 11.3). There were more male smokers and ex-smokers. Males had a higher level of HbA_{1c}, BP, weight and TG but lower BMI and cholesterol levels at baseline (Table 1).

Metabolic outcomes

There was a significant decrease in HbA_{1c} between baseline and follow-up of 1.0 ± 0.04% (10.6 ± 0.4 mmol/mol), with no gender difference. The decrease in systolic BP was 6.3 ± 0.4 mm Hg and in diastolic BP 2.7 ± 0.2 mm Hg ($p < 0.0001$ for both). The effect of treatment on BP was the same in both genders. There was a significant decrease in total-cholesterol, LDL and TG of 0.39 ± 0.03 mmol/l, 0.32 ± 0.02 mmol/l and 0.22 ± 0.05 mmol/l, respectively. There was no change in HDL levels overall ($p = 0.2$). As expected, females had higher HDL levels than males, both at baseline and at follow-up ($p < 0.0001$). This gender difference was also seen for total- and LDL cholesterol levels where females had higher levels at both baseline and follow-up. The effect of treatment on lipid levels was equal in both genders.

ABC control

In general, the proportion of patients achieving full ABC control according to national guideline treatment targets ($HbA_{1c} < 7\%$ [< 53 mmol/mol]), LDL < 2.5 mmol/l (< 100 mg/dl, patients without previous CVD) or < 1.8 mmol/l (< 70 mg/dl, patients with previous CVD), and BP < 130/80 mm Hg) increased from 4% to 15% ($p < 0.0001$). More females were achieving all three treatment targets at both baseline ($p = 0.047$) and at follow-up ($p = 0.014$).

Patients achieving the HbA_{1c} target increased from 31% to 58% ($p < 0.0001$), the BP target from 24% to 34% ($p < 0.0001$), and the LDL target from 52% to 65% ($p = 0.002$, Figure 2). If the BP target was relaxed from < 130/80 mm Hg to < 140/85 mm Hg the percentage achieving the BP target increased from 43% at baseline to 58% at follow-up ($p < 0.0001$), and consequently full ABC control from 8% at baseline to 24% at follow-up ($p < 0.0001$).

Changes in pharmacological treatment

The most common antidiabetic drug at baseline was metformin, which 58.4% of the patients were on, followed by sulphonyl urea (SU), 38.4%, and insulin, 19.5% (Figure 3). Only a small proportion of patients were on dipeptidyl peptidase 4 (DPP-4) inhibitors, 7.0%, glucagon-like peptide 1 (GLP-1) analogues, 3.9%, or other antidiabetic drug, 4.2%. In general there was an increase in the use of medication during the program. The largest increase was seen in use of metformin to 75.3%, insulin to 36.9% and GLP1-analogues to 11.6%. While SU only increased slightly to 41.8%, DPP-4 inhibitors to 9.6% and other antidiabetics 4.3%.

As part of the multifactorial treatment program, we also observed an increase in use of antihypertensive drugs to 75.3%, lipid lowering drugs to 75.9% and acetylsalicylic acid (ASA) to 69.6%.

Changes in cardiovascular risk

Estimated baseline and follow-up cardiovascular risk according to the used risk engines are shown in Table 2. Using the Swedish NDR model which predicts the 5 year risk of a new CVD event in a diabetic population, we observed a relative risk reduction of 15.2% (95% CI: 14.5-15.9). The UKPDS risk engine showed a relative risk reduction of 30.9% (95% CI: 30.3-31.5) in the 5 year CHD risk estimate. Females had a lower risk than males both at

baseline and at follow-up according to both risk models ($p < 0.0001$). Meanwhile, both according to the Swedish NDR model and the UKPDS risk engine, females had a smaller relative risk reduction compared to males ($p < 0.0001$).

Discussion

This study shows that a short term targeted multifactorial treatment program in a specialized clinical setting can improve metabolic outcome measures and CVD risk in patients with type 2 diabetes and high prevalence of complications. This confirms that multifactorial treatment not only works in a clinical study setting, but is also feasible and effective in real world clinical practice. With a specialized group of health care providers and a structured treatment and educational program that focuses on lifestyle intervention, self-management training and pharmacological treatment of hyperglycemia, hypertension and dyslipidemia, it is possible to accomplish significant CVD risk reductions in a high risk population with diabetes.

Treatment targets

Intensive multifactorial intervention in high risk patients has previously been shown to reduce CVD and mortality (7), and a recent 21 years follow-up of the Steno-2 study population shows that patients in the intensive-therapy group survived for a median of 7.9 years longer than the conventional-therapy group patients (17). Here we show that the same treatment program also works in clinical practice in a more diverse population, and results in a substantial reduction of 5- and 10-year CVD risk as estimated by two of the available and commonly used risk engines. In terms of risk factor intervention, glucose control continuous to be the greatest challenge to diabetes care. Nonetheless, all but 21% of patients changed from a higher to a lower HbA_{1c} category in this follow-up. For example, 84% of patients with an $HbA_{1c} < 6.5\%$ (< 48 mmol/mol) remained < 6.5% (< 48 mmol/mol) and 75% of patients

with an HbA_{1c} > 9% (> 75 mmol/mol) improved their HbA_{1c} to ≤ 9% (≤ 75 mmol/mol). Importantly, the improvement in glycaemic control was not accompanied by a general increase in weight. In fact, although we found that 15% of those in the normal weight category shifted to the overweight category when comparing the changes in BMI categories, 15% of those who were in the obese or overweight category dropped to a lower weight category. The weight gain observed in some patients is probably explained by the increased use of insulin, while weight loss in others can be explained by an increased use of GLP-1 receptor agonist treatment in recent years along with lifestyle management including dietary and physical activity advice.

With focus on hyperglycemia, hypertension and dyslipidemia, we found an increase in the proportion of patients achieving the recommended targets that are comparable to intervention studies (18, 19). Here, the relative proportion of patients achieving HbA_{1c} < 53 mmol/mol (7%) nearly doubled, BP < 130/80 mm Hg increased by 42% and LDL < 2.5 mmol/l by 25%. The T2C treatment program in this complex high-risk cohort resulted in a higher prevalence of risk factors in control equal to what has been observed in the more general diabetes population in the National Health and Nutrition Examination Surveys (NHANES) from 2007 to 2010 (20). The NHANES data differ in the way that their data was cross-sectional with participants with self-reported diabetes, without any distinction between type 1 and type 2, and with a different risk profile. Our population was more selected by being referred from their GP and requiring specialized care, which means they either had more comorbidities or a more complex treatment than the general patient with type 2 diabetes. For HbA_{1c} 58% in our cohort achieved the treatment target vs 53% in the NHANES cohort and for LDL-cholesterol 65% vs 56%, respectively. But for BP there was a big difference, 34% in our cohort vs. 51% in the NHANES cohort. This could be due to a higher prevalence of high BP in a group of

patients selected for complex disease with long duration. We did observe a time trend in the data as the proportion of patients achieving the stringent BP target increased from 23% in 2001 to 44% in 2015. The same improvement trend over time was observed in the proportion of patients achieving all three ABC targets; 7% in 2001 increasing to an average of 16% from 2006 and forward in our material and in the NHANES data from 7% in 1999-2002 to 19% in 2007-2010.

Use of CVD risk engines

To estimate the CVD risk in patients with type 2 diabetes is helpful to follow-up on treatment and to target further measures to patients at risk. In this study we used two different CVD risk engines to estimate the effect of the treatment program. The UKPDS risk engine is diabetes-specific and has several advantages as it incorporates HbA_{1c} and diabetes duration as continuous variables (12). However, it is still not ideal as it is based on the patients recruited by UKPDS for randomization in a clinical trial two decades ago before newer and more effective treatments were available or widely used (e.g. statins, angiotensin converting enzyme inhibitors and antidiabetic drugs). Accordingly, recent validation showed poor calibration and overestimation of the CHD risk (21). A model that seems more suitable for our population is the Swedish NDR risk model, which is based on a more recent and nationwide population, reflecting a more diverse population and taking into account the history of previous CVD and BMI. By using this model we found a relative reduction in the estimated 5-year CVD risk of 16%, after approximately eight months, despite the increase in age and diabetes duration. Notably, the fact that 26% of the patients had a prior CVD diagnosis at baseline reflects the high risk profile and complexity of the population that was referred to the treatment program. This of course does not normalise their actual risk, which will still be high, but can be a motivating factor for the patients that there are some

modifiable risk factors that can reduce their risk. In comparison, the population used in the Swedish model had a mean risk of 11.9% and a 5-year risk of fatal/non-fatal CVD of more than 10% is defined as high risk. According to this 92% of our population was in high risk at baseline. The UKPDS risk engine which estimates the risk of the first CHD event in 5 or 10 years, gives a lower 5 and 10 year risk estimate at baseline than the Swedish model, 7.4% and 17.1% respectively. This is nearly the same as the 10-year risk found in a NHANES population from 2007 to 2012 of 16.5% if no risk factors were in control and 10.2% if all risk factors were in control when using the same risk engine (22).

Interestingly, both the NDR and UKPDS risk engines estimated a higher CVD risk reduction in males than in females. This, perhaps expected finding, can be due to a relatively greater HbA_{1c} reduction seen in males, which is used in both the NDR and the UKPDS risk engines. However, this alone could not explain the whole difference, as the gender difference remained significant after excluding HbA_{1c} from the equation. This in spite a higher percentage of females achieved the metabolic targets.

Strengths and limitations

Strengths of this study include the validity of data with repeated recordings of the HbA1c and BP at each visit, and that it includes a large cohort of patients treated under real-life conditions such that results might have greater external validity than the highly selected populations in randomized controlled trials (RCT). Still, we cannot rule out that there might be a selection bias in terms of more motivated patients being referred to the clinic, and by exclusion of those who did not show up.

As a result of using a database and a register, we do not have complete data on all patients and therefore the cohort size changes a bit as results are based on those without missing values. Another limitation is that there is a lack of patient reported outcomes, such as adverse

events of drugs and general well-being. This was not possible to extract from the electronic medical records. Furthermore we cannot be sure that the patients going through a treatment program actually completed the program or was discharged for other reasons. It is also important to acknowledge that most of the treatment programs analyzed here were completed before many of the new anti-diabetic treatments, as GLP1-analogs and sodium-glucose co-transporter 2 (SGLT2)-inhibitors, were widely used and before acceptance of a more personalized treatment as recommended in the position statement from ADA and EASD in 2012 (23). Another limitation of this study is the use risk engines that only give an estimate of the CVD risk and that UKPDS is based on a population many years prior to ours and treatment guidelines were not the same.

Meanwhile, the data serves as a baseline benchmark for real world data studies as to what can be achieved in routine clinical practice before these treatments and guidelines get wider use and implementation. The use of a more individualized treatment approach with involvement of the patient in decision making is increasingly used in the treatment programs at the moment and is expected to increase adherence to therapy. Furthermore, the combination of a more individualized HbA_{1c} target and a broader selection of antidiabetic, antihypertensive and dyslipidemia treatment will likely increase the proportion of patients achieving their treatment goals and thereby reduce their CVD risk and mortality. Specifically, since the EMPA-REG OUTCOME trial showed a 38% and the LEADER trial a 22% relative risk reduction in deaths from CVD events (24, 25) in patients with type 2 diabetes and a high risk of cardiovascular events, this gives us further treatment options in this patient group. Therefore constant evaluation of the effects of our treatments on the risk of CVD or mortality is necessary. Combining these drugs, the treatment program evaluated here, and an individualized approach would be a logical next step for future studies.

Conclusion

This study of patients with type 2 diabetes who undergo structured treatment program lasting less than one year show that it is possible to increase the proportion of patients achieving the target levels for HbA_{1c}, BP, and LDL, thereby reducing their estimated CVD and CHD risk. To the strengths of such a structured program we count the focus on treatment targets by a multidisciplinary team and the fact that it is time limited, which reduces clinical inertia and costs. Our results show that intensive treatment is not only effective in the RCT setting, but also in clinical practice and should encourage other health care systems to establish similar programs.

Conflicts of interest

NS, BC and HV were employed at Steno Diabetes Center A/S, now known as Steno Diabetes Center Copenhagen and MR was employed there when the study was initiated. Steno Diabetes Center A/S was a research hospital working in the Danish National Health Service and owned by Novo Nordisk A/S. NS and BC own shares in Novo Nordisk A/S.

Funding

This study has been funded by Innovation Fund Denmark

Contribution statement

NS and BC were responsible for data management and statistical analysis. NS and MR were responsible for interpretation of data and writing of the article. HV was responsible interpretation and critical revision of the article. All authors fully approved the final version of the article.

Data sharing statement

Clinical data will be available at request, but information on diagnosis and medication is not allowed to be shared by the Danish National Patient Register or Statistics Denmark.

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Figure legends

Figure 1 - Flow chart of the treatment program. Visit A: Visit at the laboratory, eye clinic and consultation with nurse. Visit B: Consultation with nurse, dietician and physician. Visit C1 and C2: Individual program with nurse. Group sessions: Module A: 'Me and my diabetes'. Module B: 'My feet and physical activity'. Module C: 'My diet'. Module D: 'My motivation and future lifestyle plans'. Visit C: Consultation with nurse and dietician. Visit D: Final visit with nurse, dietician and endocrinologist. After approximately 8 months patients with no complications are referred back to general practice and those with micro- or macrovascular complications are referred to the outpatient clinic.

Figure 2 - Proportion of patients achieving the treatment targets for HbA_{1c}, LDL cholesterol, systolic and diastolic blood pressure at baseline and at follow-up.

Figure 3 - Proportion of patients on pharmacological treatment at baseline and follow-up. SU, sulfonylurea; DPP-4 i, Dipeptidyl peptidase 4 inhibitor; GLP-1, Glucagon-like peptide 1; OAD, oral antidiabetic drug; RAS, Renin angiotensin system; ASA, Acetylsalicylic acid

Table 1 Baseline characteristics of the study cohort

	N	All	Females (*n* = 1,732)	Males (*n* = 2,567)
Age (years)	4,299	59.3 (12.4)	59.9 (12.9)	58.9 (12.1)
Weight (kg)	4,256	91.5 (21.2)	84.4 (20.4)	96.3 (20.4)
Body mass index (kg/m^2)	4,236	31.0 (6.6)	31.8 (7.4)	30.3 (4.4)
Smokers, N (%)	4,071	1,629 (37.9)	622 (35.9)	1,007 (39.5)
Caucasians, N (%)	4,289	3,724 (87)	1,457 (84)	2,267 (89)
Diabetes and complications				
Duration of type 2 diabetes (years)	4,252	7.1 (6.5)	7.3 (6.6)	6.9 (6.5)
GAD65 antibodies ≥25 U/mL, N (%)	2,376	116 (2.7)	59 (3.4)	57 (2.2)
HbA_{1c} (%)	4,253	8.2 (3.9)	8.1 (3.9)	8.2 (19)
HbA_{1c} (mmol/mol)	4,253	66 (19)	65 (19)	66 (19)
Fasting p-glucose (mmol/L)	2,850	9.9 (3.6)	9.6 (3.4)	10.0 (3.7)
Fasting c-peptide (pmol/L) Median (IQR)	2,898	1050 (706-1500)	1050 (699–1517)	1050 (711-1478)
Prior cardiovascular disease, N (%)†	4,299	1,127 (26)	400 (23)	727 (28)
Microalbuminuria, N (%)	4,299	787 (18)	254 (15)	533 (21)
Macroalbuminuria, N (%)	4,299	211 (5)	47 (3)	164 (6)
eGFR (mL/min)	1,335	78 (17)	77 (18)	79 (16)
Simple retinopathy, N (%)	3,859	1134 (29)	422 (27)	712 (31)
Proliferative retinopathy, N (%)	3,859	56 (1)	25 (2)	31 (1)
Peripheral neuropathy, N (%)	2,343	549 (23)	140 (15)	409 (29)
Blood pressure				
Systolic blood pressure (mm Hg)	4,280	141.7 (21.7)	140.5 (22.5)	142.6 (21.1)
Diastolic blood pressure (mm Hg)	4,280	82.5 (11.5)	80.8 (11.4)	83.6 (11.5)

Table 1 Baseline characteristics of the study cohort

	N	All	Females (*n* = 1,732)	Males (*n* = 2,567)
Lipids				
Total cholesterol (mmol/L)	3,946	4.7 (1.2)	4.9 (1.3)	4.6 (1.2)
LDL cholesterol (mmol/L)	3,946	2.5 (1.0)	2.6 (1.0)	2.5 (1.0)
HDL cholesterol (mmol/L)	3,946	1.2 (0.4)	1.3 (0.4)	1.2 (0.4)
Triglycerides (mmol/L) Median (IQR)	3,946	1.7 (1.2–2.5)	1.7 (1.2–2.5)	1.7 (1.2-2.6)
Medication				
Metformin, N (%)	4,299	2511 (58)	1025 (59)	1486 (58)
Sulfonylurea, N (%)	4,299	1652 (38)	673 (39)	979 (38)
DPP-4 inhibitor, N (%)	4,299	303 (7)	126 (7)	177 (7)
GLP-1 analog, N (%)	4,299	168 (4)	73 (4)	95 (4)
Insulin, N (%)	4,299	836 (19)	346 (20)	490 (19)
Other OAD, N (%)	4,299	179 (4)	67 (4)	112 (4)
RAS blockade, N (%)	4,299	2027 (47)	736 (17)	1291(30)
All antihypertensive drugs, N (%)	4,299	2678 (62)	1099 (26)	1579 (37)
Lipid lowering drug, N (%)	4,299	1988 (46)	776 (45)	1212 (47)
Acetylsalicylic acid, N (%)	4,299	1538 (36)	530 (31)	1008 (39)

Values are means (SDs) unless stated otherwise.
†Prior CVD was defined as one or more of the following: myocardial infarction, heart surgery, ischaemic heart disease, heart insufficiency, vascular surgery, stroke, transitory cerebral ischaemia, amputation.
CVD, cardiovascular disease; GAD, glutamic acid decarboxylase; HbA_{1c}, haemoglobin A_{1c}; HDL, high-density lipoprotein; LDL, low-density lipoprotein; DPP-4, Dipeptidyl peptidase 4; GLP-1, Glucagon-like peptide 1; OAD, oral antidiabetic drug; RAS, Renin angiotensin system.

Table 2 Estimated CVD or CHD risk

	Baseline	Follow-up
Estimated CVD 5-year risk: NDR Risk engine:		
All	29.8 (19.6-44.6) [a]	25.0 (16.6-37.4) [b,] *
F	24.9 (15.9-37.0)	21.1 (13.7-31.1)*
M	34.0 (22.6-48.2)	28.1 (19.1-41.2)*
Estimated CHD 5-year risk: UKPDS Risk Engine:		
All	7.4 (3.9-13.7) [c]	5.0 (2.7-9.2) [d,] *
F	4.8 (2.6-8.7)	3.3 (1.9-5.9)*
M	9.6 (5.3-16.7)	6.4 (3.7-11.3)*
Estimated CHD 10-year risk: UKPDS Risk Engine:		
All	17.1 (9.3-30.4) [c]	11.8 (6.5-21.1) [d,] *
F	11.4 (6.1-20.0)	7.9 (4.5-14.0)*
M	22.1 (12.6-36.2)	15.0 (9.0-25.4)*

Estimated CVD risk according to the Swedish Nationa Register (NDR) risk engine and the estimated CHD risk according to the UKPDS risk engine. Data is median risk in % (IQR).
a $n = 3,865$; b $n = 3,730$; c $n = 3,895$; d $n = 3,757$, * $P < 0.0001$.

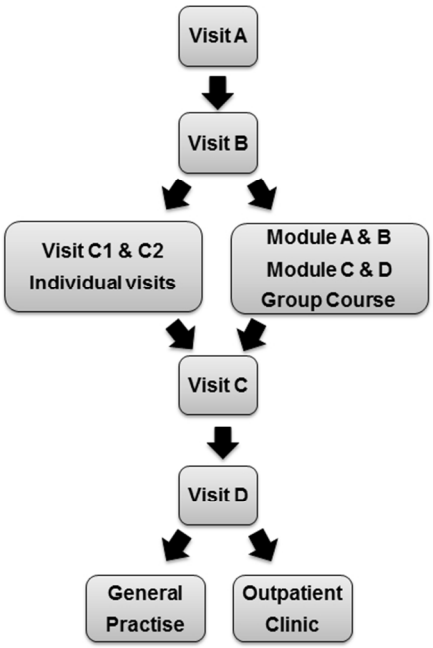

Figure 1 Flow chart of the treatment program. Visit A: Visit at the laboratory, eye clinic and consultation with nurse. Visit B: Consultation with nurse, dietician and physician. Visit C1 and C2: Individual program with nurse. Group sessions: Module A: 'Me and my diabetes'. Module B: 'My feet and physical activity'. Module C: 'My diet'. Module D: 'My motivation and future lifestyle plans'. Visit C: Consultation with nurse and dietician. Visit D: Final visit with nurse, dietician and endocrinologist. After approximately 8 months patients with no complications are referred back to general practice and those with micro- or macrovascular complications are referred to the outpatient clinic.

254x190mm (96 x 96 DPI)

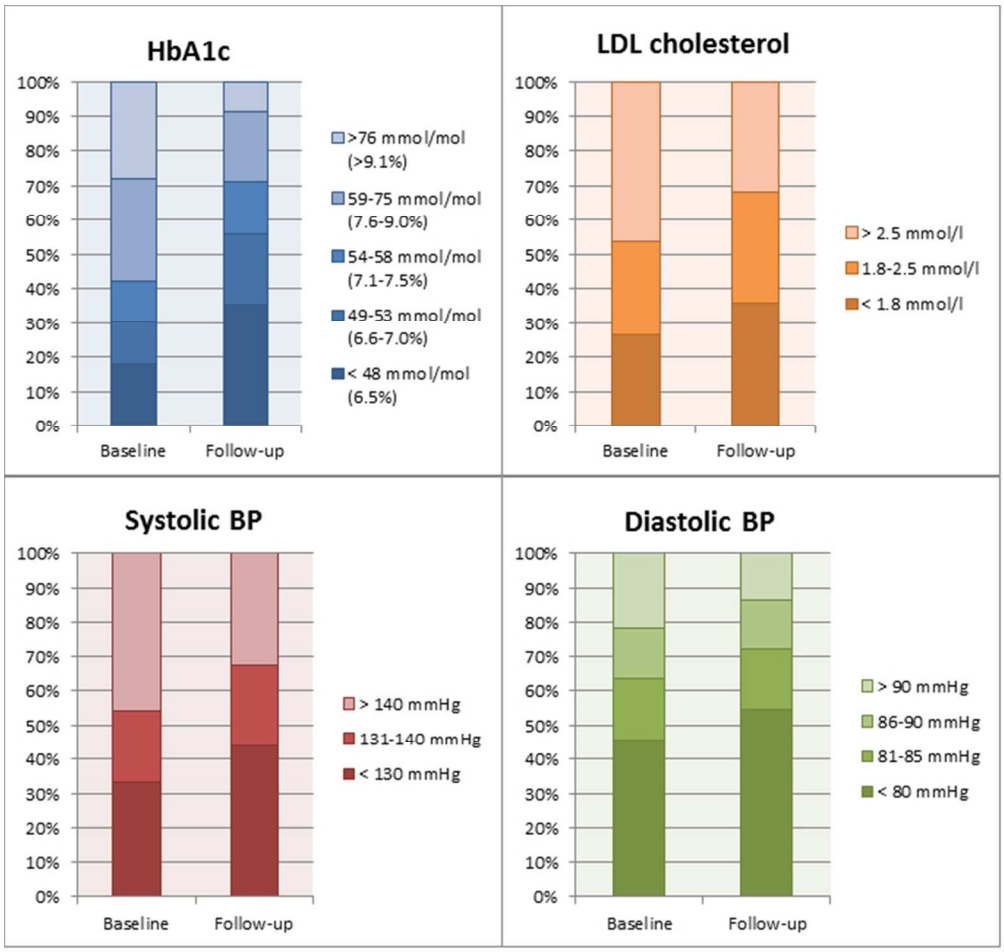

Figure 2 Proportion of patients achieving the treatment targets for HbA1c, LDL cholesterol, systolic and diastolic blood pressure at baseline and at follow-up.

180x171mm (96 x 96 DPI)

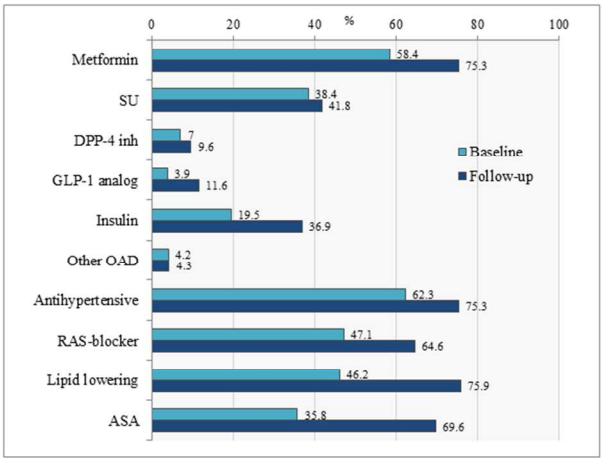

Figure 3 - Proportion of patients on pharmacological treatment at baseline and follow-up. SU, sulfonylurea; DPP-4 inh, Dipeptidyl peptidase 4 inhibitor; GLP-1, Glucagon-like peptide 1; OAD, oral antidiabetic drug; RAS, Renin angiotensin system; ASA, Acetylsalicylic acid

254x190mm (96 x 96 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	21 (Table 1)
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	9-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Impact of a multifactorial treatment program on clinical outcomes and cardiovascular risk estimates: a retrospective cohort study from a specialized diabetes centre in Denmark

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019214.R1
Article Type:	Research
Date Submitted by the Author:	18-Dec-2017
Complete List of Authors:	Safai, Narges; Steno Diabetes Center Copenhagen, Patient Care Carstensen, Bendix; Steno Diabetes Center Copenhagen, Department of Clinical Epidemiology Vestergaard, Henrik; The Novo Nordisk Foundation, Center for Basic Metabolic Research, Section of Metabolic Genetics; Steno Diabetes Center Copenhagen, Patient Care Ridderstråle, Martin; Novo Nordisk AS; Lunds Universitet, Department of Clinical Sciences
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Epidemiology, Diabetes and endocrinology, Medical management
Keywords:	Type 2 diabetes, Glycemic control, Outcomes, CVD risk, Multifactorial treatment

Title page

Impact of a multifactorial treatment program on clinical outcomes and cardiovascular risk estimates: a retrospective cohort study from a specialized diabetes centre in Denmark

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Number of tables: 2

Number of figures: 3

Abstract

Objectives: To investigate the impact of a multifactorial treatment program in a real-life setting on clinical outcomes and estimated cardiovascular disease (CVD) risk.

Design: A retrospective observational cohort study, using data from the electronic medical records and national registers.

Setting: Tertiary diabetes centre in Denmark.

Participants: Patients with type 2 diabetes (n=4,299) referred to a program with focus on treatment of hyperglycaemia, hypertension and dyslipidaemia, between Jan 1st 2001 and April 1st 2016.

Outcomes: Primary outcomes were changes in HbA_{1c}, blood pressure and LDL cholesterol as well as proportion reaching treatment targets, together with changes in antidiabetic, antihypertensive and lipid lowering treatment. Our secondary outcome was to investigate the impact on estimated CVD risk. Linier mixed model for repeated measurements were used for continuous variables and logistic regression for dichotomous variables.

Results: The patients achieved a mean ± SD decrease in HbA_{1c}, systolic and diastolic blood pressure (BP), and LDL cholesterol of 1.0±0.04% (10.6±0.4 mmol/mol), 6.3±0.4 mmHg, 2.7±0.2 mmHg and 0.32±0.02 mmol/l, respectively (p<0.0001). The proportion of patients who met the treatment goal for HbA_{1c} (<7% [<53mmol/mol]) increased from 31% to 58% (p <0.0001); for BP (<130/80 mm Hg) from 24% to 34% (p <0.0001), and for LDL cholesterol (<2.5 mmol/l (patients without previous CVD) or <1.8 mmol/l (patients with previous CVD)) from 52% to 65%. Those reaching all three guideline treatment targets increased from 4% to 15% (p<0.0001), and when relaxing the BP target to <140/85 from 8% to 24%. The estimated CVD risk was relatively reduced by 15.2% using the Swedish National Diabetes Register Risk Engine and 30.9% using the UKPDS risk engine.

Conclusions: Our data supports that short term multifactorial treatment of patients with glycaemic dysregulation in a specialist outpatient setting is both achievable and effective, and associated with a clinically meaningful improvement in CVD risk.

Strengths and limitations of this study

- Large cohort of dysregulated patients with type 2 diabetes under real-world conditions and strong validity of data with repeated recordings of clinical measurements and access to national registries.
- Selection bias in terms of more motivated and high risk patients being referred to the clinic, and by exclusion of those who did not show up.
- The use of risk engines can only give an estimate of the CVD risk and the UKPDS risk engine is based on a population many years prior to ours where treatment guidelines were different.

Keywords: Type 2 diabetes, glycaemic control, outcomes, CVD risk and multifactorial treatment

Introduction

Type 2 diabetes is an increasing global health threat. It is estimated that 439 million people will be diagnosed with diabetes by 2030 (1). Type 2 diabetes is associated with an increased risk of microvascular complications such as nephropathy, neuropathy, and retinopathy as well as macrovascular disease, resulting in a decreased life expectancy and substantial personal and societal expenses (2). Ensuring good glycaemic control remains the most effective therapeutic measure to reduce the risk of developing microvascular disease (3, 4). Multifactorial treatment with tight control of glycaemia, blood pressure (BP) and lipids, accompanied by acetylsalicylic acid and lifestyle advice, is known to reduce progression of microvascular complications, cardiovascular disease (CVD), and mortality by 50% in patients with type 2 diabetes and microalbuminuria (5-7). Consequently, diabetes guidelines have advocated an intensified treatment approach aiming at addressing and reducing all CVD risk factors in patients with diabetes since several years (8, 9).

For most patients, sufficient glycaemic, BP and lipid control can be achieved in a primary care setting but in high risk patients, or in patients with complex treatment regimens, the proportion of patients who achieve metabolic control in primary care is lower (10, 11). In this situation, in most health care systems, high risk patients are referred to specialist clinics for evaluation. A broad risk factor intervention in this subgroup has proven particularly effective in the Steno-2 study (5). However, it remains unknown whether the results seen in the study setting can be achieved in clinical practice.

The overall aim of this study was to describe how the multifactorial intervention methods from the Steno-2 study perform in a larger scale clinical setting. Our primary objective was to describe changes in metabolic outcomes and pharmacological treatment as a result of such

structured short term intervention and to test for gender differences. Our secondary objective was to evaluate the impact on estimated CVD risk by using two different risk assessment tools: the UKPDS Risk Engine (12), and the 5-year Swedish National Diabetes Registry (NDR) risk model (13).

Methods

Design and setting

This study is based on patients referred to Steno Diabetes Center (SDC), a tertiary multidisciplinary and highly specialized diabetes centre in the Capital Region of Denmark. It serves as one out of three referral centres with a catchment area of over 1.7 million people and provides diabetes care on a permanent basis to about 5.600 patients. During the Steno-2 study, SDC designed a treatment program algorithm specifically for patients with type 2 diabetes and glycaemic dysregulation. The primary goal of the program is to improve patient quality of life and reduce mortality by prevention of acute and chronic complications of diabetes. This is done by motivating and encouraging self-management, professional support in behavioural changes, and pharmacological treatment according to national and international guidelines. The SDC Type 2 Clinic (T2C) opened in 2001, providing care for patients referred from general practitioners (GPs) or other hospitals in the region. Patients were referred to the clinic either as newly diagnosed with a need for education and start of treatment, requiring a shift to insulin treatment, having micro- or macrovascular complications, or having glycaemic dysregulation in spite of attempts to control the disease by the GP. The program, which is still running and is the same for all patients, involves a consultation with a nurse, a dietician, and a physician in a structured order with specific assignments and is comparable to the intensive treatment arm of the Steno-2 study (Figure 1). The individual visits are, depending on the need, complemented by optional group-based

theme sessions with the overall aim of facilitating patient empowerment and with phone consultations from a nurse. The treatment program consist of self-management training with a focus on knowledge, lifestyle behaviour including diet, physical activity and smoking cessation, skills to improve glycaemic control such as self-monitoring of blood glucose and skills to prevent and identify complications. Furthermore, there is focus on pharmacological treatment of hyperglycaemia, hypertension and dyslipidaemia. After approximately eight months, patients were evaluated for referral back to their GP, or to continue at the SDC outpatient clinic. The structure of program has remained unchanged in the study period while e.g. medications used have followed updated treatment guidelines. The Danish treatment guidelines have followed the international guidelines from EASD and ADA and were revised in 2003, 2011 and 2014 (14-16). We defined the baseline and evaluation follow-up visits as the first and last visit to the T2C, respectively. This study is a retrospective observational study with demographics, clinical, and laboratory information extracted from the electronic medical records and laboratory database of SDC.

Study population

We included all patients who had finalized a treatment program between 1st of January 2001 and 1st of April 2016 (n = 4,489), and to avoid no-shows, once off or very brief consultations we excluded patients with a treatment duration under 30 days (i.e. between the baseline and follow-up visits, n = 190). We ended up with a total of n = 4,299 patients. 16% of the patients were subsequently re-referred to the clinic, but we only included their first treatment program here.

Subject characteristics

Laboratory analyses at the baseline visit were encouraged to be fasting and included: glucose, HbA_{1c}, haemoglobin, creatinine, total-cholesterol, high-density lipoprotein-cholesterol (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides (TG), C-peptide and urine albumin. At all in-between visits and at follow-up an HbA_{1c}, BP and weight were measured. All laboratory and anthropometric measurements were recorded using standardized procedures at the SDC accredited laboratory (ISO 15189). Body mass index (BMI) was calculated from weight and height (kg/m^2). A person was considered overweight at BMI $\geq$ 25 kg/m^2, and obese at BMI $\geq$ 30 kg/m^2. For BP and heart rate automated oscillometric blood pressure recorders were used (AND UA-787plus, A&D medical, California, USA). Smoking status was obtained at every visit.

Diabetes complications and pharmacological treatment

Micro albuminuria was here defined as a morning urine sample with urine albumin of 30-300 mg/L or urine albumin to creatinine ratio > 30 mg/g to 300 mg/g at the first visit. Macro albuminuria likewise but with a value > 300 mg/L or > 300 mg/g. Peripheral neuropathy was defined by examining vibration sensation with a biothesiometer and using an age-adjusted threshold (17). Information on cardiovascular disease was obtained from The National Patient Register and included diagnosis from 1977 till 2015 and procedures from 1995 till 2015. Prior CVD was defined as one or more of the following: myocardial infarction, heart surgery, ischaemic heart disease, heart insufficiency, atrial fibrillation, vascular surgery, stroke, transitory cerebral ischaemia and amputations using ICD-8 and ICD-10 codes.

Information on medication was obtained by Register of Medicinal Products Statistics, where individual-level data on all prescription drugs sold in Danish community pharmacies since 1994 has been recorded and administered by Statistics Denmark (18). A person was defined as being on a treatment at baseline if they had purchased a prescribed drug less than 180 days

before their first visit and at follow-up if they purchased a prescribed drug after their first visit and less than 30 days after their last visit.

Permission to use data from the patient register was obtained from the Danish Data Protection Agency (ref. number: 2007-58-0015) and from the Danish Patient Safety Authority.

CVD risk

To evaluate the effect of changes in metabolic outcomes on the estimated risk of CVD, we calculated CVD risk at baseline and at follow-up using two different risk assessment tools: a Swedish risk model specific for type 2 diabetes (13) and the UKPDS Risk Engine (12) . The Swedish model is based on patients with type 2 diabetes using 12 predictors: sex, age, diabetes duration, TG, HDL cholesterol, HbA1c, systolic BP, BMI, smoking status, albuminuria, atrial fibrillation and previous CVD. It is derived from a large observational sample of patients (n = 24,288) in the Swedish National Diabetes Register (NDR) followed from 2002 to 2007 and estimates the 5-year risk of CVD. The UKPDS Risk Engine is also type 2 diabetes-specific and based on 4,540 patients from the UKPDS trial (1977 to 1991). It includes HbA_{1c} as a continuous variable and calculates the risk of developing a new coronary heart disease (CHD) event.

Statistical methods

The primary outcomes were changes in blood glucose control (HbA_{1c}), BP and lipids from first visit (baseline) to end of treatment (follow-up evaluation visit) and to explore gender differences in outcomes. Furthermore we investigated how many patients reached the recommended targets for HbA_{1c} (A), BP (B) and LDL cholesterol (C) according to national guidelines (14), collectively referred to as ABC control: HbA_{1c} < 7% (< 53 mmol/mol), BP < 130/80 mm Hg and LDL cholesterol < 2.5 mmol/l (< 100 mg/dl, patients without previous

CVD) or < 1.8 mmol/l (< 70 mg/dl, patients with previous CVD). For blood lipids, the T2C program assumed they would not deteriorate if they were on target at baseline and measurements were only repeated in case they were not at target at baseline. Accordingly, for this analysis a last observation carried forward approach was used to impute missing data. *T* test was used for gender differences at baseline and at follow-up. Comparison between baseline and follow-up was made using mixed model for repeated measurements (MMRM) for continuous variables with the subject as a random effect and logistic regression for dichotomous variables e.g. pharmacological treatment. McNemar test was used to compare changes in categorical variables. For risk estimates, exact 95%-confidence intervals (CI) were calculated. SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC) was used for database management and all of the above-mentioned analyses.

Results

Study cohort characteristics

Baseline characteristics of the study cohort are shown in Table 1. The majority of patients were Caucasians, and 19% were diagnosed with diabetes within a year before their referral. There were more males (n = 2,567) than females (n = 1,732) but no difference in treatment duration: median treatment program duration was 8.4 months (IQR: 6.1, 11.3). There were more male smokers and ex-smokers. Males had a higher level of HbA_{1c}, BP, weight and TG but lower BMI and cholesterol levels at baseline (Table 1).

Metabolic outcomes

There was a significant decrease in HbA_{1c} between baseline and follow-up of 1.0 ± 0.04% (10.6 ± 0.4 mmol/mol), with no gender difference. The decrease in systolic BP was 6.3 ± 0.4

mm Hg and in diastolic BP 2.7 ± 0.2 mm Hg ($p < 0.0001$ for both). The effect of treatment on BP was the same in both genders. There was a significant decrease in total-cholesterol, LDL and TG of 0.39 ± 0.03 mmol/l, 0.32 ± 0.02 mmol/l and 0.22 ± 0.05 mmol/l, respectively. There was no change in HDL levels overall ($p = 0.2$). As expected, females had higher HDL levels than males, both at baseline and at follow-up ($p < 0.0001$). This gender difference was also seen for total- and LDL cholesterol levels where females had higher levels at both baseline and follow-up. The effect of treatment on lipid levels was equal in both genders.

ABC control

In general, the proportion of patients achieving full ABC control according to national guideline treatment targets increased from 4% to 15% ($p < 0.0001$). More females were achieving all three treatment targets at both baseline ($p = 0.047$) and at follow-up ($p = 0.014$). Patients achieving the HbA_{1c} target increased from 31% to 58% ($p < 0.0001$), the BP target from 24% to 34% ($p < 0.0001$), and the LDL target from 52% to 65% ($p = 0.002$, Figure 2). If the BP target was relaxed from < 130/80 mm Hg to < 140/85 mm Hg the percentage achieving the BP target increased from 43% at baseline to 58% at follow-up ($p < 0.0001$), and consequently full ABC control from 8% at baseline to 24% at follow-up ($p < 0.0001$).

Changes in pharmacological treatment

The most common antidiabetic drug at baseline was metformin, which 58.4% of the patients were on, followed by sulphonyl urea (SU), 38.4%, and insulin, 19.5% (Figure 3). Only a small proportion of patients were on dipeptidyl peptidase 4 (DPP-4) inhibitors, 7.0%, glucagon-like peptide 1 (GLP-1) analogues, 3.9%, or other antidiabetic drug, 4.2%. In general there was an increase in the use of medication during the program. The largest increase was seen in use of metformin to 75.3%, insulin to 36.9% and GLP1-analogues to

11.6%. While SU only increased slightly to 41.8%, DPP-4 inhibitors to 9.6% and other antidiabetics 4.3%.

As part of the multifactorial treatment program, we also observed an increase in use of antihypertensive drugs to 75.3%, lipid lowering drugs to 75.9% and acetylsalicylic acid (ASA) to 69.6%.

Changes in cardiovascular risk

Estimated baseline and follow-up cardiovascular risk according to the used risk engines are shown in Table 2. Using the Swedish NDR model which predicts the 5 year risk of a new CVD event in a diabetic population, we observed a relative risk reduction of 15.2% (95% CI: 14.5-15.9). The UKPDS risk engine showed a relative risk reduction of 30.9% (95% CI: 30.3-31.5) in the 5 year CHD risk estimate. Females had a lower risk than males both at baseline and at follow-up according to both risk models ($p < 0.0001$). Meanwhile, both according to the Swedish NDR model and the UKPDS risk engine, females had a smaller relative risk reduction compared to males ($p < 0.0001$).

Discussion

This study shows that a short term targeted multifactorial treatment program in a specialized clinical setting can improve metabolic outcome measures and CVD risk in patients with type 2 diabetes and high prevalence of complications. This confirms that multifactorial treatment not only works in a clinical study setting, but is also feasible and effective in real world clinical practice. With a specialized group of health care providers and a structured treatment and educational program that focuses on lifestyle intervention, self-management training and

pharmacological treatment of hyperglycaemia, hypertension and dyslipidaemia, it is possible to accomplish significant CVD risk reductions in a high risk population with diabetes.

ABC control

Intensive multifactorial intervention in high risk patients has previously been shown to reduce CVD and mortality (7), and a recent 21 years follow-up of the Steno-2 study population shows that patients in the intensive-therapy group survived for a median of 7.9 years longer than the conventional-therapy group patients (19). Here we show that the same treatment program also works in clinical practice in a more diverse population, and results in a substantial reduction of 5- and 10-year CVD risk as estimated by two of the available and commonly used risk engines. In terms of risk factor intervention, glucose control continuous to be the greatest challenge to diabetes care. Nonetheless, all but 21% of patients changed from a higher to a lower HbA_{1c} category in this follow-up. Importantly, the improvement in glycaemic control was not accompanied by a general increase in weight. In fact, although we found that 15% of those in the normal weight category shifted to the overweight category when comparing the changes in BMI categories, 15% of those who were in the obese or overweight category dropped to a lower weight category. The weight gain observed in some patients is probably explained by the increased use of insulin, while weight loss in others can be explained by an increased use of GLP-1 receptor agonist treatment in recent years along with lifestyle management including dietary and physical activity advice.

With focus on hyperglycaemia, hypertension and dyslipidaemia, we found an increase in the proportion of patients achieving the recommended targets that are comparable to intervention studies (20, 21). Here, the relative proportion of patients achieving $HbA_{1c} < 53$ mmol/mol (7%) nearly doubled, BP < 130/80 mm Hg increased by 42% and LDL < 2.5 mmol/l by 25%.

The T2C treatment program in this complex high-risk cohort resulted in a higher prevalence of risk factors in control equal to what has been observed in the more general diabetes population in the National Health and Nutrition Examination Surveys (NHANES) from 2007 to 2010 (22). The NHANES data differ in the way that their data was cross-sectional with participants with self-reported diabetes, without any distinction between type 1 and type 2, and with a different risk profile. Our population was more selected by being referred from their GP and requiring specialized care, which means they either had more comorbidities or a more complex treatment than the general patient with type 2 diabetes. For HbA_{1c} 58% in our cohort achieved the treatment target vs 53% in the NHANES cohort and for LDL-cholesterol 65% vs 56%, respectively. But for BP there was a big difference, 34% in our cohort vs. 51% in the NHANES cohort. This could be due to a higher prevalence of high BP in this group of patients selected with complex disease and long diabetes duration. We did observe a time trend in the data as the proportion of patients achieving the stringent BP target increased from 23% in 2001 to 44% in 2015. The same improvement trend over time was observed in the proportion of patients achieving all three ABC targets; 7% in 2001 increasing to an average of 16% from 2006 and forward in our material and in the NHANES data from 7% in 1999-2002 to 19% in 2007-2010.

CVD risk

To estimate the CVD risk in patients with type 2 diabetes is helpful to follow-up on treatment and to target further measures to patients at risk. In this study we used two different CVD risk engines to estimate the effect of the treatment program. The UKPDS risk engine is diabetes-specific and has several advantages as it incorporates HbA_{1c} and diabetes duration as continuous variables (12). However, it is still not ideal as it is based on the patients recruited by UKPDS for randomization in a clinical trial two decades ago before newer and more

effective treatments were available or widely used (e.g. statins, angiotensin converting enzyme inhibitors and antidiabetic drugs). Accordingly, recent validation showed poor calibration and overestimation of the CHD risk (23). A model that seems more suitable for our population is the Swedish NDR risk model, which is based on a more recent and nationwide population, reflecting a more diverse population and taking into account the history of previous CVD and BMI. By using this model we found a relative reduction in the estimated 5-year CVD risk of 16%, after approximately eight months, despite the increase in age and diabetes duration. Notably, the fact that 26% of the patients had a prior CVD diagnosis at baseline reflects the high risk profile and complexity of the population that was referred to the treatment program. This of course does not normalise their actual risk, which will still be high, but can be a motivating factor for the patients that there are some modifiable risk factors that can reduce their risk. In comparison, the population used in the Swedish model had a mean risk of 11.9% and a 5-year risk of fatal/non-fatal CVD of more than 10% is defined as high risk. According to this 92% of our population was in high risk at baseline. The UKPDS risk engine which estimates the risk of the first CHD event in 5 or 10 years, gives a lower 5 and 10 year risk estimate at baseline than the Swedish model, 7.4% and 17.1% respectively. This is nearly the same as the 10-year risk found in a NHANES population from 2007 to 2012 of 16.5% if no risk factors were in control and 10.2% if all risk factors were in control when using the same risk engine (24).

Interestingly, both the NDR and UKPDS risk engines estimated a higher risk reduction in males than in females. This, perhaps expected finding, can be due to a relatively greater HbA_{1c} reduction seen in males, which is used in both the NDR and the UKPDS risk engines. However, this alone could not explain the whole difference, as the gender difference remained significant after excluding HbA_{1c} from the equation. This in spite a higher percentage of females achieved the metabolic targets.

Strengths and limitations

Strengths of this study include the validity of data with repeated recordings of the HbA_{1c} and BP at each visit, and that it includes a large cohort of patients treated under real-life conditions such that results might have greater external validity than the highly selected populations in randomized controlled trials (RCT). Still, we cannot rule out that there might be a selection bias in terms of more motivated patients being referred to the clinic, and by exclusion of those who did not show up.

As a result of using a database and a register, we do not have complete data on all patients and therefore the cohort size changes a bit as results are based on those without missing values. Another limitation is that there is a lack of patient reported outcomes, such as adverse events of drugs and general well-being. This was not possible to extract from the electronic medical records. Furthermore we cannot be sure that the patients going through a treatment program actually completed the program or was discharged for other reasons. It is also important to acknowledge that most of the treatment programs analysed here were completed before many of the new anti-diabetic treatments, as GLP1-analogs and sodium-glucose co-transporter 2 (SGLT2)-inhibitors, were widely used and before acceptance of a more personalized treatment as recommended in the position statement from ADA and EASD in 2012 (16). Another limitation of this study is the use of risk engines that only give an estimate of the CVD or CHD risk and that UKPDS is based on a population many years prior to ours and treatment guidelines were not the same.

Meanwhile, the data serves as a baseline benchmark for real world data studies as to what can be achieved in routine clinical practice before these treatments and guidelines get wider use and implementation. The use of a more individualized treatment approach with involvement of the patient in decision making is increasingly used in the treatment programs at the

moment and is expected to increase adherence to therapy. Furthermore, the combination of a more individualized HbA_{1c} target and a broader selection of antidiabetic, antihypertensive and dyslipidaemia treatment will likely increase the proportion of patients achieving their treatment goals and thereby reduce their CVD risk and mortality. Specifically, since the EMPA-REG OUTCOME trial showed a 38% and the LEADER trial a 22% relative risk reduction in deaths from CVD events in patients with type 2 diabetes and a high risk of cardiovascular events (25, 26), this gives us further treatment options in this patient group. Therefore constant evaluation of the effects of our treatments on the risk of CVD or mortality is necessary. Combining these drugs, the treatment program evaluated here, and an individualized approach would be a logical next step for future studies.

Conclusion

This study of patients with type 2 diabetes who undergo structured treatment program lasting less than one year show that it is possible to increase the proportion of patients achieving the target levels for HbA_{1c}, BP, and LDL, thereby reducing their estimated CVD and CHD risk. To the strengths of such a structured program we count the focus on treatment targets by a multidisciplinary team and the fact that it is time limited, which reduces clinical inertia and costs. Our results show that intensive treatment is not only effective in the RCT setting, but also in clinical practice and should encourage other health care systems to establish similar programs.

Conflicts of interest

NS, BC and HV were employed at Steno Diabetes Center A/S, now known as Steno Diabetes Center Copenhagen and MR was employed there when the study was initiated. Steno Diabetes Center A/S was a research hospital working in the Danish National Health Service and owned by Novo Nordisk A/S. NS and BC own shares in Novo Nordisk A/S.

Funding

This study has been funded by Innovation Fund Denmark

Contribution statement

NS and BC were responsible for data management and statistical analysis. NS and MR were responsible for interpretation of data and writing of the article. HV was responsible interpretation and critical revision of the article. All authors fully approved the final version of the article.

Data sharing statement

Clinical data will be available at request, but information on diagnosis and medication is not allowed to be shared by the Danish National Patient Register or Statistics Denmark.

Uncategorized References

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Figure legends

Figure 1 - Flow chart of the treatment program. Visit A: Visit at the laboratory, eye clinic and consultation with nurse. Visit B: Consultation with nurse, dietician and physician. Visit C1 and C2: Individual program with nurse. Group sessions: Module A: 'Me and my diabetes'. Module B: 'My feet and physical activity'. Module C: 'My diet'. Module D: 'My motivation and future lifestyle plans'. Visit C: Consultation with nurse and dietician. Visit D: Final visit with nurse, dietician and endocrinologist. After approximately 8 months patients with no complications are referred back to general practice and those with micro- or macrovascular complications are referred to the outpatient clinic.

Figure 2 - Proportion of patients achieving the treatment targets for HbA_{1c}, LDL cholesterol, systolic and diastolic blood pressure at baseline and at follow-up.

Figure 3 - Proportion of patients on pharmacological treatment at baseline and follow-up.

Table 1 Baseline characteristics of the study cohort

	N	All	Females (*n* = 1,732)	Males (*n* = 2,567)
Age (years)	4,299	59.3 (12.4)	59.9 (12.9)	58.9 (12.1)
Weight (kg)	4,256	91.5 (21.2)	84.4 (20.4)	96.3 (20.4)
Body mass index (kg/m^2)	4,236	31.0 (6.6)	31.8 (7.4)	30.3 (4.4)
Smokers, N (%)	4,071	1,629 (37.9)	622 (35.9)	1,007 (39.5)
Caucasians, N (%)	4,289	3,724 (87)	1,457 (84)	2,267 (89)
Diabetes and complications				
Duration of type 2 diabetes (years)	4,252	7.1 (6.5)	7.3 (6.6)	6.9 (6.5)
Diabetes duration < 1 year, N (%)	4,252	828 (19.5)	311 (18.1)	517 (20.4)
GAD65 antibodies ≥25 U/mL, N (%)	2,376	116 (2.7)	59 (3.4)	57 (2.2)
HbA_{1c} (%)	4,253	8.2 (3.9)	8.1 (3.9)	8.2 (19)
HbA_{1c} (mmol/mol)	4,253	66 (19)	65 (19)	66 (19)
Fasting p-glucose (mmol/L)	2,850	9.9 (3.6)	9.6 (3.4)	10.0 (3.7)
Fasting c-peptide (pmol/L) Median (IQR)	2,898	1050 (706-1500)	1050 (699–1517)	1050 (711-1478)
Prior cardiovascular disease, N (%)†	4,299	1,127 (26)	400 (23)	727 (28)
Microalbuminuria, N (%)	4,299	787 (18)	254 (15)	533 (21)
Macroalbuminuria, N (%)	4,299	211 (5)	47 (3)	164 (6)
eGFR (mL/min)	1,335	78 (17)	77 (18)	79 (16)
Simple retinopathy, N (%)	3,859	1134 (29)	422 (27)	712 (31)
Proliferative retinopathy, N (%)	3,859	56 (1)	25 (2)	31 (1)
Peripheral neuropathy, N (%)	2,343	549 (23)	140 (15)	409 (29)
Blood pressure				
Systolic blood pressure (mm Hg)	4,280	141.7 (21.7)	140.5 (22.5)	142.6 (21.1)

Table 1 Baseline characteristics of the study cohort

	N	All	Females (*n* = 1,732)	Males (*n* = 2,567)
Diastolic blood pressure (mm Hg)	4,280	82.5 (11.5)	80.8 (11.4)	83.6 (11.5)
Lipids				
Total cholesterol (mmol/L)	3,946	4.7 (1.2)	4.9 (1.3)	4.6 (1.2)
LDL cholesterol (mmol/L)	3,946	2.5 (1.0)	2.6 (1.0)	2.5 (1.0)
HDL cholesterol (mmol/L)	3,946	1.2 (0.4)	1.3 (0.4)	1.2 (0.4)
Triglycerides (mmol/L) Median (IQR)	3,946	1.7 (1.2–2.5)	1.7 (1.2–2.5)	1.7 (1.2-2.6)
Medication				
Metformin, N (%)	4,299	2511 (58)	1025 (59)	1486 (58)
Sulfonylurea, N (%)	4,299	1652 (38)	673 (39)	979 (38)
DPP-4 inhibitor, N (%)	4,299	303 (7)	126 (7)	177 (7)
GLP-1 analogue, N (%)	4,299	168 (4)	73 (4)	95 (4)
Insulin, N (%)	4,299	836 (19)	346 (20)	490 (19)
Other OAD, N (%)	4,299	179 (4)	67 (4)	112 (4)
RAS blockade, N (%)	4,299	2027 (47)	736 (17)	1291(30)
All antihypertensive drugs, N (%)	4,299	2678 (62)	1099 (26)	1579 (37)
Lipid lowering drug, N (%)	4,299	1988 (46)	776 (45)	1212 (47)
Acetylsalicylic acid, N (%)	4,299	1538 (36)	530 (31)	1008 (39)

Values are means (SDs) unless stated otherwise.
†Prior CVD was defined as one or more of the following: myocardial infarction, heart surgery, ischaemic heart disease, heart insufficiency, vascular surgery, stroke, transitory cerebral ischaemia, amputation.
CVD, cardiovascular disease; GAD, glutamic acid decarboxylase; HbA_{1c}, haemoglobin A_{1c}; HDL, high-density lipoprotein; LDL, low-density lipoprotein; DPP-4, Dipeptidyl peptidase 4; GLP-1, Glucagon-like peptide 1; OAD, oral antidiabetic drug; RAS, Renin angiotensin system.

Table 2 Estimated CVD or CHD risk

	Baseline	Follow-up
Estimated CVD 5-year risk: NDR Risk engine:		
All	29.8 (19.6-44.6) [a]	25.0 (16.6-37.4) [b,] *
F	24.9 (15.9-37.0)	21.1 (13.7-31.1)*
M	34.0 (22.6-48.2)	28.1 (19.1-41.2)*
Estimated CHD 5-year risk: UKPDS Risk Engine:		
All	7.4 (3.9-13.7) [c]	5.0 (2.7-9.2) [d,] *
F	4.8 (2.6-8.7)	3.3 (1.9-5.9)*
M	9.6 (5.3-16.7)	6.4 (3.7-11.3)*
Estimated CHD 10-year risk: UKPDS Risk Engine:		
All	17.1 (9.3-30.4) [c]	11.8 (6.5-21.1) [d,] *
F	11.4 (6.1-20.0)	7.9 (4.5-14.0)*
M	22.1 (12.6-36.2)	15.0 (9.0-25.4)*

Estimated CVD risk according to the Swedish Nationa Register (NDR) risk engine and the estimated CHD risk according to the UKPDS risk engine. Data is median risk in % (IQR).
a $n = 3,865$; b $n = 3,730$; c $n = 3,895$; d $n = 3,757$, * $P < 0.0001$.

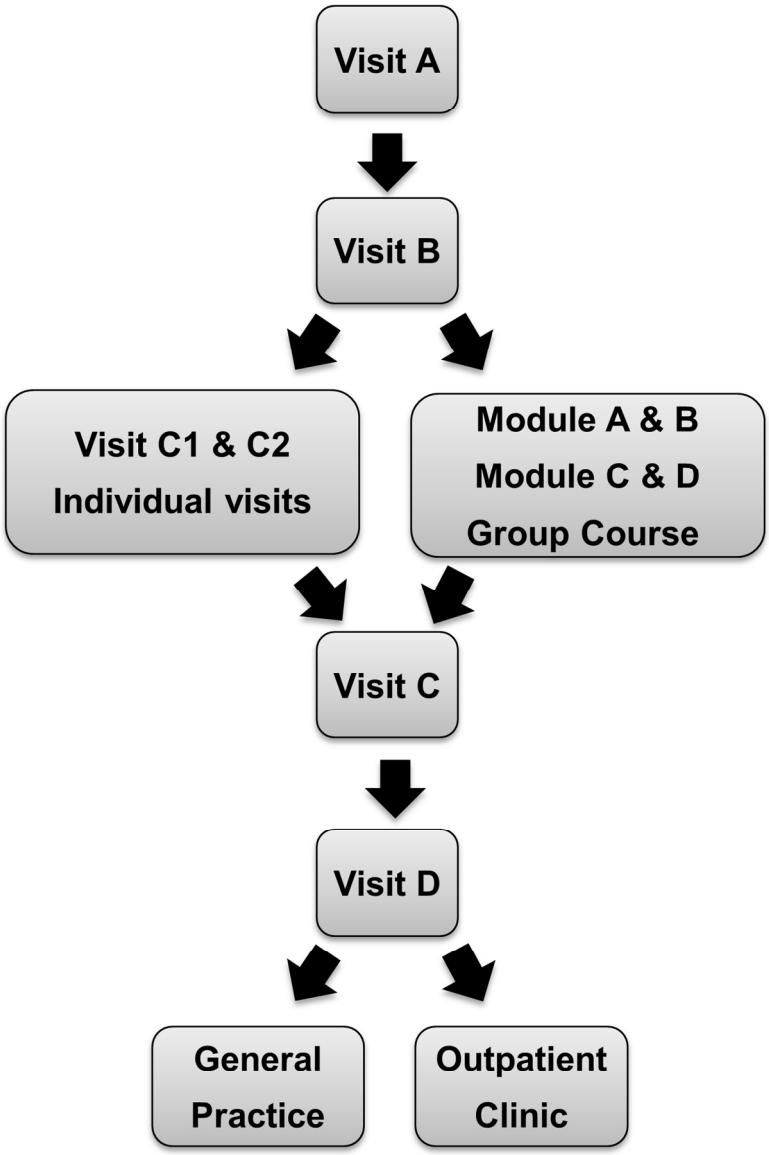

Figure 1 - Flow chart of the treatment program. Visit A: Visit at the laboratory, eye clinic and consultation with nurse. Visit B: Consultation with nurse, dietician and physician. Visit C1 and C2: Individual program with nurse. Group sessions: Module A: 'Me and my diabetes'. Module B: 'My feet and physical activity'. Module C: 'My diet'. Module D: 'My motivation and future lifestyle plans'. Visit C: Consultation with nurse and dietician. Visit D: Final visit with nurse, dietician and endocrinologist. After approximately 8 months patients with no complications are referred back to general practice and those with micro- or macrovascular complications are referred to the outpatient clinic.

121x170mm (300 x 300 DPI)

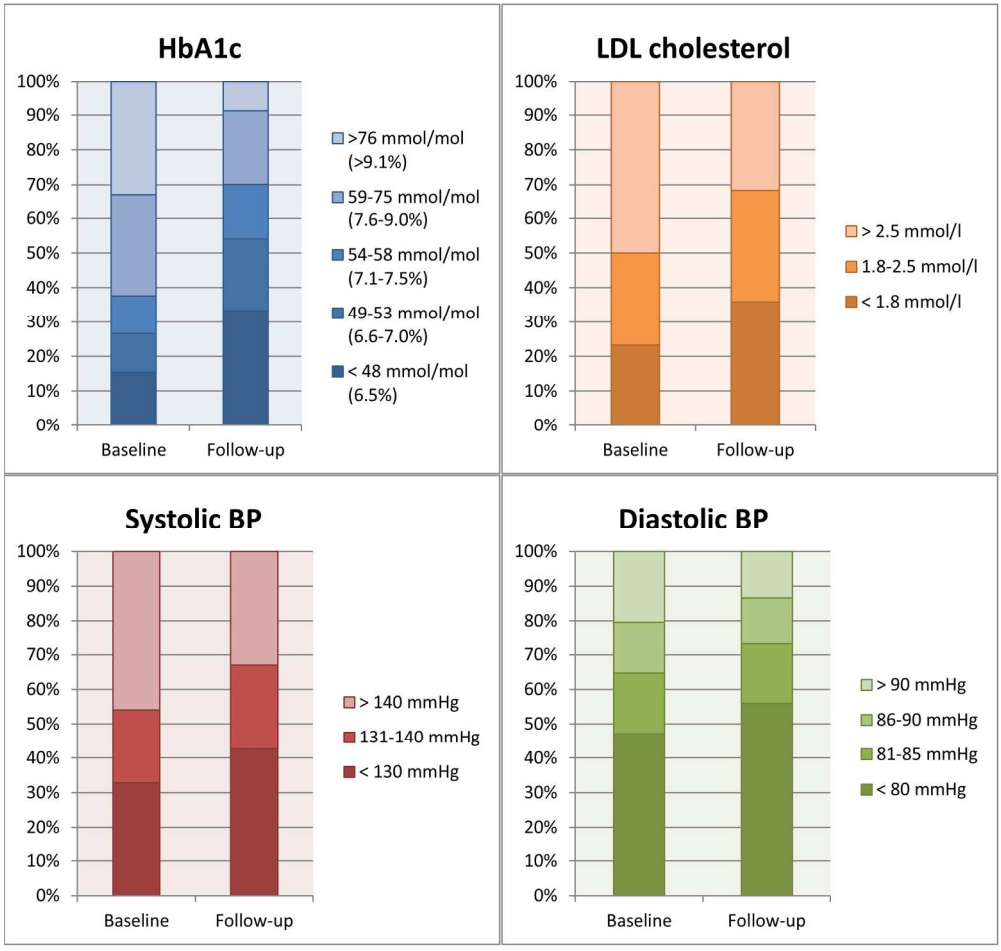

Figure 2 - Proportion of patients achieving the treatment targets for HbA1c, LDL cholesterol, systolic and diastolic blood pressure at baseline and at follow-up.

183x174mm (300 x 300 DPI)

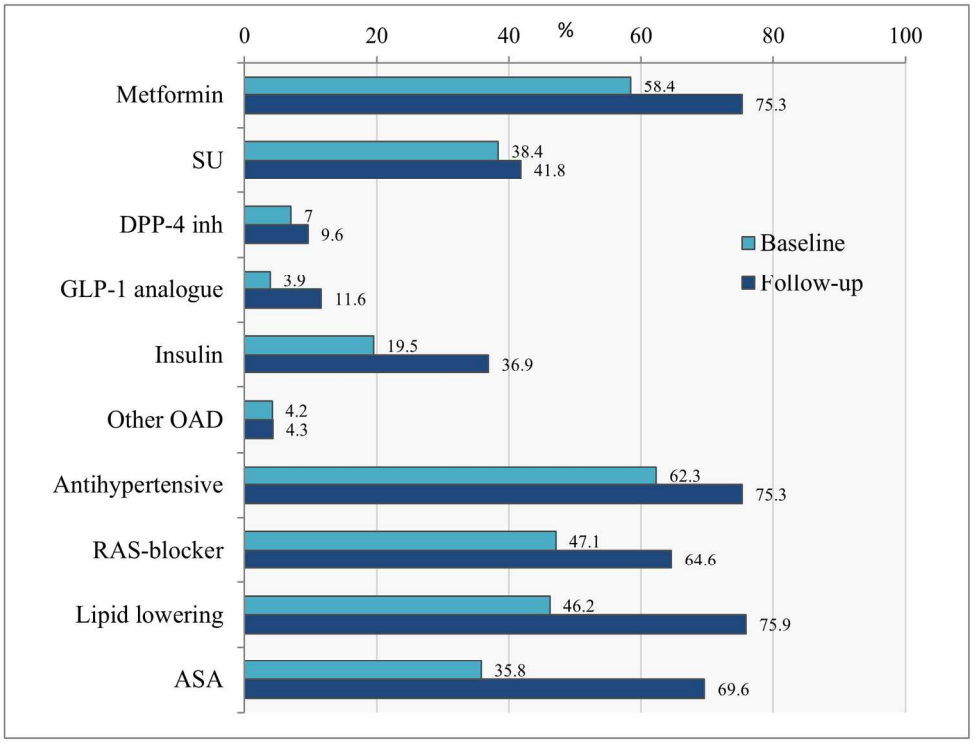

Figure 3 - Proportion of patients on pharmacological treatment at baseline and follow-up.

156x120mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	21 (Table 1)
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	9-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Impact of a multifactorial treatment program on clinical outcomes and cardiovascular risk estimates: a retrospective cohort study from a specialized diabetes centre in Denmark

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019214.R2
Article Type:	Research
Date Submitted by the Author:	23-Jan-2018
Complete List of Authors:	Safai, Narges; Steno Diabetes Center Copenhagen, Patient Care Carstensen, Bendix; Steno Diabetes Center Copenhagen, Department of Clinical Epidemiology Vestergaard, Henrik; The Novo Nordisk Foundation, Center for Basic Metabolic Research, Section of Metabolic Genetics; Steno Diabetes Center Copenhagen, Patient Care Ridderstråle, Martin; Novo Nordisk AS; Lunds Universitet, Department of Clinical Sciences
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Epidemiology, Diabetes and endocrinology, Medical management
Keywords:	Type 2 diabetes, Glycemic control, Outcomes, CVD risk, Multifactorial treatment

Title page

Impact of a multifactorial treatment program on clinical outcomes and cardiovascular risk estimates: a retrospective cohort study from a specialized diabetes centre in Denmark

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Number of tables: 2

Number of figures: 3

Abstract

Objectives: To investigate the impact of a multifactorial treatment program in a real-life setting on clinical outcomes and estimated cardiovascular disease (CVD) risk.

Design: A retrospective observational cohort study, using data from the electronic medical records and national registers.

Setting: Tertiary diabetes centre in Denmark.

Participants: Patients with type 2 diabetes (n=4,299) referred to a program with focus on treatment of hyperglycaemia, hypertension and dyslipidaemia, between Jan 1st 2001 and April 1st 2016.

Outcomes: Primary outcomes were changes in HbA_{1c}, blood pressure and LDL cholesterol as well as proportion reaching treatment targets. Our secondary outcome was to investigate changes in antidiabetic, antihypertensive and lipid lowering treatment, together with the impact on estimated CVD risk. Linear mixed model for repeated measurements were used for continuous variables and logistic regression for dichotomous variables.

Results: The patients achieved a mean ± SD decrease in HbA_{1c}, systolic and diastolic blood pressure (BP), and LDL cholesterol of 1.0±0.04% (10.6±0.4 mmol/mol), 6.3±0.4 mmHg, 2.7±0.2 mmHg and 0.32±0.02 mmol/l, respectively (p<0.0001). The proportion of patients who met the treatment goal for HbA_{1c} (<7% [<53mmol/mol]) increased from 31% to 58% (p <0.0001); for BP (<130/80 mm Hg) from 24% to 34% (p <0.0001), and for LDL cholesterol (<2.5 mmol/l (patients without previous CVD) or <1.8 mmol/l (patients with previous CVD)) from 52% to 65%. Those reaching all three guideline treatment targets increased from 4% to 15% (p<0.0001), and when relaxing the BP target to <140/85 from 8% to 24%. The estimated CVD risk was relatively reduced by 15.2% using the Swedish National Diabetes Register Risk Engine and 30.9% using the UKPDS risk engine.

Conclusions: Our data supports that short term multifactorial treatment of patients with glycaemic dysregulation in a specialist outpatient setting is both achievable and effective, and associated with a clinically meaningful improvement in CVD risk.

Strengths and limitations of this study

- Large cohort of dysregulated patients with type 2 diabetes under real-world conditions and strong validity of data with repeated recordings of clinical measurements and access to national registries.
- Selection bias in terms of more motivated and high risk patients being referred to the clinic, and by exclusion of those who did not show up.
- The use of risk engines can only give an estimate of the CVD risk and the UKPDS risk engine is based on a population many years prior to ours where treatment guidelines were different.

Keywords: Type 2 diabetes, glycaemic control, outcomes, CVD risk and multifactorial treatment

Introduction

Type 2 diabetes is an increasing global health threat. It is estimated that 439 million people will be diagnosed with diabetes by 2030 (1). Type 2 diabetes is associated with an increased risk of microvascular complications such as nephropathy, neuropathy, and retinopathy as well as macrovascular disease, resulting in a decreased life expectancy and substantial personal and societal expenses (2). Ensuring good glycaemic control remains the most effective therapeutic measure to reduce the risk of developing microvascular disease (3, 4). Multifactorial treatment with tight control of glycaemia, blood pressure (BP) and lipids, accompanied by acetylsalicylic acid and lifestyle advice, is known to reduce progression of microvascular complications, cardiovascular disease (CVD), and mortality by 50% in patients with type 2 diabetes and microalbuminuria (5-7). Consequently, diabetes guidelines have advocated an intensified treatment approach aiming at addressing and reducing all CVD risk factors in patients with diabetes since several years (8, 9).

For most patients, sufficient glycaemic, BP and lipid control can be achieved in a primary care setting but in high risk patients, or in patients with complex treatment regimens, the proportion of patients who achieve metabolic control in primary care is lower (10, 11). In this situation, in most health care systems, high risk patients are referred to specialist clinics for evaluation. A broad risk factor intervention in this subgroup has proven particularly effective in the Steno-2 study (5). However, it remains unknown whether the results seen in the study setting can be achieved in clinical practice.

The overall aim of this study was to describe how the multifactorial intervention methods from the Steno-2 study perform in a larger scale clinical setting. Our primary objective was to describe changes in metabolic outcomes as a result of such structured short term intervention

and to test for gender differences. Our secondary objective was to describe the pharmacological changes and to evaluate the impact on estimated CVD risk by using two different risk assessment tools: the UKPDS Risk Engine (12), and the 5-year Swedish National Diabetes Registry (NDR) risk model (13).

Methods

Design and setting

This study is based on patients referred to Steno Diabetes Center (SDC), a tertiary multidisciplinary and highly specialized diabetes centre in the Capital Region of Denmark. It serves as one out of three referral centres with a catchment area of over 1.7 million people and provides diabetes care on a permanent basis to about 5.600 patients. During the Steno-2 study, SDC designed a treatment program algorithm specifically for patients with type 2 diabetes and glycaemic dysregulation. The primary goal of the program is to improve patient quality of life and reduce mortality by prevention of acute and chronic complications of diabetes. This is done by motivating and encouraging self-management, professional support in behavioural changes, and pharmacological treatment according to national and international guidelines. The SDC Type 2 Clinic (T2C) opened in 2001, providing care for patients referred from general practitioners (GPs) or other hospitals in the region. Patients were referred to the clinic either as newly diagnosed with a need for education and start of treatment, requiring a shift to insulin treatment, having micro- or macrovascular complications, or having glycaemic dysregulation in spite of attempts to control the disease by the GP. The program, which is still running and is the same for all patients, involves a consultation with a nurse, a dietician, and a physician in a structured order with specific assignments and is comparable to the intensive treatment arm of the Steno-2 study (Figure 1). The individual visits are, depending on the need, complemented by optional group-based

theme sessions with the overall aim of facilitating patient empowerment and with phone consultations from a nurse. The treatment program consist of self-management training with a focus on knowledge, lifestyle behaviour including diet, physical activity and smoking cessation, skills to improve glycaemic control such as self-monitoring of blood glucose and skills to prevent and identify complications. Furthermore, there is focus on pharmacological treatment of hyperglycaemia, hypertension and dyslipidaemia. After approximately eight months, patients were evaluated for referral back to their GP, or to continue at the SDC outpatient clinic. The structure of program has remained unchanged in the study period while e.g. medications used have followed updated treatment guidelines. The Danish treatment guidelines have followed the international guidelines from EASD and ADA and were revised in 2003, 2011 and 2014 (14-16). We defined the baseline and evaluation follow-up visits as the first and last visit to the T2C, respectively. This study is a retrospective observational study with demographics, clinical, and laboratory information extracted from the electronic medical records and laboratory database of SDC.

Study population

We included all patients who had finalized a treatment program between 1st of January 2001 and 1st of April 2016 (n = 4,489), and to avoid no-shows, once off or very brief consultations we excluded patients with a treatment duration under 30 days (i.e. between the baseline and follow-up visits, n = 190). We ended up with a total of n = 4,299 patients. 16% of the patients were subsequently re-referred to the clinic, but we only included their first treatment program here. All data was anonymized prior to analysis.

Subject characteristics

Laboratory analyses at the baseline visit were encouraged to be fasting and included: glucose, HbA_{1c}, haemoglobin, creatinine, total-cholesterol, high-density lipoprotein-cholesterol (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides (TG), C-peptide and urine albumin. At all in-between visits and at follow-up an HbA_{1c}, BP and weight were measured. All laboratory and anthropometric measurements were recorded using standardized procedures at the SDC accredited laboratory (ISO 15189). Body mass index (BMI) was calculated from weight and height (kg/m^2). A person was considered overweight at BMI $\geq$ 25 kg/m^2, and obese at BMI $\geq$ 30 kg/m^2. For BP and heart rate automated oscillometric blood pressure recorders were used (AND UA-787plus, A&D medical, California, USA). Smoking status was obtained at every visit.

Diabetes complications and pharmacological treatment

Micro albuminuria was here defined as a morning urine sample with urine albumin of 30-300 mg/L or urine albumin to creatinine ratio > 30 mg/g to 300 mg/g at the first visit. Macro albuminuria likewise but with a value > 300 mg/L or > 300 mg/g. Peripheral neuropathy was defined by examining vibration sensation with a biothesiometer and using an age-adjusted threshold (17). Information on cardiovascular disease was obtained from The National Patient Register and included diagnosis from 1977 till 2015 and procedures from 1995 till 2015. Prior CVD was defined as one or more of the following: myocardial infarction, heart surgery, ischaemic heart disease, heart insufficiency, atrial fibrillation, vascular surgery, stroke, transitory cerebral ischaemia and amputations using ICD-8 and ICD-10 codes.

Information on medication was obtained by Register of Medicinal Products Statistics, where individual-level data on all prescription drugs sold in Danish community pharmacies since 1994 has been recorded and administered by Statistics Denmark (18). A person was defined as being on a treatment at baseline if they had purchased a prescribed drug less than 180 days

before their first visit and at follow-up if they purchased a prescribed drug after their first visit and less than 30 days after their last visit.

Permission to use data has been obtained from the Danish Data Protection Agency (ref. number: 2007-58-0015) and from the Danish Patient Safety Authority. According to Danish Committee law register studies do not require an approval from the National Committee on Health Research Ethics.

CVD risk

To evaluate the effect of changes in metabolic outcomes on the estimated risk of CVD, we calculated CVD risk at baseline and at follow-up using two different risk assessment tools: a Swedish risk model specific for type 2 diabetes (13) and the UKPDS Risk Engine (12) . The Swedish model is based on patients with type 2 diabetes using 12 predictors: sex, age, diabetes duration, TG, HDL cholesterol, HbA1c, systolic BP, BMI, smoking status, albuminuria, atrial fibrillation and previous CVD. It is derived from a large observational sample of patients (n = 24,288) in the Swedish National Diabetes Register (NDR) followed from 2002 to 2007 and estimates the 5-year risk of CVD. The UKPDS Risk Engine is also type 2 diabetes-specific and based on 4,540 patients from the UKPDS trial (1977 to 1991). It includes HbA_{1c} as a continuous variable and calculates the risk of developing a new coronary heart disease (CHD) event.

Statistical methods

The primary outcomes were changes in blood glucose control (HbA_{1c}), BP and lipids from first visit (baseline) to end of treatment (follow-up evaluation visit) and to explore gender differences in outcomes. Furthermore we investigated how many patients reached the recommended targets for HbA_{1c} (A), BP (B) and LDL cholesterol (C) according to national

guidelines (14), collectively referred to as ABC control: HbA_{1c} < 7% (< 53 mmol/mol), BP < 130/80 mm Hg and LDL cholesterol < 2.5 mmol/l (< 100 mg/dl, patients without previous CVD) or < 1.8 mmol/l (< 70 mg/dl, patients with previous CVD). For blood lipids, the T2C program assumed they would not deteriorate if they were on target at baseline and measurements were only repeated in case they were not at target at baseline. Accordingly, for this analysis a last observation carried forward approach was used to impute missing data. *T* test was used to test for gender differences at baseline or at follow-up. Comparison between baseline and follow-up was made using mixed model for repeated measurements (MMRM) for continuous variables adjusting for gender and baseline values and with the subject as a random effect. For dichotomous variables e.g. pharmacological treatment, logistic regression models were used adjusting for gender. McNemar test was used to compare changes in categorical variables. For risk estimates, exact 95%-confidence intervals (CI) were calculated. SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC) was used for database management and all of the above-mentioned analyses.

Results

Study cohort characteristics

Baseline characteristics of the study cohort are shown in Table 1. The majority of patients were Caucasians, and 19% were diagnosed with diabetes within a year before their referral. There were more males (n = 2,567) than females (n = 1,732) but no difference in treatment duration: median treatment program duration was 8.4 months (IQR: 6.1, 11.3). There were more male smokers and ex-smokers. Males had a higher level of HbA_{1c}, BP, weight and TG but lower BMI and cholesterol levels at baseline (Table 1).

Metabolic outcomes

There was a significant decrease in HbA_{1c} between baseline and follow-up of 1.0 ± 0.04% (10.6 ± 0.4 mmol/mol), with no gender difference. The decrease in systolic BP was 6.3 ± 0.4 mm Hg and in diastolic BP 2.7 ± 0.2 mm Hg ($p < 0.0001$ for both). The effect of treatment on BP was the same in both genders. There was a significant decrease in total-cholesterol, LDL and TG of 0.39 ± 0.03 mmol/l, 0.32 ± 0.02 mmol/l and 0.22 ± 0.05 mmol/l, respectively. There was no change in HDL levels overall ($p = 0.2$). As expected, females had higher HDL levels than males, both at baseline and at follow-up ($p < 0.0001$). This gender difference was also seen for total- and LDL cholesterol levels where females had higher levels at both baseline and follow-up. The effect of treatment on lipid levels was equal in both genders.

ABC control

In general, the proportion of patients achieving full ABC control according to national guideline treatment targets increased from 4% to 15% ($p < 0.0001$). More females were achieving all three treatment targets at both baseline ($p = 0.047$) and at follow-up ($p = 0.014$). Patients achieving the HbA_{1c} target increased from 31% to 58% ($p < 0.0001$), the BP target from 24% to 34% ($p < 0.0001$), and the LDL target from 52% to 65% ($p = 0.002$, Figure 2). If the BP target was relaxed from < 130/80 mm Hg to < 140/85 mm Hg the percentage achieving the BP target increased from 43% at baseline to 58% at follow-up ($p < 0.0001$), and consequently full ABC control from 8% at baseline to 24% at follow-up ($p < 0.0001$).

Changes in pharmacological treatment

The most common antidiabetic drug at baseline was metformin, which 58.4% of the patients were on, followed by sulphonyl urea (SU), 38.4%, and insulin, 19.5% (Figure 3). Only a small proportion of patients were on dipeptidyl peptidase 4 (DPP-4) inhibitors, 7.0%,

glucagon-like peptide 1 (GLP-1) analogues, 3.9%, or other antidiabetic drug, 4.2%. In general there was an increase in the use of medication during the program. The largest increase was seen in use of metformin to 75.3%, insulin to 36.9% and GLP1-analogues to 11.6%. While SU only increased slightly to 41.8%, DPP-4 inhibitors to 9.6% and other antidiabetics 4.3%.

As part of the multifactorial treatment program, we also observed an increase in use of antihypertensive drugs to 75.3%, lipid lowering drugs to 75.9% and acetylsalicylic acid (ASA) to 69.6%.

Changes in cardiovascular risk

Estimated baseline and follow-up cardiovascular risk according to the used risk engines are shown in Table 2. Using the Swedish NDR model which predicts the 5 year risk of a new CVD event in a diabetic population, we observed a relative risk reduction of 15.2% (95% CI: 14.5-15.9). The UKPDS risk engine showed a relative risk reduction of 30.9% (95% CI: 30.3-31.5) in the 5 year CHD risk estimate. Females had a lower risk than males both at baseline and at follow-up according to both risk models ($p < 0.0001$). Meanwhile, both according to the Swedish NDR model and the UKPDS risk engine, females had a smaller relative risk reduction compared to males ($p < 0.0001$).

Discussion

This study shows that a short term targeted multifactorial treatment program in a specialized clinical setting can improve metabolic outcome measures and CVD risk in patients with type 2 diabetes and high prevalence of complications. This confirms that multifactorial treatment not only works in a clinical study setting, but is also feasible and effective in real world

clinical practice. With a specialized group of health care providers and a structured treatment and educational program that focuses on lifestyle intervention, self-management training and pharmacological treatment of hyperglycaemia, hypertension and dyslipidaemia, it is possible to accomplish significant CVD risk reductions in a high risk population with diabetes.

ABC control

Intensive multifactorial intervention in high risk patients has previously been shown to reduce CVD and mortality (7), and a recent 21 years follow-up of the Steno-2 study population shows that patients in the intensive-therapy group survived for a median of 7.9 years longer than the conventional-therapy group patients (19). Here we show that the same treatment program also works in clinical practice in a more diverse population, and results in a substantial reduction of 5- and 10-year CVD risk as estimated by two of the available and commonly used risk engines. In terms of risk factor intervention, glucose control continuous to be the greatest challenge to diabetes care. Nonetheless, all but 21% of patients changed from a higher to a lower HbA_{1c} category in this follow-up. Importantly, the improvement in glycaemic control was not accompanied by a general increase in weight. In fact, although we found that 15% of those in the normal weight category shifted to the overweight category when comparing the changes in BMI categories, 15% of those who were in the obese or overweight category dropped to a lower weight category. The weight gain observed in some patients is probably explained by the increased use of insulin, while weight loss in others can be explained by an increased use of GLP-1 receptor agonist treatment in recent years along with lifestyle management including dietary and physical activity advice.

With focus on hyperglycaemia, hypertension and dyslipidaemia, we found an increase in the proportion of patients achieving the recommended targets that are comparable to intervention

studies (20, 21). Here, the relative proportion of patients achieving HbA_{1c} < 53 mmol/mol (7%) nearly doubled, BP < 130/80 mm Hg increased by 42% and LDL < 2.5 mmol/l by 25%. The T2C treatment program in this complex high-risk cohort resulted in a higher prevalence of risk factors in control equal to what has been observed in the more general diabetes population in the National Health and Nutrition Examination Surveys (NHANES) from 2007 to 2010 (22). The NHANES data differ in the way that their data was cross-sectional with participants with self-reported diabetes, without any distinction between type 1 and type 2, and with a different risk profile. Our population was more selected by being referred from their GP and requiring specialized care, which means they either had more comorbidities or a more complex treatment than the general patient with type 2 diabetes. For HbA_{1c} 58% in our cohort achieved the treatment target vs 53% in the NHANES cohort and for LDL-cholesterol 65% vs 56%, respectively. But for BP there was a big difference, 34% in our cohort vs. 51% in the NHANES cohort. This could be due to a higher prevalence of high BP in this group of patients selected with complex disease and long diabetes duration. We did observe a time trend in the data as the proportion of patients achieving the stringent BP target increased from 23% in 2001 to 44% in 2015. The same improvement trend over time was observed in the proportion of patients achieving all three ABC targets; 7% in 2001 increasing to an average of 16% from 2006 and forward in our material and in the NHANES data from 7% in 1999-2002 to 19% in 2007-2010.

CVD risk

To estimate the CVD risk in patients with type 2 diabetes is helpful to follow-up on treatment and to target further measures to patients at risk. In this study we used two different CVD risk engines to estimate the effect of the treatment program. The UKPDS risk engine is diabetes-specific and has several advantages as it incorporates HbA_{1c} and diabetes duration as

continuous variables (12). However, it is still not ideal as it is based on the patients recruited by UKPDS for randomization in a clinical trial two decades ago before newer and more effective treatments were available or widely used (e.g. statins, angiotensin converting enzyme inhibitors and antidiabetic drugs). Accordingly, recent validation showed poor calibration and overestimation of the CHD risk (23). A model that seems more suitable for our population is the Swedish NDR risk model, which is based on a more recent and nationwide population, reflecting a more diverse population and taking into account the history of previous CVD and BMI. By using this model we found a relative reduction in the estimated 5-year CVD risk of 16%, after approximately eight months, despite the increase in age and diabetes duration. Notably, the fact that 26% of the patients had a prior CVD diagnosis at baseline reflects the high risk profile and complexity of the population that was referred to the treatment program. This of course does not normalise their actual risk, which will still be high, but can be a motivating factor for the patients that there are some modifiable risk factors that can reduce their risk. In comparison, the population used in the Swedish model had a mean risk of 11.9% and a 5-year risk of fatal/non-fatal CVD of more than 10% is defined as high risk. According to this 92% of our population was in high risk at baseline. The UKPDS risk engine which estimates the risk of the first CHD event in 5 or 10 years, gives a lower 5 and 10 year risk estimate at baseline than the Swedish model, 7.4% and 17.1% respectively. This is nearly the same as the 10-year risk found in a NHANES population from 2007 to 2012 of 16.5% if no risk factors were in control and 10.2% if all risk factors were in control when using the same risk engine (24).

Interestingly, both the NDR and UKPDS risk engines estimated a higher risk reduction in males than in females. This, perhaps expected finding, could be due to the higher CVD risk in males at baseline, but could also be due to a relatively greater HbA_{1c} reduction seen in males, which is used in both the NDR and the UKPDS risk engines. However, the gender difference

remained significant after excluding HbA_{1c} from the equation. This in spite a higher percentage of females achieved the metabolic targets.

Strengths and limitations

Strengths of this study include the validity of data with repeated recordings of the HbA_{1c} and BP at each visit, and that it includes a large cohort of patients treated under real-life conditions such that results might have greater external validity than the highly selected populations in randomized controlled trials (RCT). Still, we cannot rule out that there might be a selection bias in terms of more motivated patients being referred to the clinic, and by exclusion of those who did not show up.

As a result of using a database and a register, we do not have complete data on all patients and therefore the cohort size changes a bit as results are based on those without missing values. Another limitation is that there is a lack of patient reported outcomes, such as adverse events of drugs and general well-being. This was not possible to extract from the electronic medical records. Furthermore we cannot be sure that the patients going through a treatment program actually completed the program or was discharged for other reasons. It is also important to acknowledge that most of the treatment programs analysed here were completed before many of the new anti-diabetic treatments, as GLP1-analogs and sodium-glucose co-transporter 2 (SGLT2)-inhibitors, were widely used and before acceptance of a more personalized treatment as recommended in the position statement from ADA and EASD in 2012 (16). Another limitation of this study is the use of risk engines that only give an estimate of the CVD or CHD risk and that UKPDS is based on a population many years prior to ours and treatment guidelines were not the same.

Meanwhile, the data serves as a baseline benchmark for real world data studies as to what can be achieved in routine clinical practice before these treatments and guidelines get wider use

and implementation. The use of a more individualized treatment approach with involvement of the patient in decision making is increasingly used in the treatment programs at the moment and is expected to increase adherence to therapy. Furthermore, the combination of a more individualized HbA_{1c} target and a broader selection of antidiabetic, antihypertensive and dyslipidaemia treatment will likely increase the proportion of patients achieving their treatment goals and thereby reduce their CVD risk and mortality. Specifically, since the EMPA-REG OUTCOME trial showed a 38% and the LEADER trial a 22% relative risk reduction in deaths from CVD events in patients with type 2 diabetes and a high risk of cardiovascular events (25, 26), this gives us further treatment options in this patient group. Therefore constant evaluation of the effects of our treatments on the risk of CVD or mortality is necessary. Combining these drugs, the treatment program evaluated here, and an individualized approach would be a logical next step for future studies.

Conclusion

This study of patients with type 2 diabetes who undergo structured treatment program lasting less than one year show that it is possible to increase the proportion of patients achieving the target levels for HbA_{1c}, BP, and LDL, thereby reducing their estimated CVD and CHD risk. To the strengths of such a structured program we count the focus on treatment targets by a multidisciplinary team and the fact that it is time limited, which reduces clinical inertia and costs. Our results show that intensive treatment is not only effective in the RCT setting, but also in clinical practice and should encourage other health care systems to establish similar programs.

Conflicts of interest

NS, BC and HV were employed at Steno Diabetes Center A/S, now known as Steno Diabetes Center Copenhagen and MR was employed there when the study was initiated. Steno Diabetes Center A/S was a research hospital working in the Danish National Health Service and owned by Novo Nordisk A/S. NS and BC own shares in Novo Nordisk A/S.

Funding

This study has been funded by Innovation Fund Denmark

Contribution statement

NS and BC were responsible for data management and statistical analysis. NS and MR were responsible for interpretation of data and writing of the article. HV was responsible interpretation and critical revision of the article. All authors fully approved the final version of the article.

Data sharing statement

Clinical data will be available at request, but information on diagnosis and medication is not allowed to be shared by the Danish National Patient Register or Statistics Denmark.

Uncategorized References

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Figure legends

Figure 1 - Flow chart of the treatment program. Visit A: Visit at the laboratory, eye clinic and consultation with nurse. Visit B: Consultation with nurse, dietician and physician. Visit C1 and C2: Individual program with nurse. Group sessions: Module A: 'Me and my diabetes'. Module B: 'My feet and physical activity'. Module C: 'My diet'. Module D: 'My motivation and future lifestyle plans'. Visit C: Consultation with nurse and dietician. Visit D: Final visit with nurse, dietician and endocrinologist. After approximately 8 months patients with no complications are referred back to general practice and those with micro- or macrovascular complications are referred to the outpatient clinic.

Figure 2 - Proportion of patients achieving the treatment targets for HbA_{1c}, LDL cholesterol, systolic and diastolic blood pressure at baseline and at follow-up.

Figure 3 - Proportion of patients on pharmacological treatment at baseline and follow-up.

Table 1 Baseline characteristics of the study cohort

	N	All	Females (*n* = 1,732)	Males (*n* = 2,567)
Age (years)	4,299	59.3 (12.4)	59.9 (12.9)	58.9 (12.1)
Weight (kg)	4,256	91.5 (21.2)	84.4 (20.4)	96.3 (20.4)
Body mass index (kg/m^2)	4,236	31.0 (6.6)	31.8 (7.4)	30.3 (4.4)
Smokers, N (%)	4,071	1,629 (37.9)	622 (35.9)	1,007 (39.5)
Caucasians, N (%)	4,289	3,724 (87)	1,457 (84)	2,267 (89)
Diabetes and complications				
Duration of type 2 diabetes (years)	4,252	7.1 (6.5)	7.3 (6.6)	6.9 (6.5)
Diabetes duration < 1 year, N (%)	4,252	828 (19.5)	311 (18.1)	517 (20.4)
GAD65 antibodies ≥25 U/mL, N (%)	2,376	116 (2.7)	59 (3.4)	57 (2.2)
HbA_{1c} (%)	4,253	8.2 (3.9)	8.1 (3.9)	8.2 (19)
HbA_{1c} (mmol/mol)	4,253	66 (19)	65 (19)	66 (19)
Fasting p-glucose (mmol/L)	2,850	9.9 (3.6)	9.6 (3.4)	10.0 (3.7)
Fasting c-peptide (pmol/L) Median (IQR)	2,898	1050 (706-1500)	1050 (699–1517)	1050 (711-1478)
Prior cardiovascular disease, N (%)†	4,299	1,127 (26)	400 (23)	727 (28)
Microalbuminuria, N (%)	4,299	787 (18)	254 (15)	533 (21)
Macroalbuminuria, N (%)	4,299	211 (5)	47 (3)	164 (6)
eGFR (mL/min)	1,335	78 (17)	77 (18)	79 (16)
Simple retinopathy, N (%)	3,859	1134 (29)	422 (27)	712 (31)
Proliferative retinopathy, N (%)	3,859	56 (1)	25 (2)	31 (1)
Peripheral neuropathy, N (%)	2,343	549 (23)	140 (15)	409 (29)
Blood pressure				
Systolic blood pressure (mm Hg)	4,280	141.7 (21.7)	140.5 (22.5)	142.6 (21.1)

Table 1 Baseline characteristics of the study cohort

	N	All	Females (*n* = 1,732)	Males (*n* = 2,567)
Diastolic blood pressure (mm Hg)	4,280	82.5 (11.5)	80.8 (11.4)	83.6 (11.5)
Lipids				
Total cholesterol (mmol/L)	3,946	4.7 (1.2)	4.9 (1.3)	4.6 (1.2)
LDL cholesterol (mmol/L)	3,946	2.5 (1.0)	2.6 (1.0)	2.5 (1.0)
HDL cholesterol (mmol/L)	3,946	1.2 (0.4)	1.3 (0.4)	1.2 (0.4)
Triglycerides (mmol/L) Median (IQR)	3,946	1.7 (1.2–2.5)	1.7 (1.2–2.5)	1.7 (1.2-2.6)
Medication				
Metformin, N (%)	4,299	2511 (58)	1025 (59)	1486 (58)
Sulfonylurea, N (%)	4,299	1652 (38)	673 (39)	979 (38)
DPP-4 inhibitor, N (%)	4,299	303 (7)	126 (7)	177 (7)
GLP-1 analogue, N (%)	4,299	168 (4)	73 (4)	95 (4)
Insulin, N (%)	4,299	836 (19)	346 (20)	490 (19)
Other OAD, N (%)	4,299	179 (4)	67 (4)	112 (4)
RAS blockade, N (%)	4,299	2027 (47)	736 (17)	1291(30)
All antihypertensive drugs, N (%)	4,299	2678 (62)	1099 (26)	1579 (37)
Lipid lowering drug, N (%)	4,299	1988 (46)	776 (45)	1212 (47)
Acetylsalicylic acid, N (%)	4,299	1538 (36)	530 (31)	1008 (39)

Values are means (SDs) unless stated otherwise.
†Prior CVD was defined as one or more of the following: myocardial infarction, heart surgery, ischaemic heart disease, heart insufficiency, vascular surgery, stroke, transitory cerebral ischaemia, amputation.
CVD, cardiovascular disease; GAD, glutamic acid decarboxylase; HbA_{1c}, haemoglobin A_{1c}; HDL, high-density lipoprotein; LDL, low-density lipoprotein; DPP-4, Dipeptidyl peptidase 4; GLP-1, Glucagon-like peptide 1; OAD, oral antidiabetic drug; RAS, Renin angiotensin system.

Table 2 Estimated CVD or CHD risk

	Baseline	Follow-up
Estimated CVD 5-year risk: NDR Risk engine:		
All	29.8 (19.6-44.6) [a]	25.0 (16.6-37.4) [b,] *
F	24.9 (15.9-37.0)	21.1 (13.7-31.1)*
M	34.0 (22.6-48.2)	28.1 (19.1-41.2)*
Estimated CHD 5-year risk: UKPDS Risk Engine:		
All	7.4 (3.9-13.7) [c]	5.0 (2.7-9.2) [d,] *
F	4.8 (2.6-8.7)	3.3 (1.9-5.9)*
M	9.6 (5.3-16.7)	6.4 (3.7-11.3)*
Estimated CHD 10-year risk: UKPDS Risk Engine:		
All	17.1 (9.3-30.4) [c]	11.8 (6.5-21.1) [d,] *
F	11.4 (6.1-20.0)	7.9 (4.5-14.0)*
M	22.1 (12.6-36.2)	15.0 (9.0-25.4)*

Estimated CVD risk according to the Swedish Nationa Register (NDR) risk engine and the estimated CHD risk according to the UKPDS risk engine. Data is median risk in % (IQR).
a $n = 3,865$; b $n = 3,730$; c $n = 3,895$; d $n = 3,757$, * $P < 0.0001$.

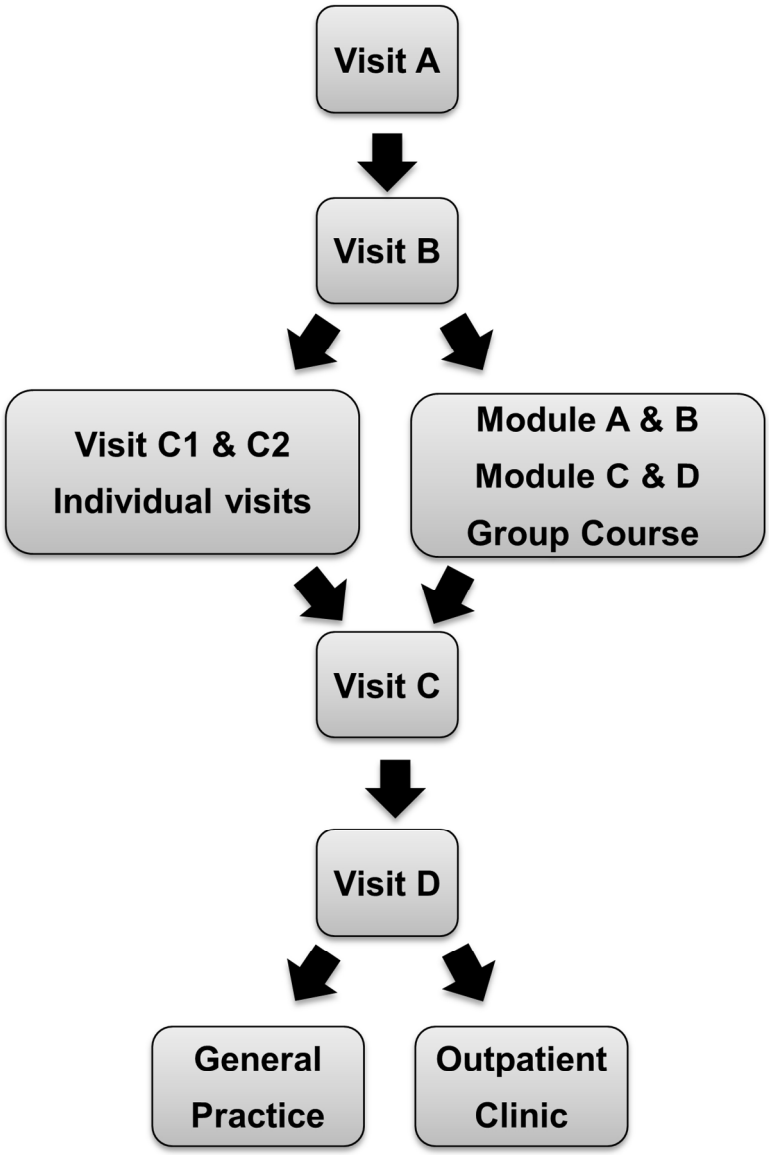

Figure 1 - Flow chart of the treatment program. Visit A: Visit at the laboratory, eye clinic and consultation with nurse. Visit B: Consultation with nurse, dietician and physician. Visit C1 and C2: Individual program with nurse. Group sessions: Module A: 'Me and my diabetes'. Module B: 'My feet and physical activity'. Module C: 'My diet'. Module D: 'My motivation and future lifestyle plans'. Visit C: Consultation with nurse and dietician. Visit D: Final visit with nurse, dietician and endocrinologist. After approximately 8 months patients with no complications are referred back to general practice and those with micro- or macrovascular complications are referred to the outpatient clinic.

121x170mm (300 x 300 DPI)

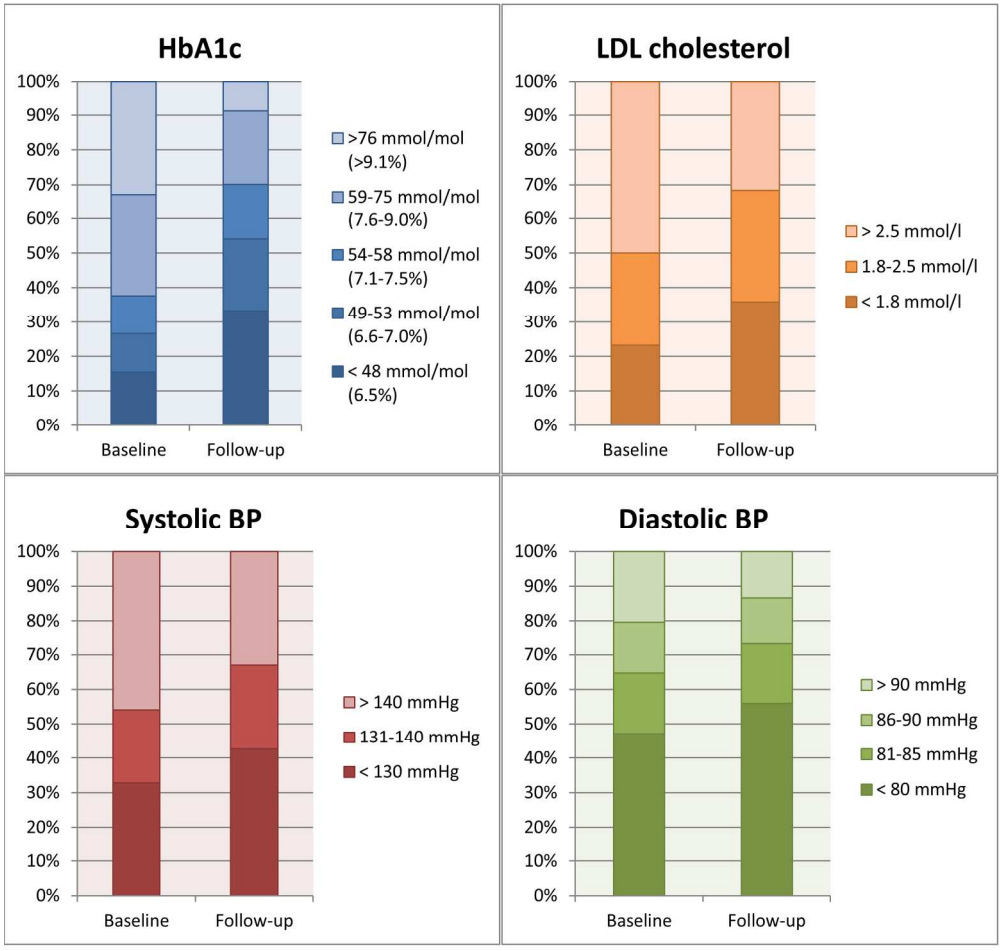

Figure 2 - Proportion of patients achieving the treatment targets for HbA1c, LDL cholesterol, systolic and diastolic blood pressure at baseline and at follow-up.

183x174mm (300 x 300 DPI)

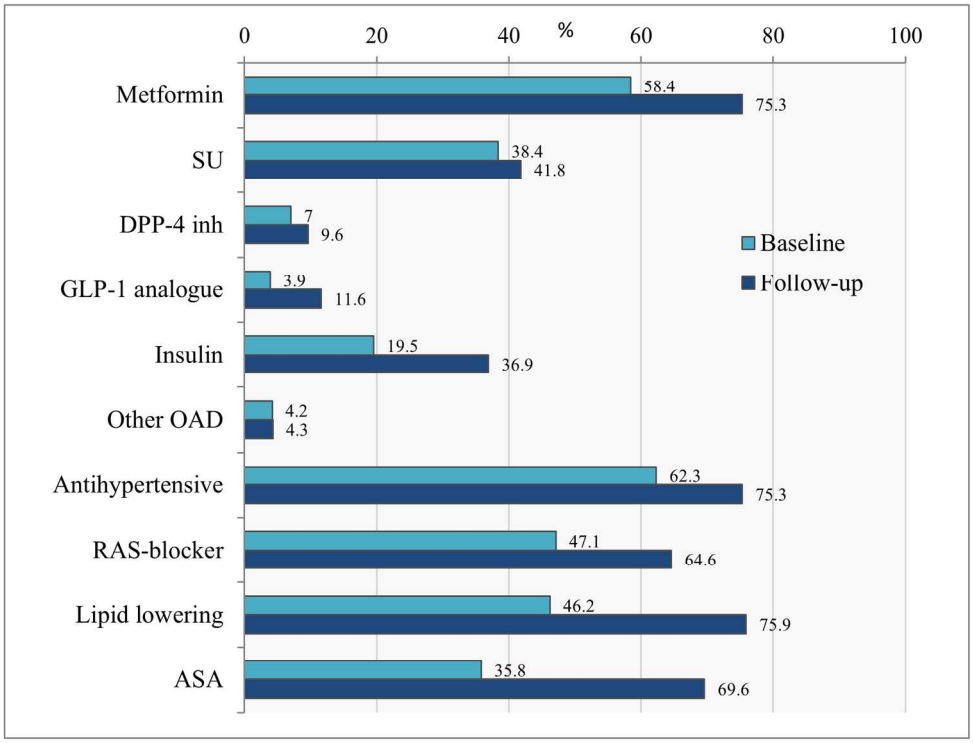

Figure 3 - Proportion of patients on pharmacological treatment at baseline and follow-up.

156x120mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	21 (Table 1)
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	9-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.