Diabetologia (2013) 56:1243–1253
DOI 10.1007/s00125-013-2893-1

ARTICLE

Structured personal care of type 2 diabetes: a 19 year follow-up of the study Diabetes Care in General Practice (DCGP)

L. J. Hansen · V. Siersma · H. Beck-Nielsen · N. de Fine Olivarius

Received: 9 November 2012 / Accepted: 27 February 2013 / Published online: 3 April 2013

Abstract
Aims/hypothesis This study is a 19 year observational follow-up of a pragmatic open multicentre cluster-randomised controlled trial of 6 years of structured personal diabetes care starting from diagnosis.
Methods A total of 1,381 patients aged ≥40 years and newly diagnosed with type 2 diabetes were followed up in national registries for 19 years. Clinical follow-up was at 6 and 14 years after diabetes diagnosis. The original 6 year intervention included regular follow-up and individualised goal setting, supported by prompting of doctors, clinical guidelines, feedback and continuing medical education (ClinicalTrials.gov NCT01074762). The registry-based endpoints were: incidence of any diabetes-related endpoint; diabetes-related death; all-cause mortality; myocardial infarction (MI); stroke; peripheral vascular disease; and microvascular disease.
Results At 14 year clinical follow-up, group differences in risk factors from the 6 year follow-up had levelled out, although the prevalence of (micro)albuminuria and level of triacylglycerols were lower in the intervention group. During 19 years of registry-based monitoring, all-cause mortality was not different between the intervention and comparison groups (58.9 vs 62.3 events per 1,000 patient-years, respectively; for structured personal care, HR 0.94, 95% CI 0.83, 1.08, p=0.40), but a lower risk emerged for fatal and non-fatal MI (27.3 vs 33.5, HR 0.81, 95% CI 0.68, 0.98, p=0.030) and any diabetes-related endpoint (69.5 vs 82.1, HR 0.83, 95% CI 0.72, 0.97, p=0.016). These differences persisted after extensive multivariable adjustment.
Conclusions/interpretation In concert with features such as prompting, feedback, clinical guidelines and continuing medical education, individualisation of goal setting and drug treatment may safely be applied to treat patients newly diagnosed with type 2 diabetes to lower the risk of diabetes complications.

Keywords Any diabetes-related endpoint · Chronic care model · Mortality · Multifactorial intervention · Myocardial infarction · Stroke · Type 2 diabetes

Abbreviations

ADDITION	Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care
DCGP	Diabetes Care in General Practice
GEE	Generalised estimating equations
IQR	Interquartile range
MI	Myocardial infarction
UKPDS	UK Prospective Diabetes Study

Introduction

Strict control of blood glucose [1, 2], BP [3, 4] or lipids [5] lowers the risk of diabetes complications, and a long-term legacy effect of intervention started at diabetes diagnosis has been proposed [6]. Although assessments of the quality of diabetes care continue to show suboptimal management [7, 8], the benefit of pursuing intensive glucose control in all patients to reduce cardiovascular disease has been questioned [9–12]. In response to this, the European Association for the Study of Diabetes (EASD) and the ADA, in a joint

Electronic supplementary material The online version of this article (doi:10.1007/s00125-013-2893-1) contains peer-reviewed but unedited supplementary material, which is available to authorised users.

L. J. Hansen · V. Siersma · N. de Fine Olivarius (✉)
Research Unit for General Practice and Section of General Practice, Department of Public Health, University of Copenhagen, Øster Farimagsgade 5, PO Box 2099, 1014 Copenhagen K, Denmark
e-mail: olivarius@sund.ku.dk

H. Beck-Nielsen
Medical Department M, Odense University Hospital, University of Southern Denmark, Odense, Denmark

position statement, have recommended individualising both treatment goals and choice of pharmacological intervention in the management of hyperglycaemia [13]. The application of evidence-based but individualised treatment schemes in daily clinical practice may be tested through multifactorial interventions, targeting health professionals, which have been shown to improve process measures and risk factors in primary care [14]. The effects of such complex interventions on cardiovascular and microvascular outcomes are, however, largely unknown.

The Diabetes Care in General Practice (DCGP) study [15] was a randomised controlled 6 year trial to assess the effect on mortality and morbidity of structured personal care compared with routine care in a population-based sample of patients newly diagnosed with clinical type 2 diabetes. This 19 year follow-up of the DCGP study assessed the long-term effectiveness of 6 years of structured personal diabetes care that was started at diagnosis in primary care. Outcomes were mortality as well as cardiovascular and microvascular complications.

Methods

Study design The DCGP was a pragmatic open cluster-randomised controlled trial (ClinicalTrials.gov NCT01074762) [15]. Of 1,902 general practitioners invited to participate in 1988, 474 (24.9%) volunteered (Fig. 1). Their practices were allocated, by random numbers, to give patients either

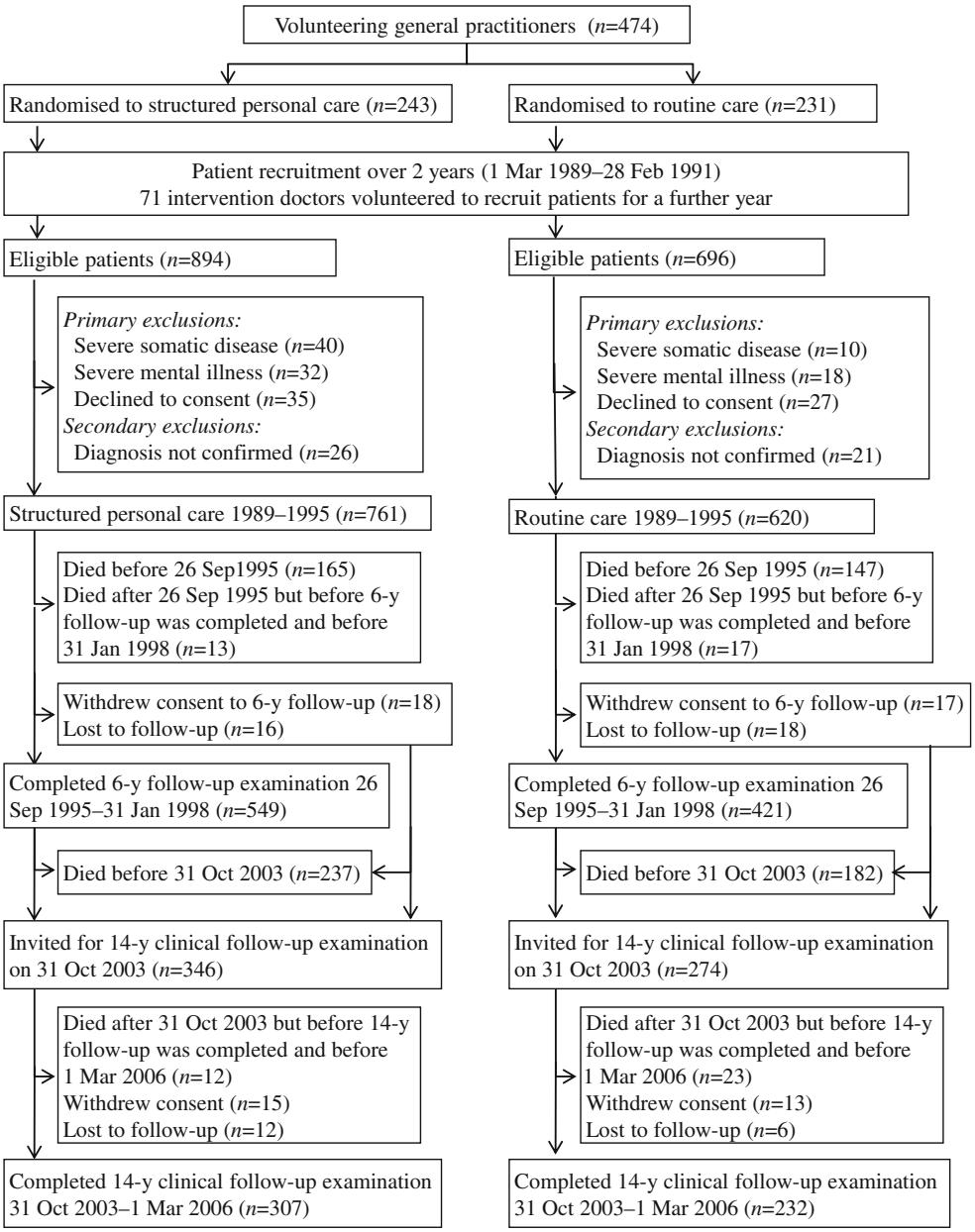

Fig. 1 Patient flow from inclusion until 14-year clinical follow-up examination

structured personal care or routine care. A detailed description of the study design has been reported previously [15]. The study was approved by the research ethics committee of Copenhagen and Frederiksberg and informed consent was given by all patients.

Patients The doctors were to include all of those on their practice list who were aged 40 or older and newly diagnosed with diabetes between 1 March 1989 and 28 February 1991. In the third year, 71 doctors in the structured-personal-care group on invitation volunteered to recruit patients for a further year (Fig. 1). These patients received the same intervention as the other patients in the structured-care group.

Following recruitment, diagnosis was confirmed by a single fasting whole-blood/plasma glucose concentration ≥7.0/8.0 mmol/l, measured at a major laboratory. Patients who were diagnosed during hospitalisation were also considered for inclusion. The protocol-based exclusion criteria were life-threatening somatic disease, severe mental illness or unwillingness to participate. For the present analyses, we excluded patients whose diagnosis was not confirmed at a major laboratory within 500 days of diagnosis [15]. Of 1,381 patients in the final study population, 1,369 (99.1%) were of Western European descent. Based on onset of insulin treatment, approximately 97.5% of the patients were considered to have type 2 diabetes.

Table 1 Treatment goals for patients in the structured-personal-care group during the trial period 1989–1995

Variable	Good control[a]	Acceptable control[b]	Poor control[c]
Fasting blood glucose (mmol/l)[d]	≤7.0	≤8.0	>8.0
Non-fasting blood glucose (mmol/l)[d]	≤9.0	≤11.0	>11.0
HbA_{1c} (%)[e]	≤7.0	≤8.5	>8.5
Diastolic BP (mmHg)	≤90	≤100	>100
Total cholesterol (mmol/l)	≤6.0	≤7.0	>7.0
Fasting triacylglycerols (mmol/l)	≤2.0	≤5.0	>5.0

General practitioners were instructed as follows. The aim is normalisation of blood glucose, BP, lipids and possibly weight. For some patients, it will be impossible or even inappropriate to try to achieve the ideal goal, but *prolonged symptoms of hyperglycaemia or hypoglycaemia must not be accepted for any patient*. From an overall therapeutic point of view, the general practitioner can choose to aim at the treatment goals in one of the three categories. The choice of category is primarily based on HbA_{1c}

[a] Normalisation of metabolism; this ideal demand is particularly relevant in young and middle-aged patients and in well-motivated older patients

[b] Acceptable metabolic regulation; this applies to some older patients and patients who are difficult to treat and/or difficult to motivate for treatment

[c] Freedom from symptoms; this category is intended to be chosen when the course of treatment has shown that any goal other than freedom from hyperglycaemic symptoms is beyond reach

[d] Capillary whole-blood glucose

[e] Reference range 5.4–7.4%

Intervention In Denmark, routine care for standard type 2 diabetes is usually managed in primary care, with costs covered by the free tax-based health insurance system. In the intervention group, follow-up every 3 months and annual screening for diabetes complications were supported by sending a questionnaire to the general practitioner 1 month before the next expected consultation [15]. The general practitioner was requested to define, together with the patient, the best possible goals, within three predefined categories of 'good', 'acceptable' and 'poor' control, for important risk factors, with emphasis on glycaemic control (Table 1). At each quarterly consultation, the general practitioner was asked to compare the achievements with the goal and consider changing either goal or treatment accordingly. In overweight patients, the general practitioner was prompted to get agreement on a small realistic weight reduction, record it and follow up accordingly. However, participants were not required to target a specific relative body weight.

The general practitioners were introduced to possible solutions to therapeutic problems through six annual half-day seminars, annual descriptive feedback reports on individual patients, and folders and leaflets for doctors and patients. Generally, the importance of diet was stressed and doctors were recommended to postpone, if possible, the start of glucose-lowering drugs until at least 3 months after diabetes diagnosis to observe the effect of any weight loss. It was suggested that the general practitioners recommend increased physical exercise and simple dietary rules: to increase complex carbohydrate to at least 50% of the diet and, in particular, to increase water-soluble fibre; to reduce fat content to a maximum of 30%; to reduce alcohol intake; and to eat five or six meals a day. In cases of persistent hyperglycaemia, metformin was recommended for patients who were overweight by clinical judgment, and glipizide or glibenclamide was suggested for patients of normal weight. In patients aged >70 years, tolbutamide was recommended. If the goal for blood glucose was not met, a combination of metformin and a sulfonylurea was suggested as the last step before starting insulin. To treat hypertension, ACE inhibitors or β blockers were recommended for most patients, but furosemide (frusemide) was preferred for patients with heart failure, and thiazides for patients aged >70 years. Lipid-lowering drugs were recommended for diet-resistant dyslipidaemia. No patient-specific advice on treatment was given to doctors, who were allowed to deviate from the recommendations in an effort to individualise treatment. The patients were never approached by the study centre.

Doctors in the routine-care group were free to choose any treatment and change it over time [15]. The study coordinating centre did not contact routine-care practices during the trial period after inclusion had stopped. On 26 September 1995, the intervention was terminated. No further attempt was made to maintain patients in randomised groups or to influence their therapy.

Registry-based monitoring over 19 years Everyone living in Denmark is registered in the Danish Civil Registration System with a permanent and unique personal identification number, which enables linkage between study populations and all national registries [16]. In the present study, the vital and emigration statuses of all patients were certified through this system, and surviving patients were censored on 31 December 2008. For one patient the vital status could not be assessed because this person had emigrated in 1992. The Danish Register of Causes of Death contains, among other things, information about underlying and possible contributory causes of death [17]. In four cases the cause of death was not recorded in this registry. The Danish National Patient Register includes information on almost all contacts with hospitals in Denmark (e.g. discharge diagnose[s] and surgical procedures performed) [18]. These two registries provided information on deaths or hospital admissions for relevant conditions (see electronic supplementary material [ESM] Table 1).

Clinical follow-up examinations 6 and 14 years after diagnosis Approximately 6 and 14 years after diabetes diagnosis, on 26 September 1995 and 31 October 2003, the general practitioners of all surviving patients were asked to do a follow-up examination (Fig. 1). The doctors recorded the following information: body weight, BP, drug treatment, severe hypoglycaemic events, number of consultations the preceding year and if the patient had ever been treated at a diabetes clinic. In questionnaires, patients gave information about smoking habits and physical activity in their leisure time. Fasting blood samples were collected at diagnosis and at the follow-up examinations and were analysed at Odense University Hospital; freshly voided morning urine samples were analysed at Århus University Hospital. Throughout the study, the fraction of HbA_{1c} was determined by the same ion-exchange HPLC protocol. The reference interval was calculated after analysis of samples from 100 blood donors (age 20–80 years, 33 men, 67 women) to be 5.4–7.4% (mean±2 SD). Quality assurance was obtained with commercial control preparations from BioRad. The means of low- and high-control samples were 6.7% (0.31%) and 10.4% (0.63%), respectively, resulting in CVs of 4.6% and 6.0% (CV=SD× 100/mean). This method was later compared with a newer HPLC method (using an automated HbA_{1c} analyser, Tosoh G7), which was aligned with the DCCT using calibrators from the European Reference Laboratory for Glycated Haemoglobin (ERL). The association between the two methods is approximately linear (R^2 0.9049, n=484, p<0.0001), and is expressed by the following algorithm: current method=0.268+1.072×DCCT-aligned method. Although it is impossible to convert individual measurements made using the current method to the newer method, the reference range of the current method (5.4–7.4%) may, with caution, be converted to 4.8–6.7% (29–50 mmol/mol), which corresponds approximately to DCCT values. A description of other variables and definitions has previously been published [15].

The 6 and 14 year clinical follow-up examinations were done for 970 (93.4%) and 539 (92.1%) of 1,039 and 585 surviving patients, respectively (Fig. 1). Because patients moved or new doctors joined or took over a practice, 147 new doctors joined the study during the first 6 years and a further 114 new doctors volunteered for the 14 year follow-up. The clustering of patients according to general practitioners and the number of patients who moved to a doctor outside the original randomisation arm throughout the trial are given in ESM Tables 2 and 3.

Statistical analysis For clinical, biochemical, behavioural and process variables the randomisation arms were compared for the patients who completed the 6 and 14 year follow-up with the p values of the corresponding regression coefficients from a multivariate generalised linear model in which the effect of randomisation group was adjusted for age, sex and diabetes duration: ordinary linear regression for continuous variables, logistic regression for binary variables and Poisson regression for count variables with $\log_e$(diabetes duration) as offset. Clustering with general practitioners was accounted for by the use of generalised estimating equations (GEE).

The outcomes used in the registry-based follow-up were made with reference to those in the UK Prospective Diabetes Study (UKPDS) [6]: any diabetes-related endpoint, diabetes-related deaths, all-cause mortality, myocardial infarction (MI), stroke, peripheral vascular disease and microvascular disease (ESM Table 1). Length of time from diagnosis to death or incident outcomes was analysed with logrank tests and Cox regression models. The proportional hazard assumption was tested by adding the interactions of each of the independent variables in the model with the natural logarithm of time to event to the model. A joint test of these interactions tested the assumption. When one or more of the interactions were significant, the hazard function was estimated separately within strata of the corresponding covariates. A sandwich estimator for the variance was used to account for clustering [19].

All variables and endpoints were analysed with SAS v9.2 (SAS Institute Inc., Cary, NC, USA) according to the intention-to-treat principle. The level of statistical significance was p<5%.

Results

At diabetes diagnosis, median age (interquartile range [IQR]) for the 1,381 patients was 65.4 (55.7–73.6) years and male:female ratio was 1.13 (733:648). The 6 and 14 year

clinical follow-up examinations were attended by a similar proportion of surviving intervention and routine-care patients (94.2% [549/583] vs 92.3% [421/456], p=0.24, and 91.9% [307/334] vs 92.4% [232/251], p=0.82, respectively, χ^2 test, Fig. 1).

At the end of intervention, the structured-personal-care group had significantly lower levels of HbA_{1c} (8.4% vs 9.0%, reference range 5.4–7.4%, p<0.0001), systolic BP (145 vs 150 mmHg, p=0.003) and total cholesterol (6.0 vs 6.1 mmol/l, p=0.033) than the routine-care group (Table 2). At 14 year clinical follow-up, group differences had levelled out, though some of the measures suggest a lasting intervention effect, with a lower level of triacylglycerols, a lower prevalence of (micro)albuminuria, and fewer referrals to a diabetes clinic.

At the end of the intervention, metformin was more widely used in the intervention group (24 vs 15%, p<0.001) than in the routine-care group, the only significant group difference in use of drugs observed [15]. In the 14 year follow-up, the two groups received similar but more intensive drug treatment (ESM Table 4).

During 19 years of registry-based monitoring, all seven predefined outcomes were experienced by a lower proportion of patients receiving structured personal care compared with patients receiving routine care (Table 3, Fig. 2). Group differences were, however, only statistically significant for any diabetes-related endpoint (HR for structured care 0.83, 95% CI 0.72, 0.97, p=0.016) and fatal or non-fatal MI (HR 0.81, 95% CI 0.68, 0.98, p=0.030). These differences persisted after extensive multivariate adjustment: HR 0.80, 95% CI 0.69, 0.92, p=0.003 and HR 0.81, 95% CI 0.67, 0.99, p=0.039, respectively. Survival was not statistically significantly associated with the intervention (HR 0.94, 95% CI 0.82, 1.08, p=0.40, with multivariate adjustment, Table 3 and Fig. 2). In the period after the intervention was terminated, there was a non-significant tendency towards lower incidence rates for structured care for most outcomes, and this propensity was most pronounced for stroke and any diabetes-related endpoint (Fig. 2, Table 3). Apart from peripheral vascular disease and microvascular disease the proportion of patients with an outcome was relatively high. For any diabetes-related endpoint the number (%) of patients in the intervention and control groups were 405 (66.3%) and 366 (73.4%). For MI the corresponding figures were 219 (31.5%) and 210 (37.3%), respectively.

Discussion

This long-term follow-up of the DCGP randomised trial of structured personal diabetes care was analysed as an observational study with extensive adjustments for clustering and confounders. During 19 years of monitoring, a statistically significantly reduced risk for MI and any diabetes-related endpoint emerged for patients in the intervention arm. No effect was shown on peripheral vascular disease and microvascular outcomes, possibly because our study was underpowered to detect group differences for these events, which were rare compared with the other outcomes in this study. In comparison with most trials from outpatient clinics [1–4, 20], our study population was small and attrition was high, mainly due to the high mortality in our ageing population-based patient sample. On one hand, the many outcomes caused by the high average age at diagnosis (65 years) endowed the study with statistical strength to analyse group differences in mortality and incidences of cardiovascular outcomes. On the other hand, in elderly patients these outcomes in particular are expected to have causes unrelated to diabetes, and the final results of this study appear as a trade-off between these underlying preconditions.

When the intervention was terminated, the between-group differences in fasting plasma glucose, HbA_{1c}, total cholesterol and BP were relatively small compared with the UKPDS glucose and hypertension trials [1, 3]. After a further 8 years, these differences in risk factors had levelled out as most risk factors improved in both treatment groups and treatment intensity had increased (Table 2, ESM Table 4). The improvements in (micro)albuminuria and fasting triacylglycerols at 14 year follow-up, however, indicates a lasting intervention effect on surrogate outcomes beyond that seen in UKPDS [6]. All things considered, these findings add to the evidence for a legacy intervention effect in type 2 diabetes on long-term development of complications, and extend them to the primary healthcare setting. They also suggest that improved outcomes may be attainable within the framework of a complex intervention with individualised treatment.

Previous research Overall, the effectiveness of different solitary quality-improvement strategies for glycaemic control in type 2 diabetes is modest. We incorporated regular follow-up, prompting of doctors, feedback on individual patients, clinical guidelines and continuing medical education for doctors in our multifaceted intervention because all these elements seem to be effective [14, 21–23]. Later, all of these aspects of chronic care were included in the chronic care model [24–26]. On top of this, we added individualised goal setting [27, 28]. In complex interventions the effect cannot easily be ascribed to single elements, but it is likely that the improvements in both risk factors and endpoints can be explained, at least partly, by the combined effect of small changes in process and lifestyle measures, which we were unable to pick up with our relatively simple data collection instruments (Table 2). The intervention probably had too little focus on smoking cessation, increased physical activity and prescription of lipid-lowering drugs (Table 2; ESM

Table 2 Clinical, biochemical, behavioural and process variables for patients who completed clinical examinations at diabetes diagnosis and at 6 and 14 year clinical follow-up

Variable	At diabetes diagnosis 1989–1992			At 6 year clinical follow-up examination 1995–1997				At 14 year clinical follow-up examination 2003–2005			
	No. of patients (structured/routine care)	Structured care	Routine care	No. of patients (structured/routine care)	Structured care	Routine care	*p* value	No. of patients (structured/routine care)	Structured care	Routine care	*p* value
Clinical											
Body weight (kg)	745/619	81.5 (71.4–93.5)	82.0 (72.0–92.0)	537/410	79.6 (69.5–90.0)	80.5 (70.0–91.5)	0.87	286/222	79.1 (69.0–91.5)	79.9 (69.0–93.0)	0.43
Systolic BP (mmHg)	755/619	150 (130–164)	145 (130–160)	546/415	145 (132–160)	150 (140–165)	0.003	300/228	140 (130–150)	140 (130–150)	0.70
Diastolic BP (mmHg)	755/619	85 (80–90)	85 (80–90)	546/415	80 (80–90)	82 (78–90)	0.71	300/228	80 (70–82)	80 (70–85)	0.74
Biochemical											
Fasting plasma glucose (mmol/l)	761/620	13.6 (10.7–16.9)	13.8 (10.7–17.1)	426/300	7.9 (6.5–10.3)	8.8 (7.2–11.6)	0.0005	286/216	7.6 (5.9–9.4)	7.6 (6.4–9.6)	0.35
HbA_{1c} (%)[a]	624/512	10.2 (8.6–11.7)	10.2 (8.7–11.9)	539/414	8.4 (7.7–9.4)	9.0 (8.0–10.3)	<0.0001	286/213	8.3 (7.5–9.2)	8.5 (7.9–9.5)	0.16
Total cholesterol (mmol/l)	740/610	6.2 (5.3–7.1)	6.2 (5.5–7.2)	538/414	6.0 (5.2–6.8)	6.1 (5.4–6.9)	0.033	291/217	4.9 (4.3–5.7)	4.9 (4.2–5.7)	0.34
Fasting triacylglycerols (mmol/l)	736/610	1.97 (1.42–2.85)	1.99 (1.39–2.96)	503/356	1.76 (1.22–2.47)	1.92 (1.28–2.78)	0.45	290/219	1.55 (1.17–2.22)	1.89 (1.24–2.47)	0.009
Serum creatinine (μmol/l)	740/611	90 (80–101)	88 (79–100)	538/414	89 (80–103)	91 (80–105)	0.83	290/218	92 (81–109)	96 (86–115)	0.52
Urinary albumin	723/595			513/394			0.60	289/214			0.015
Normal		414 (57.3)	324 (54.5)		318 (62.0)	229 (58.1)			154 (53.3)	92 (43.0)	
Microalbuminuria		246 (34.0)	206 (34.6)		173 (33.7)	143 (36.3)			118 (40.8)	96 (44.9)	
Proteinuria		63 (8.7)	65 (10.9)		22 (4.3)	22 (5.6)			17 (5.9)	26 (12.1)	
Behavioural											
Current smoking[b]	742/604	264 (35.6)	208 (34.4)	504/399	162 (32.1)	116 (29.1)	0.30	273/201	71 (26.0)	47 (23.4)	0.47
Sedentary activity[b]	741/604	210 (28.3)	162 (26.8)	500/401	143 (28.6)	128 (31.9)	0.51	275/206	80 (29.1)	59 (28.6)	0.93
Process of care											
No. of diabetes-related consultations last year[b,d]				549/420	4 (3–6)	4 (2–6)	0.035	292/221	4 (2–5)	4 (1–6)	0.045
No. ever treated at diabetes clinic[b]				549/421	92 (16.8)	111 (26.4)	0.002	300/229	137 (45.7)	131 (57.2)	0.023
No. of hospital admissions since diagnosis[c]				549/421	1 (0–2)	1 (0–3)	0.95	307/232	5 (2–9)	5 (2–10)	0.29
No. with severe hypoglycaemia since diagnosis (6 years) or during the last year (14 years)[b]				547/419	18 (3.3)	15 (3.6)	0.76	299/229	19 (6.4)	11 (4.8)	0.46

Values are medians (IQRs) or numbers (percentages of group). The median (IQR) time from diagnosis until 6 year follow-up was 5.57 years (4.96–6.16 years) in the structured-personal-care group and 5.85 years (5.30–6.45 years) in the routine-care group. The corresponding time from diagnosis to date of 14 year follow-up was 13.75 years (13.07–14.48 years) and 14.01 years (13.38–14.50 years), respectively

p values are from multivariate generalised linear models (ordinary linear regression for continuous variables, logistic regression for binary variables and Poisson regression for count variables with $\log_e$[diabetes duration] as offset) where the effect of structured care vs routine care is adjusted for age, sex and diabetes duration. Clustering with general practitioners is accounted for by the use of GEE

[a] The diagnostic value is limited to measurements from within 45 days of diabetes diagnosis; reference range 5.4–7.4%

[b] Data from questionnaires to patients (behavioural) or their general practitioners (process of care)

[c] The Danish National Patient Register provided this information from diabetes diagnosis until the day of the 6 year follow-up examination or until 31 December 2005 for the 14 year follow-up examination

[d] The mean numbers of diabetes-related consultations last year for structured/routine care at 6 and 14 year follow-up were 5.1/4.4 and 3.9/4.6, respectively

No., number

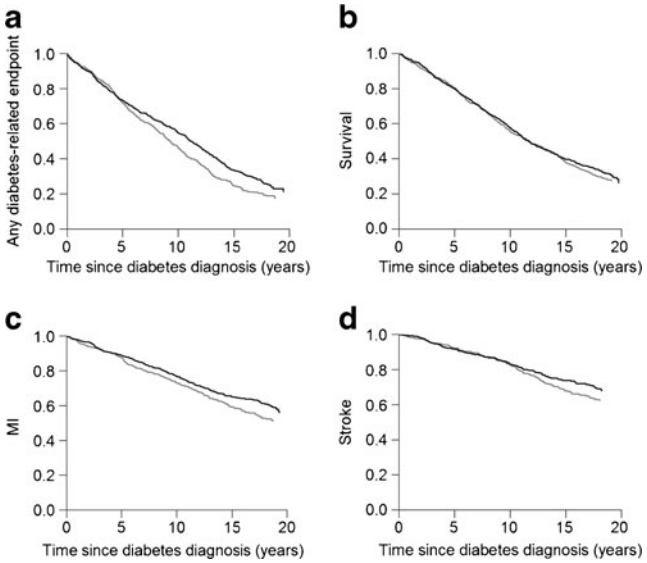

Fig. 2 Kaplan–Meier plots showing the proportion of patients without four selected outcomes since diabetes diagnosis: (**a**) any diabetes-related endpoint (p=0.010); (**b**) all-cause mortality (p=0.38); (**c**) MI (p=0.033); and (**d**) stroke (p=0.16). Black line, structured-personal-care group; grey line, routine-care group. p values are from unadjusted logrank tests

Table 4), and, in general, the patients might have benefitted from more intensive theory-based patient education and support [29].

In blood glucose trials testing intensive multipharmacological treatment to target, adverse weight gain is common [1, 9–11, 20]. In the DCGP study, in which it was recommended that treatment goals for risk factors including weight be negotiated by the doctor and patient, an average weight loss was maintained for 14 years in both groups. In the intervention group, doctors had been asked not to start drug treatment before the patients had experienced the effects of their own efforts to shape a new lifestyle [15, 30]. Other lifestyle interventions have been shown to reduce the use of medication for diabetes considerably [31], and diet may be the most important component of such interventions [32].

Patients' absolute risk of developing a cardiovascular outcome was greater than in other diabetes trials [1, 3, 6, 9–11, 33, 34] (Table 3). For MI defined as in the present analyses, a meta-analysis [12] of these trials [1, 10, 11, 34] found event rates of 13.3 and 14.7 per 1,000 patient-years in intervention and control groups, respectively, and HR 0.90 (95% CI 0.82, 0.99). In the DCGP study the corresponding figures were event rates of 27.3 and 33.5 per 1,000 patient-years and HR 0.81 (95% CI 0.67, 0.99) (Table 3). Thus, the incidence of MI in DCGP was twice that of major cardiovascular outcome studies of intensive glucose control in type 2 diabetes, and the absolute risk reduction for intensive care was four times greater. Relatively old patients may be more compliant than younger patients [35], and the personalised care may be particularly well taken up by elderly patients, which could contribute to the explanation of our results.

Further strengths and weaknesses The study was originally conducted and reported as a cluster-randomised trial [15]. The present analyses are not described in the protocol, and are therefore interpreted as observational and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [36], with adjustment for confounders and clustering.

Our main results rest on long-term follow-up in major Danish registries. The vital status and cause of death could be confirmed for 99.9% and 99.7% of study participants, respectively. The Danish Register of Causes of Death has covered the entire population of Denmark since 1875 [17], and the Danish National Patient Registry has covered 99.4% of discharges from Danish hospitals since 1977 [37]. From 1995 onwards the registry has also included emergency room and outpatient clinic visits, but the registry has only covered all contacts with hospitals in Denmark since 2007, primarily because registrations from the few and small private specialised hospitals were missing [18]. However, these hospitals are not supposed to be contributors of information about the outcomes in this study. Both registries have changed registration and coding practices on several occasions, and the concepts and definitions of diseases have changed; new diagnostic criteria for MI were introduced in 2000, for example. In the nationwide DCGP study these time-dependent changes in registration are unlikely to cause differential misclassification according to treatment allocation. The validity has not been established for all the registry-based diagnoses in Table 3, but for MI as primary diagnosis or underlying cause of death the predictive value was 93.6% and the sensitivity was 77.6% in comparison with definite or possible MI as diagnosed in the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Project in Denmark [38]. In a small retrospective audit of patient records, the predictive value of the stroke diagnosis in the Danish National Patient Register was 81–86% [39].

While our registry data in Table 3 are relatively strong, our results in Table 2 from the clinical follow-up of surviving patients must be interpreted in view of the slightly unequal attrition across randomisation groups. Similarly, even for those re-examined at 6 and 14 year follow-up, data may be missing differentially according to outcomes. Estimations of biochemical variables, however, were centralised and quality controlled.

In the registry-based follow-up, detailed information enabled us to make extensive adjustments for a wide spectrum of clinically relevant confounding factors, which, for most

Table 3 Outcomes from registry-based monitoring during 19 years from diabetes diagnosis

Endpoint and follow-up period (years after diabetes diagnosis)	No. without the outcome at baseline (structured/routine care)	No. of patients with outcome (%)			Absolute risk (events per 1,000 patient-years)		HR for structured care (95% CI)[b]					
		Structured care	Routine care	*p* value[a]	Structured care	Routine care	Adjusted for clustering only	*p* value	Adjusted for age, sex, clustering and diabetes duration[c]	*p* value	Multivariate adjustment[d]	*p* value
Any diabetes-related endpoint												
0–19 years	611/499	405 (66.3)	366 (73.4)	0.012	69.5	82.1	0.83 (0.72, 0.97)	0.016	0.83 (0.72, 0.96)	0.010	0.80 (0.69, 0.92)	0.003
0–6 years	611/499	165 (27.0)	153 (30.7)	0.20	61.3	66.7	0.93 (0.74, 1.16)	0.51	0.92 (0.74, 1.15)	0.48	0.92 (0.73, 1.17)	0.50
6–19 years	409/318	240 (58.7)	213 (67.0)	0.018	76.5	98.4	0.77 (0.64, 0.93)	0.006	0.76 (0.62, 0.94)	0.013	0.81 (0.63, 1.03)	0.086
Diabetes-related deaths												
0–19 years	759/618	327 (43.1)	278 (45.0)	0.48	36.9	39.0	0.95 (0.80, 1.11)	0.50	0.96 (0.82, 1.13)	0.63	0.98 (0.82, 1.17)	0.83
0–6 years	759/618	106 (14.0)	92 (14.9)	0.62	29.0	30.1	0.97 (0.74, 1.28)	0.82	0.96 (0.73, 1.27)	0.77	1.01 (0.75, 1.37)	0.94
6–19 years	594/471	221 (37.2)	186 (39.5)	0.44	42.5	45.7	0.93 (0.76, 1.13)	0.46	0.96 (0.78, 1.17)	0.67	0.99 (0.78, 1.27)	0.94
All-cause mortality												
0–19 years	761/620	522 (68.6)	444 (71.6)	0.25	58.9	62.3	0.94 (0.83, 1.08)	0.40	0.95 (0.83, 1.09)	0.46	0.94 (0.82, 1.08)	0.40
0–6 years	761/620	165 (21.7)	147 (23.7)	0.39	45.1	48.0	0.95 (0.75, 1.19)	0.64	0.93 (0.74, 1.18)	0.55	0.95 (0.74, 1.23)	0.69
6–19 years	596/473	357 (59.9)	297 (62.8)	0.35	68.7	73.0	0.94 (0.80, 1.10)	0.44	1.00 (0.84, 1.18)	0.97	0.98 (0.81, 1.19)	0.85
MI												
0–19 years	696/563	219 (31.5)	210 (37.3)	0.024	27.3	33.5	0.81 (0.68, 0.98)	0.030	0.84 (0.69, 1.01)	0.060	0.81 (0.67, 0.99)	0.039
0–6 years	696/563	76 (10.9)	75 (13.3)	0.17	22.1	27.3	0.84 (0.61, 1.14)	0.25	0.84 (0.62, 1.15)	0.28	0.87 (0.63, 1.21)	0.42
6–19 years	541/424	143 (26.4)	135 (31.8)	0.046	30.5	38.4	0.80 (0.64, 1.00)	0.047	0.85 (0.67, 1.08)	0.18	0.95 (0.71, 1.28)	0.75
Stroke												
0–19 years	727/591	156 (21.5)	146 (24.7)	0.15	19.5	22.8	0.85 (0.68, 1.06)	0.16	0.86 (0.69, 1.07)	0.17	0.93 (0.75, 1.17)	0.54
0–6 years	727/591	61 (8.4)	50 (8.5)	0.96	17.9	17.4	1.04 (0.71, 1.51)	0.85	1.03 (0.71, 1.48)	0.88	1.11 (0.76, 1.61)	0.59
6–19 years	541/435	95 (17.6)	96 (22.1)	0.082	20.6	27.1	0.76 (0.57, 1.01)	0.061	0.77 (0.55, 1.03)	0.071	0.72 (0.51, 1.02)	0.068
Peripheral vascular disease												
0–19 years	757/615	35 (4.6)	34 (5.5)	0.47	4.0	4.9	0.82 (0.50, 1.35)	0.44	0.84 (0.51, 1.39)	0.50	0.86 (0.51, 1.44)	0.56
0–6 years	757/615	9 (1.2)	11 (1.8)	0.36	2.5	3.6	0.69 (0.29, 1.65)	0.40	0.66 (0.27, 1.60)	0.35	0.71 (0.28, 1.79)	0.47
6–19 years	591/464	26 (4.4)	23 (5.0)	0.70	5.1	5.8	0.87 (0.47, 1.63)	0.67	0.78 (0.39, 1.53)	0.47	0.99 (0.45, 2.18)	0.98
Microvascular disease												
0–19 years	758/620	98 (12.9)	83 (13.4)	0.81	11.6	12.3	0.93 (0.68, 1.26)	0.63	0.95 (0.70, 1.29)	0.73	0.88 (0.63, 1.21)	0.43
0–6 years	758/620	29 (3.8)	21 (3.4)	0.64	8.1	6.9	1.18 (0.70, 1.99)	0.53	1.22 (0.73, 2.05)	0.44	1.20 (0.67, 2.16)	0.54
6–19 years	576/457	69 (12.0)	62 (13.6)	0.48	14.2	16.7	0.84 (0.59, 1.19)	0.32	0.81 (0.55, 1.20)	0.30	0.90 (0.57, 1.40)	0.63

Values are from patients who did not have the outcome at diabetes diagnosis (0–19 years; 0–6 years) or 6 year follow-up (6–19 years). Outcomes are registry-based (by 31 December 2008), see ESM Table 1. Four patients with no information on cause of death were excluded

[a] *p* value from a Rao–Scott χ^2 test: a Pearson χ^2 test adjusted for clustering of patients with general practitioners

[b] HR is calculated in a Cox proportional hazard regression model. The corresponding 95% CI and *p* values are determined using a sandwich estimator for the variance to account for clustering

[c] Only the 6–19 year follow-up was adjusted for diabetes duration. The baseline hazard is estimated separately for each of five age groups, 40–49, 50–59, 60–69, 70–79 and ≥80 years, to account for possible violations of the proportional hazard assumption

[d] Besides clustering, these analyses are adjusted for age, sex and basic school education at diabetes diagnosis. In addition, the 0–6 year and 0–19 year follow-up analyses are adjusted for the following data from diabetes diagnosis: living alone, BMI, hypertension, diagnostic plasma glucose, total cholesterol, fasting triacylglycerols, smoking habits, physical activity and current or former cancer. Similarly, the 6–19 year follow-up analyses are additionally adjusted for the following data from 6 year follow-up: diabetes duration, living alone, BMI, hypertension, HbA_{1c}, total cholesterol, fasting triacylglycerols, smoking habits, physical activity, current or former cancer and glucose-lowering medication. In the multivariate models, the number of patients with complete data varies from 1,020 to 1,267 or from 522 to 751 when adjusting for diagnostic or 6 year follow-up variables, respectively

No., number

outcomes, did not change the risk estimates decisively. This may also be because the indirect randomisation was successful (Table 2), though patient inclusion was done without concealing treatment allocation.

It is likely that the results of the DCGP study can be generalised to the general population of patients with type 2 diabetes because: (1) the study was conducted in general practice, where most patients with type 2 diabetes are treated; (2) the study sample was population-based; (3) patients were included with no upper age limit, and the present results from older patients with higher baseline cardiovascular risk may even widen the generalisability of findings from other studies; (4) the elements of the intervention resemble standard procedures in general practice; and (5) a relatively high number of general practices participated. The fact that general practitioners volunteered for the study may have increased the treatment quality in the routine-care group [40], in which doctors were supposed to do their best and where risk factors were better controlled than in, for example, the conventional treatment group in UKPDS [1]. Between 1988 and 1996 all Danish general practitioners received five diabetes guidelines by post [41–43], which may have decreased the size of the effect of the intervention. The same may be said about the considerable movement of patients between practices during the first 14 years after diagnosis (ESM Table 3). During the 6 years of intervention, however, a doctor who took over an intervention patient was instructed as for any other intervention doctor.

Clinical implications and perspectives The Steno-2 study was a demonstration trial from secondary care showing convincing risk reductions by multifaceted intervention to achieve strict targets directed at a group at high risk of death and complications [20, 44]. In the Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen-Detected Diabetes in Primary Care (ADDITION) study from general practice a similar target-driven intensive-treatment algorithm applied to patients with type 2 diabetes detected by screening did not reduce cardiovascular events, possibly because the general improvements in diabetes care lowered the achievable differences in treatment between trial arms [45].

The DCGP intervention was applied in 1989–1995, before a more intensive treatment regimen addressing blood glucose, BP and dyslipidaemia was implemented. Although a healthy survivor effect may have contributed, the effect of these new guidelines on both risk factor level (Table 2) and drug treatment (ESM Table 4) at the 14 year follow-up in 2003–2005 seems evident in both treatment arms, which makes the present analyses well suited for estimating the effect of an early intervention starting at diagnosis.

In concert with the 10-year follow-up of the UKPDS study [6] and the non-significant improvements in outcome in the ADDITION study [45], the DCGP study indicates long-term clinical benefits of early improvement in the metabolic management of older patients with less well-controlled type 2 diabetes.

In agreement with the recommendations of contemporary clinical guidelines [13], the treatment efforts in the DCGP study were individualised, but the clinical guidelines and treatment targets used in the DCGP study should be updated to contemporary standards. Nowadays, patient involvement may be facilitated by a computerised decision aid that includes the calculated risk of complications and many relevant patient characteristics, such as age, sex, social background and comorbidity. In this way the emerging need for personalised treatment in type 2 diabetes, based on both scientific evidence and patient preferences [46], may be met and even better results obtained than in the present study.

Conclusions

In general practice, 6 years of structured personal care starting from diabetes diagnosis was associated with a reduced risk of MI and any diabetes-related endpoint during 19 years of registry-based monitoring, but survival did not differ between treatment groups. This took place without any overall increase in medication and occurrence of hypoglycaemia, and an average weight loss was sustained. This study is relevant to daily clinical practice because the elements of the complex multifaceted DCGP intervention are relatively easy to implement, and because the study participants were sampled from the general population, with no upper age limit, and were treated in general practice, as is the case for most people with type 2 diabetes. The results indicate that individualisation of both goal setting and choice of pharmacological interventions may be safely included in a multifaceted contemporary treatment regimen. Finally, the results lend support to the assumption that enhanced quality of early diabetes treatment, starting at diabetes diagnosis, is important for lowering the long-term risk of diabetes complications.

Acknowledgements We thank the patients, general practitioners and ophthalmologists who volunteered to take part in this study. We acknowledge the assistance of L. Bergsøe and W. Karlslund, Research Unit for General Practice, and N. Vesti Nielsen, University Eye Clinic, Rigshospitalet, Copenhagen, Denmark.

Funding Major funding for this study was received from the Danish Medical Research Council, the Danish Research Foundation for General Practice, the Health Insurance Foundation, the Danish Ministry of Health, Novo Nordisk Farmaka Denmark, the Pharmacy Foundation and the Novo Nordisk Foundation.

Duality of interest H. Beck-Nielsen has received payment for lectures from Novo Nordisk. All other authors declare that there is no duality of interest associated with their contribution to this manuscript.

Contribution statement LJH and NdFO developed the research question and wrote the protocol for this follow-up study. LJH was responsible for data collection in the 14 year clinical follow-up study. VS performed the statistical analyses. NdFO was responsible for the original study design, the randomisation and the intervention delivery as well as data collection and data analysis for the 6 year follow-up study. NdFO and HB-N developed the clinical guidelines for use in the study and taught at the annual seminars. All authors made substantial contributions to the analysis and interpretation of data. The paper was written by NdFO and LJH while VS and HB-N revised it critically for important intellectual content. LJH and NdFO obtained funding. All authors have approved the final version of the manuscript. NdFO is guarantor.

References

1. UK Prospective Diabetes Study (UKPDS) Group (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352:837–853
2. Ray KK, Seshasai SR, Wijesuriya S et al (2009) Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet 373:1765–1772
3. UK Prospective Diabetes Study (UKPDS) Group (1998) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 317:703–713
4. Turnbull F, Neal B, Algert C et al (2005) Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med 165:1410–1419
5. Kearney PM, Blackwell L, Collins R et al (2008) Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 371:117–125
6. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA (2008) 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 359:1577–1589
7. Calvert M, Shankar A, McManus RJ, Lester H, Freemantle N (2009) Effect of the quality and outcomes framework on diabetes care in the United Kingdom: retrospective cohort study. BMJ 338:b1870
8. Hippisley-Cox J, Pringle M (2004) Prevalence, care, and outcomes for patients with diet-controlled diabetes in general practice: cross sectional survey. Lancet 364:423–428
9. Gerstein HC, Miller ME, Genuth S et al (2011) Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med 364:818–828
10. Duckworth W, Abraira C, Moritz T et al (2009) Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 360:129–139
11. Patel A, MacMahon S, Chalmers J et al (2008) Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 358:2560–2572
12. Yudkin JS, Richter B, Gale EA (2010) Intensified glucose lowering in type 2 diabetes: time for a reappraisal. Diabetologia 53:2079–2085
13. Inzucchi SE, Bergenstal RM, Buse JB et al (2012) Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 55:1577–1596
14. Shojania KG, Ranji SR, McDonald KM et al (2006) Effects of quality improvement strategies for type 2 diabetes on glycemic control: a meta-regression analysis. JAMA 296:427–440
15. Olivarius NdeF, Beck-Nielsen H, Andreasen AH, Horder M, Pedersen PA (2001) Randomised controlled trial of structured personal care of type 2 diabetes mellitus. BMJ 323:970–975
16. Pedersen CB, Gotzsche H, Moller JO, Mortensen PB (2006) The Danish Civil Registration System. A cohort of eight million persons. Dan Med Bull 53:441–449
17. Helweg-Larsen K (2011) The Danish Register of Causes of Death. Scand J Publ Health 39:26–29
18. Lynge E, Sandegaard JL, Rebolj M (2011) The Danish National Patient Register. Scand J Publ Health 39:30–33
19. Kalbfleisch JD, Prentice RL (2002) The statistical analysis of failure time data. Wiley, New York
20. Gaede P, Vedel P, Parving HH, Pedersen O (1999) Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. Lancet 353:617–622
21. Griffin S (1998) Diabetes care in general practice: meta-analysis of randomised control trials. BMJ 317:390–396
22. Renders CM, Valk GD, Griffin S, Wagner EH, Eijk JThMv, Assendelft WJJ (2001) Interventions to improve the management of diabetes mellitus in primary care, outpatient and community settings. Cochrane Database Syst Rev, issue 1, Art. no.: CD001481. doi: 10.1002/14651858
23. Guldberg TL, Lauritzen T, Kristensen JK, Vedsted P (2009) The effect of feedback to general practitioners on quality of care for people with type 2 diabetes. A systematic review of the literature. BMC Fam Pract 10:30
24. Wagner EH, Austin BT, von Korff M (1996) Improving outcomes in chronic illness. Manag Care Q 4:12–25
25. Bodenheimer T, Wagner EH, Grumbach K (2002) Improving primary care for patients with chronic illness. JAMA 288:1775–1779
26. Bodenheimer T, Wagner EH, Grumbach K (2002) Improving primary care for patients with chronic illness: the chronic care model, part 2. JAMA 288:1909–1914
27. Bodenheimer T, Handley MA (2009) Goal-setting for behavior change in primary care: an exploration and status report. Patient Educ Couns 76:174–180
28. Naik AD, Palmer N, Petersen NJ et al (2011) Comparative effectiveness of goal setting in diabetes mellitus group clinics: randomized clinical trial. Arch Intern Med 171:453–459
29. Echouffo-Tcheugui JB, Simmons RK, Williams KM et al (2009) The ADDITION-Cambridge trial protocol: a cluster—randomised controlled trial of screening for type 2 diabetes and intensive treatment for screen-detected patients. BMC Publ Health 9:136
30. Olivarius NdeF, Andreasen AH, Siersma V, Richelsen B, Beck-Nielsen H (2006) Changes in patient weight and the impact of antidiabetic therapy during the first 5 years after diagnosis of diabetes mellitus. Diabetologia 49:2058–2067
31. Wing RR (2010) Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. Arch Intern Med 170:1566–1575
32. Andrews RC, Cooper AR, Montgomery AA et al (2011) Diet or diet plus physical activity versus usual care in patients with newly diagnosed type 2 diabetes: the Early ACTID randomised controlled trial. Lancet 378:129–139
33. Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR (2008) Long-term follow-up after tight control of blood pressure in type 2 diabetes. N Engl J Med 359:1565–1576
34. Gerstein HC, Miller ME, Byington RP et al (2008) Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 358:2545–2559

35. Walker EA, Molitch M, Kramer MK et al (2006) Adherence to preventive medications: predictors and outcomes in the Diabetes Prevention Program. Diabetes Care 29:1997–2002
36. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP (2007) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 335:806–808
37. The National Board of Health (1981) Aktiviteten i sygehusvæsenet 1979 [The activity in the hospital service 1979]. Sundhedsstyrelsen, Copenhagen [report in Danish]
38. Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M (2003) The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. J Clin Epidemiol 56:124–130
39. Krarup LH, Boysen G, Janjua H, Prescott E, Truelsen T (2007) Validity of stroke diagnoses in a National Register of Patients. Neuroepidemiology 28:150–154
40. Pringle M, Stewart-Evans C, Coupland C, Williams I, Allison S, Sterland J (1993) Influences on control in diabetes mellitus: patient, doctor, practice, or delivery of care? BMJ 306:630–634
41. Lauritzen T, Christiansen J, Faber O et al (1991) Non-insulin dependent diabetes—NIDDM. Clinical guidelines for practitioners, 1st edn. Danish College of General Practitioners, Copenhagen
42. Lauritzen T, Christiansen J, Faber O et al (1994) Non-insulin dependent diabetes—NIDDM. Clinical guidelines for practitioners, 2nd edn. Danish College of General Practitioners, Copenhagen
43. Lauritzen T, Christiansen J, Faber O et al (1996) Non-insulin dependent diabetes—NIDDM. Clinical guidelines for practitioners, 3rd edn. Danish College of General Practitioners, Copenhagen
44. Gaede P, Lund-Andersen H, Parving HH, Pedersen O (2008) Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 358:580–591
45. Griffin SJ, Borch-Johnsen K, Davies MJ et al (2011) Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. Lancet 378:156–167
46. Montori VM, Fernandez-Balsells M (2009) Glycemic control in type 2 diabetes: time for an evidence-based about-face? Ann Intern Med 150:803–808