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

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Summary

Background Intensive treatment of multiple cardiovascular risk factors can halve mortality among people with established type 2 diabetes. We investigated the effect of early multifactorial treatment after diagnosis by screening.

Methods In a pragmatic, cluster-randomised, parallel-group trial done in Denmark, the Netherlands, and the UK, 343 general practices were randomly assigned screening of registered patients aged 40–69 years without known diabetes followed by routine care of diabetes or screening followed by intensive treatment of multiple risk factors. The primary endpoint was first cardiovascular event, including cardiovascular mortality and morbidity, revascularisation, and non-traumatic amputation within 5 years. Patients and staff assessing outcomes were unaware of the practice's study group assignment. Analysis was done by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00237549.

Findings Primary endpoint data were available for 3055 (99·9%) of 3057 screen-detected patients. The mean age was 60·3 (SD 6·9) years and the mean duration of follow-up was 5·3 (SD 1·6) years. Improvements in cardiovascular risk factors (HbA_{1c} and cholesterol concentrations and blood pressure) were slightly but significantly better in the intensive treatment group. The incidence of first cardiovascular event was 7·2% (13·5 per 1000 person-years) in the intensive treatment group and 8·5% (15·9 per 1000 person-years) in the routine care group (hazard ratio 0·83, 95% CI 0·65–1·05), and of all-cause mortality 6·2% (11·6 per 1000 person-years) and 6·7% (12·5 per 1000 person-years; 0·91, 0·69–1·21), respectively.

Interpretation An intervention to promote early intensive management of patients with type 2 diabetes was associated with a small, non-significant reduction in the incidence of cardiovascular events and death.

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Introduction

Type 2 diabetes mellitus is common, expensive to manage, and associated with a substantial burden of morbidity and mortality, particularly owing to cardiovascular complications.[1] Risk of cardiovascular events and death can be halved among patients with longstanding diabetes and microalbuminuria by intensive multifactorial treatment.[2,3] Treatment of individual risk factors, such as blood pressure,[4,5] cholesterol,[6] and glucose,[7] is effective. Outcomes might be improved if this approach were used early in the course of the disease.[8] The effect of starting multifactorial treatment from the time of diagnosis is unknown.

Type 2 diabetes is detectable well before it is clinically diagnosed[9] and many patients already have evidence of diabetic complications and potentially modifiable cardiovascular risk factors at the time of diagnosis.[10] Early detection by screening is not associated with harmful psychological effects[11] and, therefore, diabetes meets many suitability criteria for screening.[12] Modelling studies have indicated that screening would be an efficient use of resources,[13] but there are several critical uncertainties that have prevented its routine widespread implementation.[14] No evidence from trials is available to show whether early intensive multifactorial treatment improves outcomes when started between detection by screening and clinical diagnosis. We did the multicentre Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care (ADDITION-Europe) to investigate this issue.

Methods

Design

The study design and rationale have been reported.[15–18] Briefly, ADDITION-Europe consisted of two phases: a screening phase and a pragmatic, cluster-randomised, parallel-group trial in Denmark, the Netherlands, and the UK (in Cambridge and Leicester). The study was approved by the ethics committee local to each study centre. All participating patients provided informed consent.

General practices in the four study areas within a maximum of 100 miles of the study centres were invited to participate according to previously reported inclusion criteria.[17–20] Between April, 2001, and December, 2006, eligible practices undertook population-based, stepwise screening of registered patients aged 40–69 years (50–69 years in the Netherlands) without known diabetes.[17–20] Screening involved calculation of a risk score from information in general practice medical records in Cambridge or calculation of a risk score from self-completed questionnaires in Denmark and the Netherlands, followed by capillary glucose testing, or by invitation to attend for an oral glucose tolerance test without previous risk assessment in Leicester.

Individuals at risk were assessed in general practice, and those diagnosed as having type 2 diabetes according to WHO criteria,[21] including the requirement for confirmatory testing on a separate occasion, were included in the study. Exclusion criteria for patients were assessed by family physicians. They were illness with a life expectancy of less than 12 months or psychological or psychiatric disorders that might invalidate informed consent, or being housebound or pregnant, or lactation.

Randomisation

The practices were randomly assigned to provide routine diabetes care or intensive multifactorial treatment in a 1:1 ratio, by statisticians in each centre, according to a computer-generated list, independent of measurement teams.

In Denmark, randomisation included stratification by county and number of full-time family physicians. In the Netherlands, practices were stratified by single-handed

	Screening programme	Intervention delivery	Outcome ascertainment
Cambridge, UK	Electronic medical records of patients aged 40–69 years searched for routinely collected information to enable calculation of Cambridge diabetes risk scores[22] Individuals with scores ≥0·17 invited by their family physcian to participate in a stepwise screening programme, including capillary RBG, FBG, and HbA_{1c} tests	Practice-based educational meetings held with family physicians and nurses to discuss treatment targets, algorithms, and lifestyle advice Audit and feedback via follow-up practice-based meetings up to twice per year Practice staff provided with educational materials for patients Small financial incentives given to family physicians*	Participants tagged for mortality with the Office for National Statistics Sensitive electronic searches of general practice records undertaken between March, 2009, and February, 2010, in which possible events highlighted and copies made of medical records Additional information obtained from hospital medical records and coroners' offices, as required
Denmark	Patients aged 40–69 years sent letters that included questions from the Danish Diabetes Risk Score Questionnaire[23] and advised recipients with scores ≥5 (high risk) to arrange an appointment with family physician for assessment, including RBG, FBG, and HbA_{1c} tests, or patients attending family physician practice asked to complete risk score questionnaire and those with scores ≥5 underwent blood glucose tests	Small group or practice-based educational meetings with family physicians and nurses to discuss treatment targets, algorithms, and lifestyle advice Audit and feedback included in follow-up group meetings up to twice per year or coordinated by post Practice staff provided with educational materials for patients Small financial incentives given to family physicians* Patients sent reminders if annual assessments overdue	National patient register searched on Dec 31, 2009, for deaths, ICD-10 codes for cardiovascular events (I08–77), and surgical amputations and revascularisations. For possible events information obtained from hospital medical records and coroners' offices, as required
Leicester, UK	All patients aged 40–69 years invited directly for an OGTT in a local testing facility	Patients referred to the DESMOND structured education programme[24] Patients offered appointments every 2 months with a diabetes nurse or family physician, in a community clinic, for 1 year, and every 4 months thereafter Clinic staff prompted to contact patients who missed appointments Small financial incentives given to family physicians*	Participants tagged for mortality with the Office for National Statistics Sensitive electronic searches of general practice records undertaken between March, 2009, and February, 2010, in which possible events highlighted and copies made of medical records Additional information obtained from hospital medical records and coroners' offices, as required
Netherlands	Patients aged 50–69 years sent letters from family physicians that included the Hoorn study Symptom Risk Questionnaire[25] and advised recipients with scores ≥4 (41 practices closest to study centre) or ≥6 (38 practices furthest from study centre) to arrange an appointment with their family physician for assessment Attending patients assessed with RGB, FBG, and OGTT (41 practices closest to study centre) or a FBG and OGTT (38 practices furthest from study centre)	Small group or practice-based educational meetings with family physicians and nurses to discuss treatment targets, algorithms, and lifestyle advice Audit and feedback included in follow-up meetings up to twice per year or coordinated by post Patients seen by diabetes nurses authorised to prescribe medication and adjust doses under supervision by family physicians Patients sent reminders if annual assessments overdue Small financial incentives given to family physicians*	General practice records searched manually and extracted endpoint and vital status information recorded on standard forms For patients who had moved practice, endpoint data obtained by telephone interview with current family physician

RBG=random blood glucose. FBG=fasting blood glucose. HbA_{1c}=glycated haemoglobin A_{1c}. ICD-10=International Classification of Diseases, version ten. OGTT=oral glucose tolerance test. DESMOND=diabetes education and self management for ongoing and newly diagnosed programme. *Payment up to equivalent of three 10 min consultations with a family physician and three 15 min consultations wit a nurse, per patient, per year, for 3 years.

Table 1: **Characteristics of screening programmes, intervention delivery, and outcome ascertainment, by study centre**

	Treatment target	Treatment threshold	Approach at baseline if threshold passed	Action at review		
				Review 1	Review 2	Review 3
HbA_{1c}	<7·0%	>6·5%	Diet	Value >threshold, prescribe metformin	Value >threshold, increase metformin dose or add a PGR, sulphonylurea, or TZD	Value >threshold, add second or third medication (PGR or sulphonurea, or TZD) and consider adding insulin
Blood pressure	≤135/85 mm Hg*	≥120/80 mm Hg	If CVD+, prescribe an ACE inhibitor titrated to maximum dose	Value >target, add thiazide diuretic or calcium-channel blocker	Value >target, add calcium-channel blocker or thiazide diuretic	Value >target, add β blocker or α blocker
Total cholesterol level without IHD	<5·0 mmol/L	≥3·5 mmol/L	Prescribe a statin	Value >target, increase statin dose up to maximum	Value >target, increase statin dose up to maximum	Value >target, consider adding a fibrate
Cholesterol level with IHD	<4·5 mmol/L	≥3·5 mmol/L	Prescribe a statin	Value >target, increase statin up to maximum dose	Value >target, continue statin titration if maximum dose not reached	Value >target, consider adding a fibrate
Aspirin†	None	None	75–80 mg daily	75–80 mg daily	75–80 mg daily	75–80 mg daily

HbA_{1c}=glycated haemoglobin A_{1c}. PGR=prandial glucose regulator. TZD=thiazolidinedione. ACE=angiotensin-converting enzyme. IHD ischaemic heart disease, CVD+=cardiovascular event or presence of cardiovascular risk factor other than diabetes. BP=blood pressure. *≤130/80 mm Hg in Leicester. †All patients receiving antihypertensive medication and without specific contraindications.

***Table 2*: Treatment recommendations and targets in the intensive treatment group**

or group status. In the UK, randomisation included minimisation for the local district hospital, the number of patients per practice with diabetes in Cambridge, and for practice demographics, deprivation status, and prevalence of type 2 diabetes in Leicester. Patients were unaware of their general practice's group assignment throughout the study.

Intervention

The characteristics of the intensive treatment intervention, which involved the addition of several features to existing diabetes care, have been described previously,[15–18] and the methods used to educate and support staff in providing intensive treatment are summarised in table 1 and on the study website. Target-driven and guideline-driven management of hyperglycaemia, blood pressure, and cholesterol levels by medical treatment and promotion of healthy lifestyles, based on the stepwise regimen used in the Steno-2 study[2] and other trial data obtained from people with type 2 diabetes,[4–6,26] was added to routine care (table 2). The same approach was used across all centres, although final decisions about prescriptions, including choice of individual drugs, were made by family physicians and patients.

For the **study website** see http://www.addition.au.dk/

Intensive treatment was promoted to the participating general practices by small group or practice-based educational meetings attended by family physicians and nurses to discuss the treatment targets and algorithms and lifestyle advice and provide supporting evidence. Audit and feedback were done in follow-up meetings held up to twice per year or were coordinated by post. All participating practices received additional funding to support the delivery of care (up to the equivalent of three 10 min consultations with a family physician and three 15 min consultations with a nurse, per patient, per year for 3 years).

See **Online** for webappendix

Family physicians were advised to consider prescribing angiotensin-converting-enzyme inhibitors for patients who had blood pressure of 120/80 mm Hg or higher, a cardiovascular risk factor other than diabetes, or who had had a previous cardiovascular event,[5] and 75 mg aspirin daily for patients who had no specific contraindications. After publication of the Heart Protection Study[27] we altered the treatment algorithm to recommend prescription of a statin to all patients with a cholesterol concentration of 3·5 mmol/L or higher at any time.

For the routine care group, family physicians were only provided with diagnostic test results. Patients received standard diabetes care, according to the recommendations applicable in each centre.[28–30]

Outcomes

The primary endpoint was a composite of first cardiovascular event, including cardiovascular mortality, cardiovascular morbidity (non-fatal myocardial infarction and non-fatal stroke), revascularisation, and non-traumatic amputation. The secondary outcomes were the individual components of the primary endpoint and all-cause mortality. Centrally trained staff assessed patients' health at baseline and after 5 years by collection of data on biochemical and anthropometric features and use of questionnaires to assess activities, including use of medication, according to standard operating procedures (see webappendix p 1). Additionally, information on prescribed medication, and data potentially linked to the endpoints were obtained from general practice records or national registers. All staff collecting data from records and undertaking health assessments were unaware of patients' treatment group allocations. For each endpoint possibly met, the relevant clinical information (eg, death certificates, post-mortem reports, medical records, hospital discharge summaries,

electrocardiographs, laboratory results, etc) were sent to two members of the expert committee within the country for independent adjudication according to an agreed protocol. Committee members were unaware of treatment allocations. Outcomes were recorded on standard case report forms. Committee members met to reach consensus over discrepancies.

The date of completion of follow-up for the primary endpoint was deemed to be the date of the first primary endpoint event, the 5-year assessment if no event occurred, or the date that the endpoint search was undertaken if the participant did not experience an event or attend follow-up.

Statistical analysis

The analysis plan was finalised before preparation of the endpoint dataset, and analysis was by intention to treat. We summarised baseline characteristics of individuals and general practices within each randomised group, by centre, and overall. We plotted the cumulative probability of the primary endpoint. To assess intervention effects we used Cox's regression to estimate hazard ratios (HRs) and 95% CI within each centre. In Leicester there were few participants and events and, therefore, we combined the endpoint data with those for Cambridge. In view of randomisation being at the practice level, we calculated robust SE that took into account the two-level structure of the data and any potential correlation between the individuals within practices. We calculated the correlation coefficients within practices for the primary endpoint. Centre-specific log HRs and SE were combined with a fixed effects meta-analysis, and we calculated the I^2 statistic to represent the proportion of variability (in log HRs) between centres owing to heterogeneity. We tested the proportional hazards assumption by including a parameter for treatment by time interaction in each centre-specific Cox's regression model.

Continuous intermediate endpoints were analysed within each centre with normal errors regression, with adjustment for the endpoint baseline values; individuals who died or who were lost to follow-up were excluded from this analysis. We calculated robust SE. We combined the estimated differences in mean change from baseline across centres with fixed effects meta-analysis. In the regression models, we included individuals with missing outcome values at baseline, according to the missing indicator method,[31] and variables with a skewed distribution were log transformed. We estimated the effect of the intervention on prescribing endpoints within each centre by use of logistic regression, and combined the estimated odds ratios across centres with fixed effects meta-analysis. We undertook sensitivity analyses by excluding follow-up clinical data obtained from general practice records, and did prespecified subgroup analyses for the primary endpoint by including interaction terms between intervention group, patient's age, and self-reported history of cardiovascular disease, which were then pooled across centres. The cumulative incidence of the composite cardiovascular endpoint was calculated with the method for competing risks described by Gooley and colleagues,[32] the competing events here being the primary endpoint and death from non-cardiovascular causes. For total mortality, Kaplan-Meier estimates of cumulative incidence were calculated. Analyses were done with STATA (version 11).

We calculated that a patient-level randomised trial would have required enrolment of 2700 individuals (1350 per treatment group) to detect a 30% reduction in the risk of the primary endpoint at a 5% significance

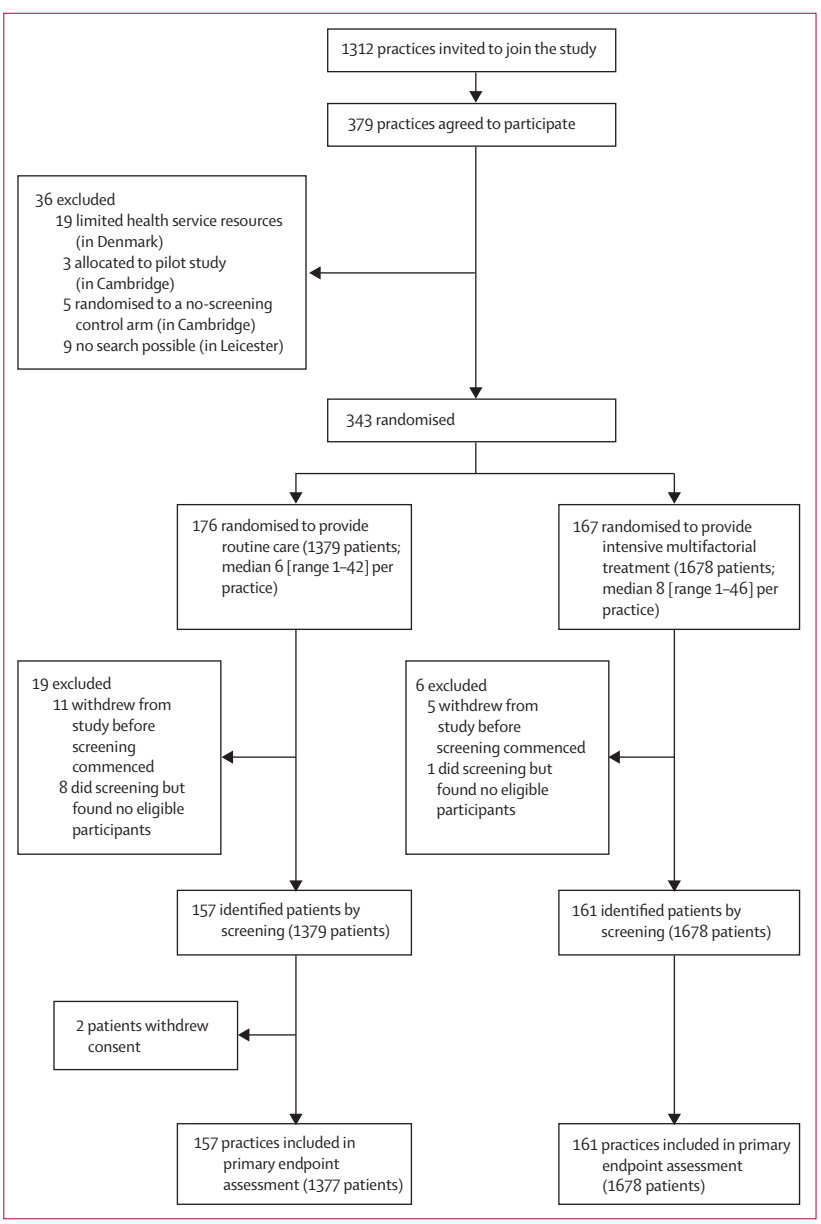

***Figure 1*: Trial profile**

	Routine care				Intensive treatment				Change from baseline to follow-up (β/OR [95% CI])
	Baseline (n=1379)		Follow-up (n=1285)		Baseline (n=1678)		Follow up (n=1574)		
	Total with data available (%)	Value	Total with data available (%)	Value	Total with data available (%)	Value	Total with data available (%)	Value	
Demographic variables									
Male sex	1379 (100%)	790 (57·3%)	NA	NA	1678 (100%)	981 (58·5%)	NA	NA	NA
Mean (SD) age at diagnosis (years)	1379 (100%)	60·2 (6·8)	NA	NA	1678 (100%)	60·3 (6·9)	NA	NA	NA
White ethnic origin	1334 (96·7%)	1246 (93·4%)	NA	NA	1607 (95·8%)	1539 (95·8%)	NA	NA	NA
Employed	1013 (73·5%)	425 (42·0%)	NA	NA	1197 (71·3%)	482 (40·3%)	NA	NA	NA
Clinical variables									
History of myocardial infarction	1286 (93·3%)	79 (6·1%)	NA	NA	1593 (94·9%)	109 (6·8%)	NA	NA	..
History of stroke	1270 (92·1%)	24 (1·9%)	NA	NA	1558 (92·8%)	45 (2·9%)	NA	NA	..
Current smoker	1347 (97·7%)	375 (27·8%)	1014 (78·9%)	187 (18·4%)	1649 (98·3%)	444 (26·9%)	1293 (82·1%)	261 (20·2%)	1·06 (0·77 to 1·45)
Median (IQR) units of alcohol per week	1183 (85·8%)	4 (1–13)	1010 (78·6%)	3 (0–10)	1492 (88·9%)	4 (1–13)	1280 (81·3%)	3 (0–10)	−0·24 (−0·77 to 0·29)
Mean (SD) BMI (kg/m²)	1342 (97·3%)	31·6 (5·6)	1112 (86·5%)	31·0 (5·6)	1615 (96·2%)	31·6 (5·6)	1405 (89·3%)	31·1 (5·7)	0·03 (−0·17 to 0·22)
Mean (SD) weight (kg)	1344 (97·5%)	90·3 (17·6)	1192 (92·8%)	88·4 (17·8)	1615 (96·2%)	90·9 (17·5)	1490 (94·7%)	89·1 (18·2)	−0·02 (−0·58 to 0·55)
Mean (SD) waist circumference (cm)	1346 (97·6%)	106·8 (13·5)	1064 (82·8%)	105·3 (13·6)	1612 (96·1%)	107·1 (13·5)	1363 (86·6%)	105·4 (13·6)	−0·30 (−1·01 to 0·42)
Median (IQR) HbA_{1c} (%)	1298 (94·1%)	6·6 (6·1–7·3)	1226 (95·4%)	6·5 (6·1–7·1)	1591 (94·8%)	6·5 (6·1–7·3)	1513 (96·1%)	6·4 (6·0–6·9)	−0·08 (−0·14 to −0·02)
Mean (SD) HbA_{1c} (%)	1298 (94·1%)	7·0 (1·5)	1226 (95·4%)	6·7 (0·95)	1591 (94·8%)	7·0 (1·6)	1513 (96·1%)	6·6 (0·95)	−0·08 (−0·14 to −0·02)
Mean (SD) systolic blood pressure (mm Hg)	1346 (97·6%)	149·8 (21·3)	1205 (93·8%)	138·1 (17·6)	1617 (96·4%)	148·5 (22·1)	1517 (96·4%)	134·8 (16·8)	−2·86 (−4·51 to −1·20)
Mean (SD) diastolic blood pressure (mm Hg)	1346 (97·6%)	86·5 (11·3)	1203 (93·6%)	80·7 (10·8)	1618 (96·4%)	86·1 (11·1)	1517 (96·4%)	79·5 (10·7)	−1·44 (−2·30 to −0·58)
Mean (SD) total cholesterol (mmol/L)	1300 (96·3%)	5·6 (1·2)	1226 (95·4%)	4·4 (0·9)	1593 (94·9%)	5·5 (1·1)	1523 (96·8%)	4·2 (0·9)	−0·27 (−0·34 to −0·19)
Median (IQR) HDL cholesterol (mmol/L)	1289 (93·5%)	1·2 (1·0–1·5)	1200 (93·3%)	1·3 (1·1–1·6)	1568 (93·4%)	1·2 (1·0–1·5)	1517 (96·4%)	1·2 (1·0–1·5)	0 (−0·03 to 0·02)
Mean (SD) LDL cholesterol (mmol/L)	1238 (89·8%)	3·5 (1·0)	1173 (91·3%)	2·3 (0·8)	1511 (90·0%)	3·4 (1·0)	1477 (93·8%)	2·1 (0·8)	−0·20 (−0·26 to −0·13)
Median (IQR) triglycerides (mmol/L)	1295 (93·9%)	1·7 (1·2–2·4)	1213 (94·4%)	1·6 (1·1–2·3)	1579 (94·1%)	1·6 (1·2–2·3)	1512 (96·1%)	1·5 (1·0–2·1)	−0·05 (−0·12 to 0·01)
Mean (SD) creatinine (μmol/L)	1266 (91·8%)	84·9 (18·6)	1208 (94·0%)	79·8 (29·9)	1565 (93·3%)	83·4 (17·1)	1513 (95·5%)	81·0 (30·5)	1·81 (0·10 to 3·53)
Self-reported drug use									
Any glucose-lowering drug	1340 (97·2%)	7 (0·5%)	1208 (94·0%)	681 (56·4%)	1609 (95·9%)	8 (0·5%)	1524 (96·8%)	990 (65·0%)	1·53 (1·25 to 1·89)
Median (IQR) total number of glucose-lowering drugs	1340 (97·2%)	0 (0–0)	1208 (94·0%)	1 (0–1)	1609 (95·9%)	0 (0–0)	1524 (96·8%)	1 (0–1)	..
Metformin	1340 (97·2%)	5 (0·4%)	1208 (94·0%)	583 (48·3%)	1609 (95·9%)	6 (0·4%)	1524 (96·8%)	835 (54·8%)	..
Sulphonylurea	1340 (97·2%)	2 (0·1%)	1208 (94·0%)	215 (17·8%)	1609 (95·9%)	2 (0·1%)	1524 (96·8%)	291 (19·1%)	..
Thiazolidinedione	1340 (97·2%)	0	1208 (94·0)	50 (4·1%)	1609 (95·9%)	0	1524 (96·8%)	69 (4·5%)	..

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	Routine care				Intensive treatment				Change from baseline to follow-up (β/OR [95% CI])
	Baseline (n=1379)		Follow-up (n=1285)		Baseline (n=1678)		Follow up (n=1574)		
	Total with data available (%)	Value	Total with data available (%)	Value	Total with data available (%)	Value	Total with data available (%)	Value	
Continued from previous page									
Insulin	1340 (97·2%)	0	1208 (94·0%)	43 (3·6%)	1609 (95·9%)	0	1524 (96·8%)	96 (6·3%)	..
Other	1340 (97·2%)	0	1208 (94·0%)	31 (2·6%)	1609 (95·9%)	0	1524 (96·8%)	81 (5·3%)	..
Any antihypertensive drugs	1340 (97·2%)	585 (43·7%)	1208 (94·0%)	911 (75·4%)	1609 (95·9%)	752 (46·7%)	1524 (96·8%)	1274 (83·6%)	1·61 (1·27 to 2·04)
Median (IQR) total number of antihypertensive drugs	1340 (97·2%)	0 (0–1)	1208 (94·0%)	2 (1–3)	1609 (95·9%)	0 (0–2)	1524 (96·8%)	2 (1–3)	..
ACE inhibitor or ARB	1340 (97·2%)	248 (18·5%)	1208 (94·0%)	721 (59·7%)	1609 (95·9%)	345 (21·4%)	1524 (96·8%)	1126 (73·9%)	1·84 (1·52 to 2·22)
β-blocker	1340 (97·2%)	252 (18·8%)	1208 (94·0%)	285 (23·6%)	1609 (95·9%)	366 (22·7%)	1524 (96·8%)	462 (30·3%)	..
Calcium-channel blocker	1340 (97·2%)	166 (12·4%)	1208 (94·0%)	326 (27·0%)	1609 (95·9%)	202 (12·6%)	1524 (96·8%)	446 (29·3%)	..
Diuretic	1340 (97·2%)	330 (24·6%)	1208 (94·0%)	529 (43·8%)	1609 (95·9%)	415 (25·8%)	1524 (96·8%)	767 (50·3%)	..
Other	1340 (97·2%)	23 (1·7%)	1208 (94·0%)	49 (4·1%)	1609 (95·9%)	32 (2·0%)	1524 (96·8%)	70 (4·6%)	..
Any cholesterol-lowering drugs	1340 (97·2%)	206 (15·4%)	1208 (94·0%)	889 (73·6%)	1609 (95·9%)	274 (17·0%)	1524 (96·8%)	1241 (81·4%)	..
Statins	1340 (97·2%)	200 (14·9%)	1208 (93·9%)	864 (71·5%)	1609 (95·9%)	271 (16·8%)	1524 (96·8%)	1217 (79·9%)	1·46 (1·20 to 1·78)
Aspirin	1340 (97·2%)	169 (12·6%)	1208 (93·9%)	504 (41·7%)	1609 (95·9%)	249 (15·5%)	1524 (96·8%)	1078 (70·7%)	..

The denominators at follow-up exclude 92 patients in the routine care group and 104 in the intensive treatment group who died between baseline and follow-up, and two others in the routine care group who withdrew from the study and for whom primary endpoint data were not available. The denominators used to calculate the percentages of individuals with a particular characteristic are the number of individuals with values for that characteristic. OR=odds ratio. NA=not applicable. BMI=body-mass index. HbA_{1c}=glycated haemoglobin A_{1c}. ACE-angiotensin-converting enzyme. ARB=angiotensin-receptor blocker.

***Table 3*: Clinical, biochemical, and treatment characteristics of patients at baseline and mean follow-up of 5·3 years**

	Routine care (n=1377)	Intensive treatment (n=1678)	Hazard ratio (95% CI)	I^2 (%)	p for routine care *vs* intensive treatment
Primary endpoint (n [%])					
Composite cardiovascular events*	117 (8·5%)	121 (7·2%)	0·83 (0·65–1·05)	0%	0·12
Secondary endpoints (n [%])					
Cardiovascular death†	22 (1·6%)	26 (1·5%)	0·88 (0·51–1·51)	52%	..
Myocardial infarction†	32 (2·3%)	29 (1·7%)	0·7 (0·41–1·21)	0%	..
Stroke†	19 (1·4%)	22 (1·3%)	0·98 (0·57–1·71)	0%	..
Revascularisation†	44 (3·2%)	44 (2·6%)	0·79 (0·53–1·18)	0%	..
Amputation†	0	0	..	..	..
Total mortality	92 (6·7%)	104 (6·2%)	0·91 (0·69–1·21)	55%	..

Hazard ratios were first estimated within each country with Cox's regression and Huber-White adjustment of SE for clustering within practice, then combined across countries with fixed-effects meta-analysis. The I^2 statistic estimates heterogeneity between countries. A p value was calculated for primary endpoint only. *Any of cardiovascular death, myocardial infarction, stroke, revascularisation, and amputation. †Component of the primary endpoint as a first event.

***Table 4*: Cardiovascular events and all-cause mortality in the two treatment groups**

level, and with 90% power. This calculation allowed for 10% loss to follow-up and assumed an event rate in the routine care group of 3% per year, on the basis of the results of the UK Prospective Diabetes Study Group (UKPDS).[26] We expected a minimum effect of clustering within general practice, with the estimated within-cluster correlation coefficient being 0·01. We assumed that the average number of participants per general practice

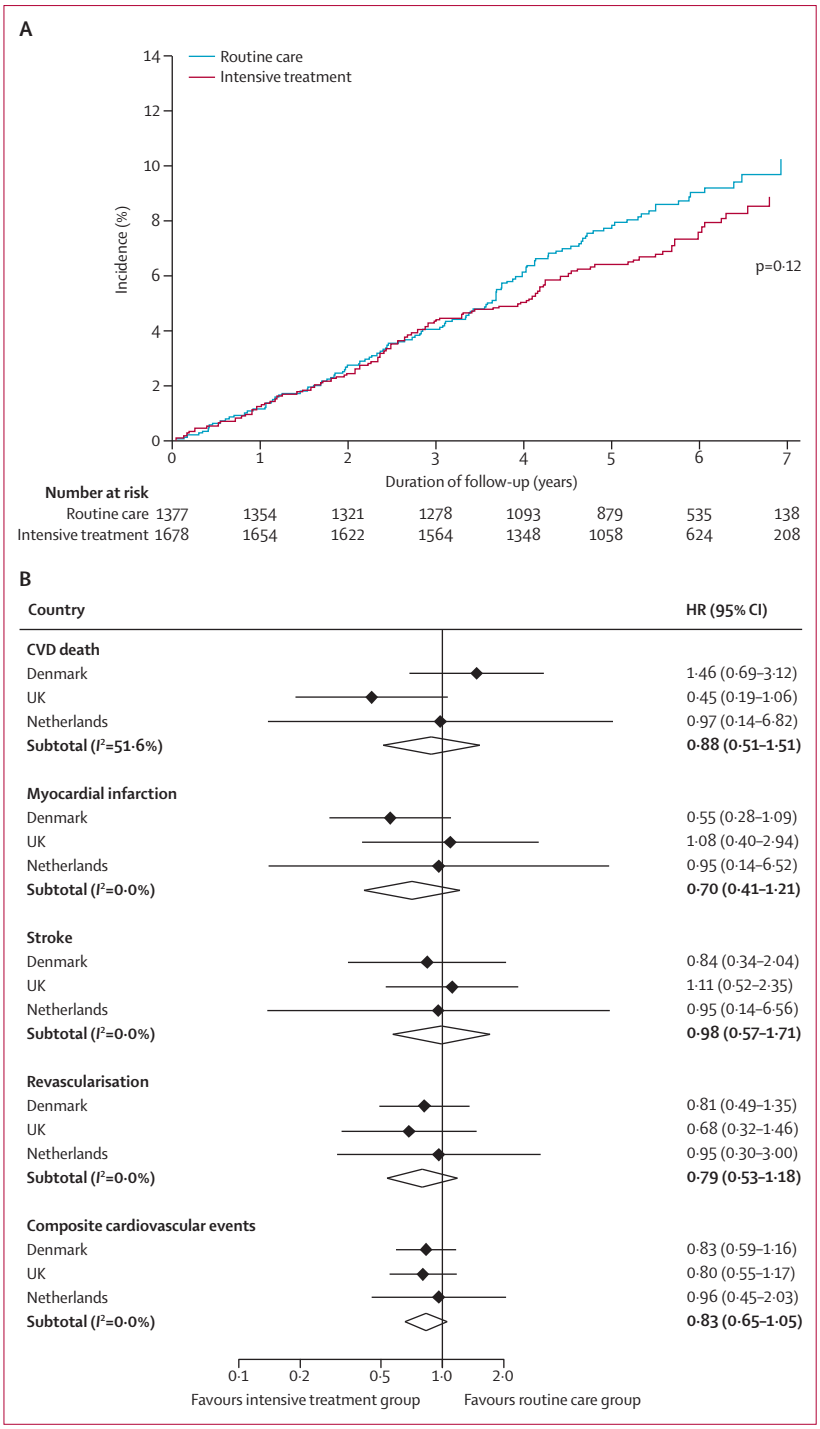

***Figure 2*: Cumulative incidence and relative risk of composite cardiovascular endpoint**
(A) Cumulative incidence curves by treatment group. The p value was calculated with Cox's regression and fixed-effects meta-analysis. (B) HRs of development of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and revascularisation as a first event (secondary endpoints), and these cardiovascular events combined (primary endpoint), by country and overall. HR=hazard ratio. CVD=cardiovascular disease.

would be 10 and, therefore, the design effect was 1·09. Thus, we inflated the estimated sample size for this cluster trial to 3000 patients in total.

Role of the funding sources
The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Of 1312 general practices invited, 379 (29%) agreed to participate in the study. 36 (9%) of these were excluded and 343 (91%) were randomised to provide routine diabetes care (n=176) or intensive multifactorial treatment (n=167; figure 1), of which 327 (routine care n=165, intensive treatment n=162) completed screening and 318 (routine care n=157, intensive treatment n=161) included eligible patients. Participating practices in the UK and the Netherlands have been described.[17,18,20] The mean patient list size was 7378 in the routine care group and 7160 in the intensive treatment group. The median prevalence of known diabetes was 3·5%. Data for the prevalence of diabetes in the Denmark practices were not available.

Screening identified 3233 patients with type 2 diabetes, of whom 3057 agreed to take part (Denmark, n=1533; Cambridge, UK, n=867; Netherlands, n=498; and Leicester, UK, n=159). The characteristics of these patients did not differ significantly from those of the 176 patients who were eligible but chose not to participate. Baseline demographic, clinical, biochemical, and treatment characteristics of patients in the two treatment groups were well matched overall (table 3). In Denmark, however, more patients were identified in practices assigned intensive treatment than in those assigned routine care (910 *vs* 623), and more patients in the former group had a history of ischaemic heart disease (International Classification of Diseases [version 10; ICD-10] codes I20–25, 102 [11·2%] *vs* 53 [8·5%]) or other cardiac diagnosis (ICD10 codes I30–52, 76 [8·4%] *vs* 28 [4·5%]). As previously described, patients overall exhibited high levels of untreated cardiovascular risk factors at diagnosis.[19]

Screening programmes varied by centre (table 1). The median number of follow-up meetings for audit and feedback was four (range two to ten). Primary endpoint data were available for 3055 (99·9%) of 3057 participants. The mean follow-up period was 5·3 (SD 1·6) years, during which 238 first cardiovascular events occurred, with similar numbers and risk in each group (table 4). The cumulative probability plot for the primary endpoint seemed to diverge after 4 years of follow-up (figure 2). In the predefined subgroup analyses, no interactions were seen between the intervention and age or previous cardiovascular event (p>0·1). Estimated HRs, however, were 1·12 (95% CI 0·70–1·79) in patients younger than 60 years and 0·70 (95% CI 0·52–0·95) in those aged 60 years and older. HRs for individual components of the composite endpoint all favoured the intensive treatment group (table 4), although none achieved significance (figure 2). No patient underwent amputation as a first

event. The correlation coefficient within clusters for the primary endpoint was 0·002 (Denmark: 0·014, UK [combined] 0·0000016, and the Netherlands 0·025), which suggests that the cluster design had little effect on study power.

196 patients died overall (60 [30·6%] cardiovascular deaths, including six patients with first events classified as myocardial infarction, two as stroke, and four as revascularisation, 97 [49·5%] cancer deaths, and 39 [19·9%] from other causes; table 4). The combined HR for death in the intensive treatment group compared with the routine care group was 0·91 (95% CI 0·69–1·21). Heterogeneity of results between countries was not significant (figure 3). In the UK, significantly fewer patients died in the intensive treatment group than in the routine care group, but in Denmark the risk in the routine care group was lower, although not significantly so. All results were unchanged after sensitivity analysis that excluded participants in the two practices for which endpoint data were obtained while aware of treatment allocation (webappendix p 2).

Of the 2859 patients still alive at 5 years, 2400 (84%) returned to a clinical research facility for follow-up health assessments. Clinical and biochemical outcomes could be obtained from general practice records for a further 328 (11·5%) participants. Compared with patients for whom follow-up data were available, the 131 with missing data were more likely to be from an ethnic minority group (10·2% *vs* 5·7%, p=0·04) and have higher baseline total cholesterol (5·9 mmol/L *vs* 5·6 mmol/L, p=0·004) and LDL cholesterol values (3·7 mmol/L *vs* 3·4 mmol/L, p=0·009). Changes in clinical and biochemical values and prescribed medications in the two groups are shown in table 3. By 5 years of follow-up improvements were seen for cardiovascular risk factors in both groups. Small but significant differences between groups were seen in change from baseline for glycated haemoglobin A_{1c} (HbA_{1c}), systolic and diastolic blood pressure and total and LDL cholesterol, in favour of the intensive treatment group. Prescription of glucose-lowering, antihypertensive, and lipid-lowering drugs increased in both groups. At follow-up more patients in the intensive treatment group were prescribed aspirin, angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers, glucose-lowering drugs, antihypertensive drugs, and lipid-lowering drugs than were those in the routine care group (table 3).

In both groups, more patients had values below target thresholds for HbA_{1c} concentrations, blood pressure, and cholesterol concentrations at follow-up than at baseline (figure 4). The proportion of patients meeting the targets was higher in the intensive treatment group than in the routine care group. The proportions of individuals reporting hypoglycaemia, as assessed by the diabetes treatment satisfaction questionnaire, did not differ (χ^2 4·44, p=0·62).[33] All results were unchanged after sensitivity analysis was done that excluded participants with follow-up clinical data obtained from general practice records.

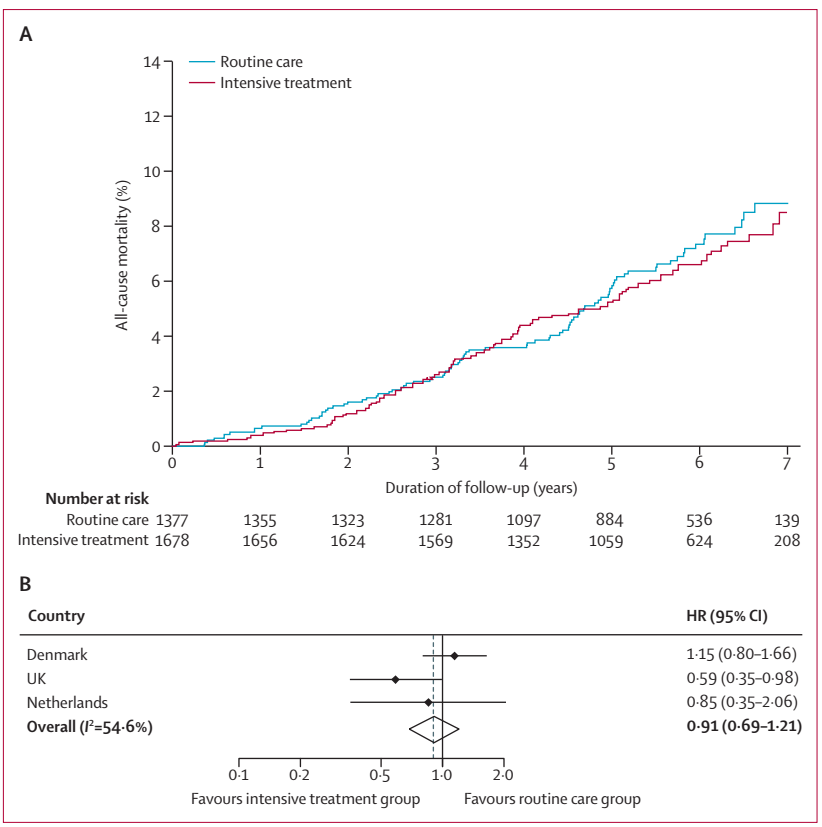

Figure 3: **Cumulative incidence and relative risk of all-cause mortality**
(A) Kaplan-Meier survival estimates by treatment group. (B) HRs of all-cause mortality, by country and overall. HR=hazard ratio. CVD=cardiovascular disease.

Discussion

An intervention to promote target-driven, intensive management of patients with type 2 diabetes detected by screening was associated with slightly, but significantly, increased prescription of treatments and improvements in cardiovascular risk factors, and with a non-significant relative reduction in the incidence of cardiovascular events at 5 years. Differences between study groups for all components of the primary endpoint favoured the intensive treatment group. Differences were greatest for myocardial infarction and smallest for stroke.

We cannot rule out the possibility that these findings were due to chance. Rates of cardiovascular events seemed to diverge after 4 years of follow-up, although the risk of adverse outcomes, including death or self-reported hypoglycaemia, was not increased. The incidence of cardiovascular events in the routine care group (8·5%) was lower than expected compared with that in newly diagnosed patients in the UKPDS (12·1%).[34] Mortality in this group (6·7%) was lower than that in patients with type 2 diabetes detected by screening in Hoorn[35] (25% over

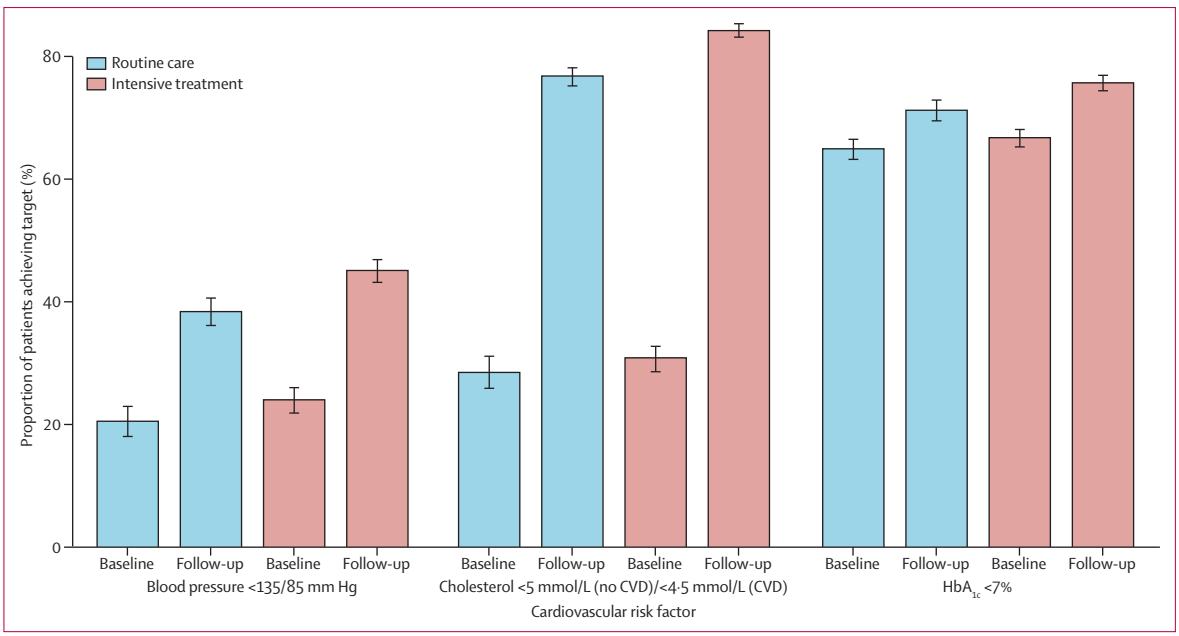

Figure 4: **Proportion of patients for whom cardiovascular risk factor values were below the intensive treatment intervention target thresholds at baseline and after 5 years of follow-up**

1 SE are shown. CVD=cardiovascular disease. HbA_{1c}=glycated haemoglobin A_{1c}.

Panel: Research in context

Systematic review

Studies have shown cardiovascular benefits with treatment to lower blood pressure and glucose and cholesterol concentrations in patients with type 2 diabetes mellitus.[4-7] Intensive multifactorial treatment halved risk of cardiovascular events and death in patients with longstanding diabetes and microalbuminuria in the STENO-2 trial.[2] We searched PubMed for relevant articles by use of "diabetes mellitus, type 2" and "cardiovascular disease" as MeSH headings and the term "randomised controlled trial" in any heading, in combination with the terms "multifactorial" or "screen*". We placed no restriction on language, year of publication, or study quality. We found no published trial evidence of the effects of multifactorial treatment on cardiovascular outcomes in individuals with screen-detected type 2 diabetes.

Interpretation

Population screening for type 2 diabetes and subsequent intensive treatment is feasible. Cardiovascular risk factors improved in the 5 years after detection by screening, and rates of first cardiovascular events and mortality were lower than expected. The small differences in prescribed treatment, and levels of cardiovascular risk factors, between groups at 5 years were associated with a non-significant 17% reduction in the incidence of cardiovascular events, with no obvious adverse consequences. The extent to which the complications of diabetes can be reduced by earlier detection and treatment remains uncertain.

10 years) and newly diagnosed patients in a study in Denmark (33% over 7·4 years).[36] In our study, mortality was similar to that reported for people of the same age without diabetes in the general population of Denmark in 1995–2006.[37] This lack of difference is likely to be due to the quality of care delivered to patients early in the course of their disease in both groups.

This trial shows that screening for type 2 diabetes and early intensive multifactorial treatment of the detected patients are feasible in general practice. In both study groups, cardiovascular risk factors, such as blood pressure and cholesterol concentrations, improved notably after diagnosis and glycaemia and weight did not increase. Absolute values for risk factors at follow-up and changes from baseline compare favourably with those in other trials in which patients were recruited at clinical diagnosis and followed up for 6 years.[34,35] Clinically important differences in risk factors between groups at 1 year,[18] however, were not maintained and were considerably smaller than those achieved in similar studies.[2,34]

Adherence to treatment algorithms might have been suboptimum in this pragmatic trial. In three centres the screening programme used risk scores, including treatment for hypertension as one of the factors to predict the risk of type 2 diabetes, which could have limited the achievable differences between groups in blood pressure. Furthermore, the trial was undertaken against a background of improvements in the delivery of diabetes care in general practice, such as that associated with the introduction of the Quality and Outcomes Framework for primary care in the UK,[38] and evidence-based

guidelines in Denmark[39] and the Netherlands,[40] which might also have lowered the achievable differences in treatment between groups.

Participants were drawn from a large, representative, population-based sample in three different European countries. They were identified by a range of different screening programmes and all were diagnosed according to WHO criteria.[21] The intensive treatment intervention incorporated various methods that encouraged changes in practitioner behaviour, and treatment algorithms and targets that were based on robust trial data.[2,4,6,26] Because the intervention was delivered mainly via family physicians and nurses, we randomised general practices rather than individuals to minimise the risk of contamination. The analyses were appropriate to the cluster design. We achieved high participant retention and independently adjudicated endpoint ascertainment in both trial groups. We assessed clinically important outcomes with standard equipment and protocols by especially trained staff members who were unaware of study group allocation. Patients with and without follow-up data differed little.

The generalisability of our findings to other settings should be considered in light of the non-random recruitment of general practices. We did, however, cover a large geographical area in each country, and the 26% of invited practices that were randomised were nationally representative for key descriptive characteristics.[17,18,20] Assessment of hypoglycaemia was imprecise, as it was limited to one question, but we believe this factor is unlikely to be biased because the questionnaire was administered in the same way to participants in the two study groups by staff unaware of study group allocations. We feel that the size of the study means that even with a potentially imprecise instrument the power was sufficient to quantify the effects of the intervention on the frequency of hypoglycaemic events. In two centres (Denmark and the Netherlands), assays used to assess biochemical factors differed slightly between baseline and follow-up, but not between groups (webappendix p 1). By necessity cluster randomisation was done before screening and recruitment of patients, a design feature that can introduce differences between groups in relation to participant characteristics. Overall, patients in the two study groups were well matched, although the intervention could have influenced the number and type of patients recruited to the intensive treatment group. This effect might have been particularly relevant in Denmark, where staff in the intensive treatment group might have been especially alert to the potential benefits of early detection and treatment and, therefore, have been more active testing in individuals at high cardiovascular risk, which could have led to the observed differences in baseline characteristics between study groups in this centre. These differences between groups might have lessened the apparent effects of the intervention and, therefore, could explain, at least partly, differences between centres, which seemed to be present but were not necessarily significant owing to the limited power of heterogeneity test.

Methods of screening, outcome assessment, and laboratory testing were standard across patient groups within centres but did differ between centres. These differences might have contributed to heterogeneity, even though interlaboratory validation suggested that methods were consistent between centres and all potential primary endpoints were adjudicated in the same way. Other sources of heterogeneity include the characteristics of patients, which varied by centre, presumably because of differences in the screening programmes and underlying populations, the delivery of the intensive treatment intervention (table 1), and other unmeasured factors.

The lower-than-expected event rate suggests that 5 years of follow-up is insufficient, and the apparent divergence from 4 years onwards suggests that further follow-up is justified to test whether early intensive multifactorial treatment reduces cardiovascular risk in the long term, as seen in the UKPDS.[8] Finally, the complex nature of the intensive treatment intervention and the pragmatic design of the trial make it difficult to say whether any components are individually associated with a reduction in cardiovascular risk.

The observed absolute and relative risks for cardiovascular events and mortality among participants with a mean HbA_{1c} concentration of around 6·5% 5 years after diagnosis, should allay concerns about early intensive treatment of hyperglycaemia.

We saw no interaction between intensive treatment and age or history of cardiovascular events, although benefits associated with this intervention seemed to be greatest in patients aged 60 years or older at diagnosis. Multifactorial treatment of screen-detected patients in both study groups was associated with improvements in cardiovascular risk factors and lower than expected rates of cardiovascular events and mortality. The small differences in treatment between groups at 5 years were associated with a non-significant 17% reduction in the incidence of cardiovascular events, with no obvious adverse consequences. We are undertaking analyses of trial data on microvascular endpoints, quality of life, functional status, and health service costs. Although there is no evidence of harm associated with screening[11] and intensive therapy,[41] the extent to which the complications of diabetes can be reduced by earlier detection and treatment remains uncertain (panel).

When compared with routine care, an intervention to promote target-driven, intensive management of patients with type 2 diabetes detected by screening was associated with small increases in the prescription of drugs and improvements in cardiovascular risk factors, but was not associated with significant reductions in the incidence of cardiovascular events or death over 5 years.

Contributors

SJG acts as guarantor for this paper. TL is Chair and KB-J Vice-Chair of the steering committee, which also included the following people, who collectively designed the study: SJG, MJD, KK, GEHMR, AS, and NJW. SJG, KB-J, MJD, KK, GEHMR, AS, NJW, and TL are principal investigators for the trial who, along with RKS and MvdD, participated in the acquisition of the data. SJS did the statistical analyses. All authors participated in the analysis and interpretation of data. SJG and RKS drafted the report. All authors participated in the critical revision of the intellectual content of the report.

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Additional study support

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Conflicts of interest

SJG has attended an advisory board for Colgate Palmolive, has received honoraria for speaking from Unilever, Eli Lilly, GlaxoSmithKline, MSD, and Novo Nordisk, and has received travel expenses from Eli Lilly; KB-J was director of the Steno Diabetes Centre, which is owned by Novo Nordisk, and holds stock in Novo Nordisk; MJD has served on advisory boards for Novo Nordisk, Eli Lilly, MSD, Bristol-Myers Squibb, and Roche, and has received honoraria for speaking from Novo Nordisk, Eli Lilly, Sanofi-Aventis, Novartis, and MSD; KK has participated in advisory boards for Novo Nordisk, Eli Lilly, MSD, Boehringer Ingelheim, and Roche, and has received honoraria for speaking from Novo Nordisk, Eli Lilly, Sanofi-Aventis, Novartis, and MSD; GEHMR has served as a consultant and participated in advisory boards for Novo Nordisk and MSD, and has received honoraria for speaking from Novo Nordisk; AS, SJS, RKS, and NJW declare that they have no conflicts of interest; MvdD has received travel expenses from Eli Lilly; and TL has received research funding from Novo Nordisk, AstraZeneca, Pfizer, GlaxoSmithKline, Servier, and HemoCue, has received honoraria for speaking from various pharmaceutical companies, and holds stock in Novo Nordisk.

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