10-year follow-up of intensive multifactorial therapy in individuals with screen-detected type 2 diabetes in primary care: the *ADDITION-Europe* randomised trial (clinical trial registration number NCT00237549)

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Summary

Background

In the *ADDITION-Europe* trial we investigated the effect over five years of promoting intensive treatment of multiple risk factors among people with screen-detected type 2 diabetes. We undertook post-hoc follow-up for a further five years to establish whether differences in treatment and cardiovascular risk factors were maintained and to assess effects on cardiovascular outcomes.

Methods

In this pragmatic, cluster-randomised, parallel-group trial, 343 general practices in Denmark, the Netherlands and the United Kingdom were randomly assigned (1:1) by computer-generated list to intensive multifactorial treatment or routine care of patients with type 2 diabetes aged 40 to 69 years identified through screening between April 2001 and December 2006. Following five year follow-up no attempts were made to maintain differences in treatment between study groups. The primary outcome was first independently adjudicated cardiovascular event up to 31/12/2014, including cardiovascular death, non-fatal myocardial infarction or stroke, revascularisation and non-traumatic amputation, identified from general practice records review and national registers. Patients and researchers assessing outcomes were unaware of practice study group allocation. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov (NCT00237549).

Findings

Sustained reductions over ten years following diagnosis were achieved for weight, HbA_{1c}, blood pressure and cholesterol in both study groups, but between-group differences that were observed at one and five years were attenuated by ten year follow-up. Primary endpoint data were available for 99% of the 3057 participants. Mean duration of 30-32follow-up was 9.61 years (SD 2.99). The incidence of first cardiovascular event was 16.1 per 1000 person years in the routine care group and 14.3 per 1000 person years in the intensive treatment group (hazard ratio 0.87, 95%CI 0.73 to 1.04), and of all-cause mortality 15.6 per 1000 person years and 14.3 per 1000 person years (hazard ratio 0.90, 95%CI 0.76 to 1.07), respectively.

Interpretation

Sustained reductions in glycaemia and related cardiovascular risk factors over ten years among people with screen-detected diabetes managed in primary care are achievable. The differences in prescribed treatment and cardiovascular risk factors in the five years following diagnosis were not maintained but were associated with a modest non-significant reduction in the incidence of cardiovascular events and death.

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INTRODUCTION

Most intervention studies informing the management of people with type 2 diabetes focus on treatment of individual risk factors. However, in practice patients receive lifestyle advice and simultaneous pharmacological treatment of several risk factors. Although there is a well-established literature concerning the long term effectiveness of control of individual risk factors, less is known about the impact of strategies that influence multiple factors. The Steno-2 trial in patients at high cardiovascular risk with longstanding diabetes and microalbuminuria showed that the risk of cardiovascular events and mortality was halved by intensive multifactorial treatment,[1,2] and that this risk reduction was sustained over time when there was less difference in risk factor control between intervention and control groups. Similarly, in the J-DOIT3 trial of patients who had been living with diabetes for 8.5 years, the risk of stroke was halved by intensive multifactorial treatment.[3] However, both of these trials were undertaken among patients who had been treated for diabetes for many years and much less is known about the effectiveness of multifactorial therapy earlier in the course of disease.

To address this uncertainty, we undertook the multi-centre Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen-Detected Diabetes in Primary Care (*ADDITION-Europe*) trial.[4-8] In this pragmatic, cluster randomised, parallel group trial 343 general practices were assigned to screening of individuals aged 40-69 years followed by routine care of type 2 diabetes, or screening plus an intervention to promote intensive treatment of multiple risk factors. The small but statistically significant differences in prescribed treatment and cardiovascular risk factors over the five years following detection of diabetes by screening were associated with a non-significant 17% reduction in risk of cardiovascular events.[8]

We report here the results of a post-hoc ten year follow-up (five year post-intervention) of the *ADDITION-Europe* trial cohort to assess the long term effects of guidelines, education, training and audit for primary care teams on cardiovascular and renal outcomes for people with diabetes detected by screening, and to quantify the long term effect of small differences in treatment and risk factors in the first five years following detection by screening.

METHODS

Design

The original study design, rationale, methods (including details of randomisation, laboratory measures and sample size calculation) and results for five year outcomes have been reported.[4-8] In brief, 379 (29%) of 1,312 invited general practices from four centres (Denmark, Cambridge UK, the Netherlands and Leicester UK) were randomised by computer-generated list to screening plus routine care of diabetes (RC), or screening followed by intensive multi-factorial treatment (IT). Allocation was concealed from patients throughout the trial. We carried out population-based stepwise screening programmes among people aged 40 to 69 years (50 to 69 years in the Netherlands), without known diabetes, between April 2001 and December 2006, as previously described.[6,7,9-11] Screening programmes varied by centre and included a risk score based on medical records (Cambridge) or self-completion questionnaires (Denmark and the Netherlands), followed by capillary glucose testing and/or an oral glucose tolerance test, or invitation to attend an oral glucose tolerance test without prior risk assessment (Leicester). Individuals were diagnosed with type 2 diabetes according to 1999 WHO criteria.[12] General practitioners assessed patients against exclusion criteria: an illness with a life expectancy of less than twelve months, housebound, pregnancy or lactation, or psychological or psychiatric problems that were likely to invalidate informed consent. Overall 3,057 eligible participants with screen-detected diabetes agreed to take part (Denmark: 1533, Cambridge UK: 867, Netherlands: 498 and Leicester UK: 159). We report a post-hoc analysis of cardiovascular and renal outcomes over ten years following randomisation including 5 years post-intervention follow-up.

Procedures

Intervention The specific characteristics of the interventions to promote intensive multifactorial treatment in the first five years in each centre have been described previously, including the methods used to educate and support staff in providing lifestyle advice and intensive treatment.[4-7] Further details are available at the study website (http://www.addition.au.dk/). We aimed to educate and support general practitioners and practice nurses in target-driven management of hyperglycaemia, blood pressure and cholesterol. Intensive treatment was promoted through the addition of several features to existing diabetes care. In Leicester patients were referred to the DESMOND structured education programme,[13] and were offered two-monthly appointments with a diabetes nurse or physician in a community peripatetic clinic for one year, and four-monthly thereafter. Clinic staff were prompted to contact patients defaulting from appointments. In the other centres small group or practice-based educational meetings were arranged with general practitioners and nurses to discuss the treatment targets and algorithms and lifestyle advice, with

supporting evidence. Audit and feedback were included in follow-up meetings up to twice per year or coordinated by post. In the Netherlands patients were seen in general practice by diabetes nurses who were authorised to prescribe medication and adjust doses under general practitioner supervision. In Denmark and Cambridge practice staff were provided with educational materials for patients. In Denmark and the Netherlands patients were sent reminders if annual measures were overdue. In all centres practices received a small amount of additional funding to support the delivery of care. The treatment algorithms, which were used in all centres, suggested a treatment threshold of 6.5% (48mmol/mol) for HbA_{1c} aiming to keep the level below 7.0% (53mmol/mol), 120/80mmHg for blood pressure aiming to keep the level below 135/85mmHg and 3.5mmol/l for total cholesterol aiming to keep the level below 4.5mmol/l in people with ischaemic heart disease and below 5.0mmol/l in people with no history of heart disease. General practitioners were advised to consider prescribing an angiotensin converting enzyme (ACE) inhibitor for patients with blood pressure ≥120/80mmHg or a previous cardiovascular event,[14] and 75mg of aspirin daily to patients without specific contraindications. Following publication of the Heart Protection Study,[15] a recommendation to prescribe a statin to all patients with a cholesterol level ≥3.5 mmol/l was included in the treatment algorithm. Although targets for treatment were specified and classes of medication recommended, prescribing decisions including choice of individual drugs were made by practitioners and patients.

Comparison In the RC group, we provided general practitioners with diagnostic test results. Patients with screen-detected diabetes received the standard diabetes care according to the recommendations applicable in 2000-2009 in each centre.[16-19] After publication of the results from five year follow-up we sent participating patients and practitioners in both study groups a newsletter explaining the findings. We made no attempts to maintain between-group differences in treatment, practitioners and patients were free to negotiate individualised treatment plans.

Outcomes

Centrally trained staff carried out health assessments following standard operating procedures at baseline and after five-years in all centres, and also after one year in three centres (Cambridge, Leicester and the Netherlands) as previously described.[8] To minimise participant burden we did not recall participants for ten year follow-up. Instead, staff collected data concerning prescribed medication and intermediate endpoints (for example body mass index, blood pressure, HbA_{1c}, plasma cholesterol and creatinine, and urine albumin/creatinine ratio (ACR)) from general practice records and national registers. Data were not consistently recorded in medical records for full lipid

profiles and smoking status. The glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease Study Equation.[20]

In Denmark these indirect methods were also used to collect data on intermediate endpoints at one year. 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 up to 31/12/2014. We collected data on potential endpoints from participants' medical records or national registers. In Denmark we searched the Civil Registration system for deaths and the national patient register for ICD10 codes for cardiovascular events (I08-I77), and surgical procedures concerning amputations (chapters KNFQ, KNHQ, KNDQ, KNCQ) and revascularisations (chapters KF and KP of the Nomesco Classification of Surgical Procedures. Sundhedsstyrelsen and Munksgaard, Copenhagen, 2005). For possible events we obtained information from hospital medical records and coroners' offices, as required. In Cambridge and Leicester participants were tagged for mortality in the England and Wales Office of National Statistics, which provided copies of participants' death certificates. We carried out sensitive electronic Read code searches of general practice records after five and then ten years of follow-up. We also used the Myocardial Infarction National Audit Project (MINAP)[21] to identify possible cardiovascular events. If a possible event was highlighted anonymised copies were made of general practice medical records for review by investigators. Additional information was obtained from hospital medical records as required. In the Netherlands an experienced general practitioner visited practices, scrutinised the electronic medical records of participating patients who had not withdrawn from the study, and extracted endpoint and vital status data onto an electronic case record form. In all centres, for each possible endpoint, we prepared packs containing relevant clinical information (such as death certificates, post mortem reports, general practice and hospital records, hospital discharge summaries, electrocardiographs and laboratory results) and sent them for independent adjudication of components of the composite cardiovascular outcome and cause of death according to an agreed protocol using standardised case report forms. All data collection, notes review and endpoint adjudication was undertaken by staff unaware of study group allocation. The date of completion of follow-up for the primary endpoint was deemed to be the date of the first primary endpoint or 31/12/2014 if no endpoint occurred. We censored participants who were lost to follow-up at their last available follow-up time based on information from medical records or national registers. The study was approved by local ethics committees in each centre. All participants provided written informed consent prior to inclusion in the original trial. They were informed of the results following five year follow-up and the plans for post-intervention follow-up and given the option of opting out.

Statistical analysis

The analysis plan was finalised prior to preparation of the endpoint dataset, and is available on the study website (http://www.addition.au.dk/). We calculated the number and percentage of participants who experienced the primary outcome (composite cardiovascular event) by randomised group, and estimated its cumulative incidence over time within each randomised group using the method for competing risks (in which death from non-cardiovascular causes is the competing event).[22] We used Cox regression, with robust standard errors to allow for within practice correlation, to estimate the hazard ratio and 95% confidence interval comparing the IT and RC groups, separately within each country.[23] Estimated hazard ratios were combined across countries using fixed effects meta-analysis; the I^2 statistic, representing the proportion of variability (in estimated log hazard ratios) between countries due to heterogeneity, was calculated. To assess the impact of deviations from the assumption of non-informative censoring, we performed a sensitivity analysis using the method described by Jackson.[24]

We tested the multiplicative interactions between randomised group and age (<60, ≥60years) and self-reported history of myocardial infarction or stroke at baseline, by including the relevant parameter in the country-specific Cox models, and then combining the estimates across countries using fixed effects meta-analysis. We calculated hazard ratios (IT vs RC) and 95% CIs within each of the subgroups, using the method described above. We used the same method to estimate the intervention effect on each of the separate components of the primary outcome (except for amputation due to the small number of events), and all-cause mortality. For all-cause mortality we also calculated Kaplan-Meier estimates of cumulative incidence over time.

We estimated the intervention effect (IT vs RC) on each secondary continuous outcome using country-specific analysis of covariance models, adjusted for the baseline value of the outcome, and with robust standard errors to allow for within practice correlations. For creatinine, ACR and eGFR we reported a ratio of geometric means. For binary outcomes reflecting prescription of various classes of medication we used country-specific logistic regression, adjusted for baseline prescribed medication, and with robust standard errors. In both cases we combined estimates across countries using fixed effects meta-analysis. We excluded participants with missing data at ten years follow-up, but for continuous outcomes we included participants with a value at ten years but missing baseline value using the missing indicator method.[25] For HbA_{1c}, systolic blood pressure and total cholesterol, we compared baseline characteristics between those with missing and non-missing values at ten years. The analysis of secondary outcomes assumed missing data at 10 years were missing at random (MAR), conditional on randomised group and baseline value. A

sensitivity analysis was performed to investigate the potential impact of plausible departures from MAR on the estimated difference between randomised groups, using the approach described by White et al,[26] which is based on jointly modelling the data and the missingness using a pattern mixture model. Analysis was undertaken using STATA v14.2 (StataCorp, College Station, Texas, USA).

Role of the funding source

The funders of the study had no role in study design, data collection, analysis and interpretation or writing of the report. SJS and SJG had full access to all the study data and final responsibility for submission for publication.

RESULTS

A total of 343 practices were randomised to routine diabetes care (n=176) or intensive multifactorial treatment (n=167) of which 317 (RC=157, IT=161) included eligible patients (figure 1) between April 2001 and December 2006. Of the 3233 individuals with screen-detected diabetes, 3057 agreed to participate (RC:1379, IT:1678), 2 withdrew and 196 were deceased within the first five years, leaving 2859 who entered follow-up from five to ten years. Baseline characteristics of participants were well matched overall as previously reported[8] and shown in table 1.

Data for clinical and biochemical outcomes were available for 75% and 80% of those still alive at ten years, respectively (supplementary table 1). There were no baseline differences in age, sex, blood pressure, cholesterol and prior history of cardiovascular disease between participants with and without missing data for HbA_{1c} at ten years. However, compared to those with complete data, those with missing data for HbA_{1c} had slightly lower mean baseline values for HbA_{1c} and body mass index, were less likely to be prescribed medication to lower blood pressure and cholesterol, but were more likely to be smokers. Compared to those with complete data for blood pressure at ten years, those with missing data were younger, consumed more alcohol, were more likely to smoke, less likely to be prescribed medication for blood pressure, and had lower body mass index but higher total cholesterol at baseline. Baseline characteristics for those with and without cholesterol data at follow-up were similar with the exception of smoking status and prescription of lipid-lowering medication (supplementary tables 2 and 3).

After ten years 85% of patients were prescribed antihypertensive medication, 78% statins and 76% glucose-lowering medication (65% metformin and 12% insulin). Sustained reductions over ten years following diagnosis were achieved for weight, HbA_{1c}, blood pressure and cholesterol in both study groups (figure 2). However, with the exception of antihypertensive medication (in particular drugs targeting the renin-angiotensin system) and aspirin, between-group differences in prescribed medication and cardiovascular risk factors at one and five years largely disappeared between five and ten year follow-up (table 1 and figure 2). Creatinine and eGFR were stable during follow-up whereas ACR increased slightly; just over half the participants had microalbuminuria at ten years (RC: 50.2%, IT: 52.9%). However, there were no differences between groups in change from baseline in renal outcomes (table 1).

Primary endpoint data were available for 99% of participants. Mean duration of follow-up was 9.61 years (SD 2.99), equating to 29384 person years (RC: 13110, IT: 16275). During this time 443 participants experienced a first cardiovascular event and 465 died. There was no significant

difference between groups in the incidence of the primary composite outcome (RC: 16.1 per 1000person years, IT: 14.3 per 1000 person years) or its components (table 2, figure 3), and in all-cause mortality and pre-defined categories of cause-specific mortality (table 3, figure 4). There were no deaths related to hypoglycaemia in either group. There was heterogeneity between countries for the myocardial infarction and revascularisation outcomes. For the primary outcome we did not observe interactions between the study groups and self-reported history of cardiovascular event at baseline. However, there was evidence of an interaction with age (p=0.046); estimated hazard ratios were 1.19 (95%CI 0.86 to 1.65) in patients less than 60 years at diagnosis and 0.74 (95%CI 0.59 to 0.93) in those aged 60 years and older. The interaction was observed in the UK and the Netherlands but not Denmark (see supplementary figure 1 and tables 4 and 5). The estimated intervention effect was stable across a wide range of deviations from the assumption of non-informative censoring (primary outcome) or missing at random (five pre-specified secondary outcomes).

DISCUSSION

An intervention to promote intensive multifactorial management of people with screen-detected type 2 diabetes was associated with small but statistically significant changes in prescribed treatment and cardiovascular risk factors (not including smoking status or weight) in the first five years after diagnosis, which were attenuated by ten years. These changes in treatment and risk factors were associated with a 13% lower risk of cardiovascular events and 10% lower risk of mortality over ten years, albeit not achieving statistical significance. Renal outcomes were similar in both groups. The association with risk of mortality was almost unchanged from five year follow-up but the association with cardiovascular risk was smaller. Between-group differences favoured the IT group for the myocardial infarction, stroke and revascularisation components of the primary endpoint, but not for cardiovascular death (within 30 days of a cardiovascular event) or amputation. Factors in support of a potential effect at ten years included the simultaneous treatment of multiple risk factors early in the course of the disease, the significant effects on modelled cardiovascular risk seen at five years,[27] and the 90% increase in the number of first cardiovascular events during post-trial monitoring thereby increasing study power. While we cannot exclude the possibility that the results were due to chance, there may be a 'legacy effect' of the intervention during the first five years after diagnosis, particularly among patients aged over 60 years at diagnosis. This might represent continuing variation between groups in some aspects of patient health behaviours and general practice care, or a lag effect of small reductions in risk factors over the first five years.

Following publication of the ACCORD trial[28] and a retrospective observational study from UK general practice,[29] which both involved people with established disease and longstanding elevated glycated haemoglobin, there was widespread concern about the effects on mortality of intensive treatment of glycaemia. Our data suggest that achieving good control of glycaemia (glycated haemoglobin below 53 mmol/mol), and related cardiovascular risk factors, for ten years following diagnosis is both feasible in primary care and safe (with respect to risk of CVD, death due to hypoglycaemia and all-cause mortality), but does necessitate polypharmacy. Intensive treatment of multiple risk factors was associated with reduced risk of cardiovascular events and death in Steno-2[1,2] and of stroke in J-DOIT3,[3] and legacy effects were reported for intensive treatment of glycaemia but not blood pressure in the UKPDS.[30,31] Compared to Steno-2,[2] UKPDS[30] and J-DOIT3,[3] *ADDITION* participants were older but had a shorter duration of diabetes, lower baseline glycated haemoglobin, higher blood pressure and higher body mass index. However, the most likely explanation for the variation between trials in effects on cardiovascular outcomes is the smaller between-group differences in risk factors in *ADDITION*, and the low rates of

cardiovascular events and mortality in both *ADDITION* and J-DOIT3.[3] Rates of amputation were low overall, lower than observed in the UKPDS,[32] and there is no obvious explanation for the apparent between-group difference which could be a chance finding.

The study has a number of strengths. The participants were recruited from a population-based sample and representative practices, albeit with little ethnic diversity. Participant retention was high, and contamination was minimised by the cluster design with appropriate allowance for potential correlation of individuals within a practice. The main limitations are the context of improvements in general practice diabetes care over the course of the trial and the incomplete adherence to the treatment algorithms by primary care teams in the IT group, both of which attenuated between-group differences in treatment and risk factors. The decision to extend follow-up was made after analysis of data at five years but the analysis plan was finalised prior to completion of data collection. Participants' baseline characteristics were well matched across study groups although the cluster design may have contributed to small differences. We minimised participant burden by collecting data from medical records and registers at ten year follow-up. However, while not influencing the primary outcome, this led to considerable missing data for intermediate outcomes. It is difficult to speculate on the likely size and direction of any resultant bias as individuals with missing data exhibited baseline characteristics associated with both higher and lower cardiovascular risk. Findings were stable across a wide range of deviations from the missing at random assumption. There was heterogeneity between centres in the approaches to screening and promoting intensive multifactorial treatment, the characteristics of participants, and the methods used to collect data on outcomes. This may have contributed to heterogeneity in effect sizes for some components of the primary outcome. However, all participants were diagnosed according to WHO criteria, treatment algorithms were consistent across centres, outcome assessment was comprehensive and undertaken by individuals unaware of study group allocation, and there was no heterogeneity for the primary outcome or mortality. The newer glucose-lowering medications such as GLP1 analogues and SGLT2 inhibitors have recently been shown to be effective in reducing risk of CVD among patients with longstanding diabetes but were prescribed to relatively few ADDITION patients. Furthermore, the intervention was multifactorial and so we cannot comment on the benefits and harms of individual medications, such as aspirin, or different classes of medications among newly diagnosed patients.

The findings of *ADDITION* have implications for policy relating to early detection and subsequent management of type 2 diabetes in the settings in which this trial was conducted. People with screen-detected diabetes demonstrated high levels of potentially modifiable cardiovascular risk

factors. Relatively small between-group differences in treatment of these risk factors in the first five years after diagnosis were associated with reductions in rates of cardiovascular events and mortality over ten years of 13% and 10%, respectively. Improvements in risk factors between diagnosis and one year follow-up in both study groups far exceeded the between-group differences and mirror those between undiagnosed and diagnosed patients. This suggests that people with type 2 diabetes derive benefit from earlier detection and treatment in the lead time between incidence and clinical diagnosis, as demonstrated in a controlled trial[33] and a modelling study.[34] Earlier detection may also reduce diabetes-related health care costs.[35] However, cost-effectiveness of earlier detection through stratified screening has not been demonstrated in randomised studies. Furthermore, given the low rate of detection of undiagnosed disease, a single round of population screening for diabetes is unlikely to influence overall population mortality,[36,37] consistent with screening programmes across a range of conditions. Moreover, as we did not include a 'no-screening' control group in all four centres, we cannot exclude the possibility that regression to the mean and chance account for some of the observed improvements in risk factors in the whole cohort.

The policy implications from the results of the ADDITION trial are influenced by the health care context in which the trial was undertaken. Primary care is well organised in the three countries participating in this study and care for people known to have diabetes is generally good. Thus, relatively speaking the differences between routine and enhanced primary care are small. In addition, there has been a considerable increase in the amount of opportunistic testing for undiagnosed diabetes in primary care and thus those who are found by the instigation of a formal mass screening programme would tend to be those earlier in the disease trajectory. In other settings where there is less frequent opportunistic testing and where primary care is less well-resourced and organised, the absolute and relative benefits of early detection and intensive risk factor management in primary care could well be greater. Paradoxically, however, screening may be much less feasible in those settings since logically attention would need to be focused on investing in primary care and improving treatment of those with disease before increasing the prevalence of diagnosed diabetes by screening.

In conclusion, sustained reductions in glycaemia and related cardiovascular risk factors over ten years among people with screen-detected diabetes managed in primary care are achievable. The between-group differences in prescribed treatment and cardiovascular risk factors in the five years following diagnosis were not maintained but were associated with a modest, non-significant reduction in the incidence of cardiovascular events and death.

Contributors

SS had full access to all of the data in the study and takes responsibility for the accuracy of the data analysis. SJG, GI, AS, E-M D, RV, DW and SS take responsibility for the integrity of the data. SJG acts as guarantor for this paper. The following collectively designed the study: TL, Knut Borch-Johnsen, SJG, NJW, GEHMR, AS, Ronald P Stolk (Department of Epidemiology, University Medical Center, Groningen, University of Groningen, The Netherlands) and Bruce H.R. Wolffenbuttel (Department of Endocrinology, University Medical Center, Groningen, University of Groningen, The Netherlands). Later MJD and KK joined the committee and Bruce Wolffenbuttel and Ronald Stolk left. Principal investigators for the original trial were: Knut Borch-Johnsen, TL, SJG, NJW, GEHMR, AS, MJD and KK. The principal investigators and Rebecca Simmons, Maureen van den Donk, GI, E-M D, RV and DW participated in the acquisition of the data. SS conducted the statistical analyses, all authors participated in the interpretation of data. SJG drafted the manuscript. All authors participated in the critical revision of the manuscript for important intellectual content.

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Figure 1: *ADDITION-Europe* trial profile

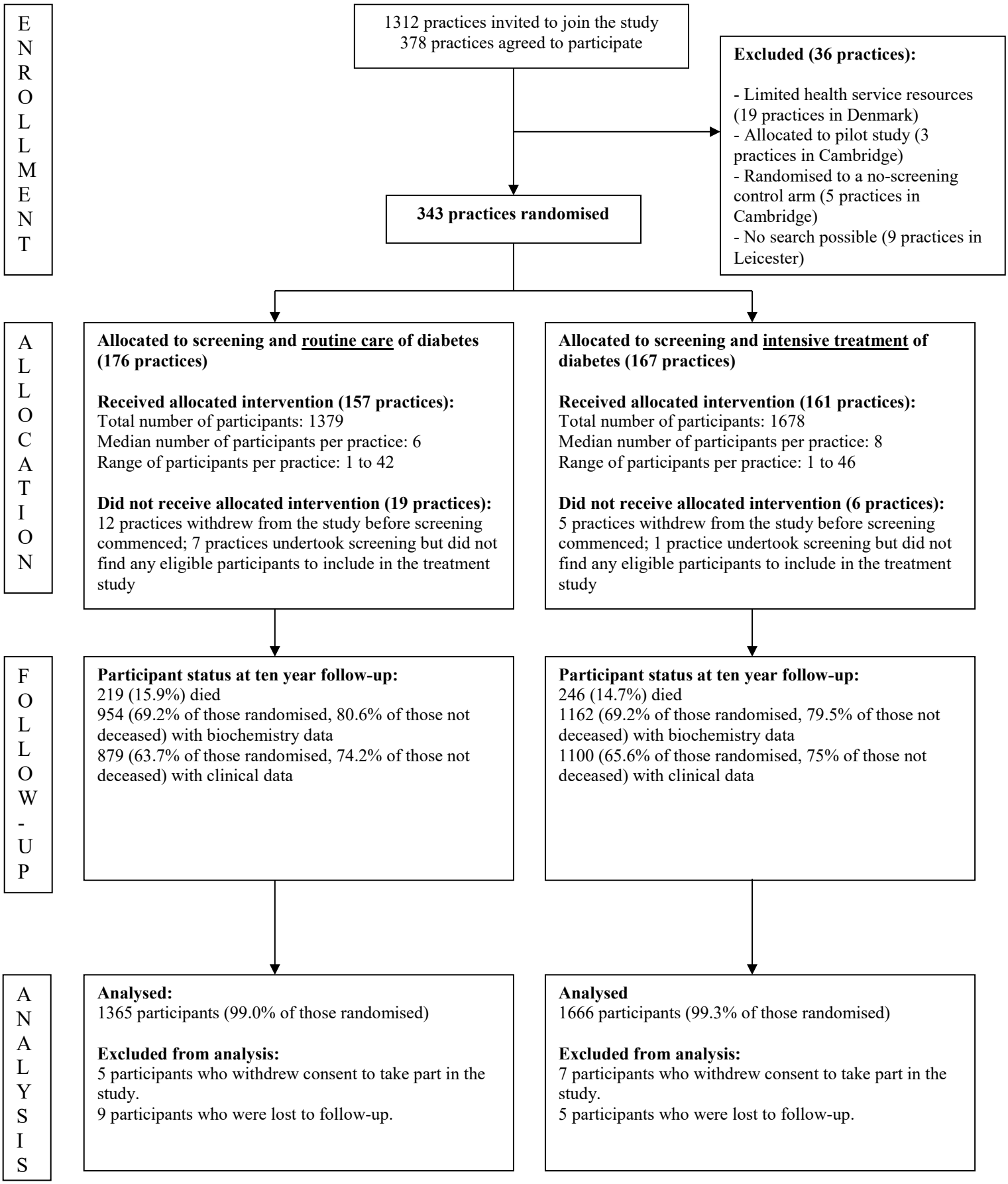


Table 1: Demographic, clinical and biochemical values and prescribed medication in the routine care and intensive treatment groups of the *ADDITION-Europe* trial at baseline and 10 year follow-up (values are shown as mean (SD) unless specified)

Characteristic	*ROUTINE CARE*						*INTENSIVE TREATMENT*						**Intensive Treatment vs Routine Care ***	
	Baseline (n=1379)			***10 year follow up***			***Baseline (n=1678)***			***10 year follow up***				
	Total with data	mean	SD	Total with data	mean	SD	Total with data	mean	SD	Total with data	mean	SD	Beta	95% CI
Demographic variables														
Male sex, n %	1379	790	57.3	-	-	-	1678	981	58.5	-	-	-	-	-
Age at diagnosis (years)	1379	60.2	6.8	-	-	-	1678	60.3	6.9	-	-	-	-	-
White ethnicity, n %	1334	1246	93.4	-	-	-	1607	1539	95.8	-	-	-	-	-
Employed, n %	1013	425	42.0	-	-	-	1197	482	40.3	-	-	-	-	-
Clinical variables														
History of myocardial infarction, n %	1286	79	6.1	-	-	-	1593	109	6.8	-	-	-	-	-
History of stroke, n %	1270	24	1.9	-	-	-	1558	45	2.9	-	-	-	-	-
Current smokers, n %	1347	375	27.8	-	-	-	1649	444	26.9	-	-	-	-	-
Median (IQR) units of alcohol/week	1183	4	1-13	-	-	-	1492	4	1-13	-	-	-	-	-
Waist circumference (cm)	1346	106.8	13.5	-	-	-	1612	107.1	13.5	-	-	-	-	-
Median (IQR) units of alcohol /week	1183	4.0	1 to 13	-	-	-	1492	4.0	1 to 13	-	-	-	-	-
BMI (kg/m^2)	1342	31.6	5.6	781	30.6	5.4	1615	31.6	5.6	1030	30.7	5.8	0.09	-0.22 to 0.41
Weight (kg)	1344	90.3	17.6	789	87.1	17.2	1615	90.9	17.5	1019	87.9	18.2	0.26	-0.63 to 1.15
HbA_{1c} (mmol/mol)	1298	53.5	16.7	954	52.6	13.1	1591	53.3	17.3	1162	51.6	11.9	-0.52	-1.52 to 0.48
Systolic blood pressure (mmHg)	1346	149.8	21.3	879	135.0	13.9	1617	148.5	22.1	1100	134.1	13.5	-0.69	-2.26 to 0.88
Diastolic blood pressure (mmHg)	1346	86.5	11.3	879	75.9	9.5	1618	86.1	11.1	1100	75.6	9.0	-0.27	-1.24 to 0.69
Total cholesterol (mmol/l)	1300	5.6	1.2	950	4.1	1.0	1593	5.5	1.1	1149	4.1	0.9	-0.08	-0.16 to -0.002
Median (IQR) creatinine (µmol/L)	1266	83.0	73.0-94.0	956	78.0	66.0-93.5	1565	82.0	72.0-93.0	1162	80.0	67.0-96.0	1.01	0.99 to 1.04
Median (IQR) alb/creat ratio (mg/mmol)	1228	0.9	0.4-2.1	753	3.0	0.8-10.0	1528	0.9	0.4-2.1	908	3.3	0.8-10.0	0.93	0.81 to 1.07
Median (IQR) eGFR ($ml/min/1.73m^2$)	1266	77.8	67.6-88.9	956	79.6	66.2-94.9	1565	78.0	68.9-89.4	1152	81.1	65.2-93.8	0.99	0.96 to 1.01

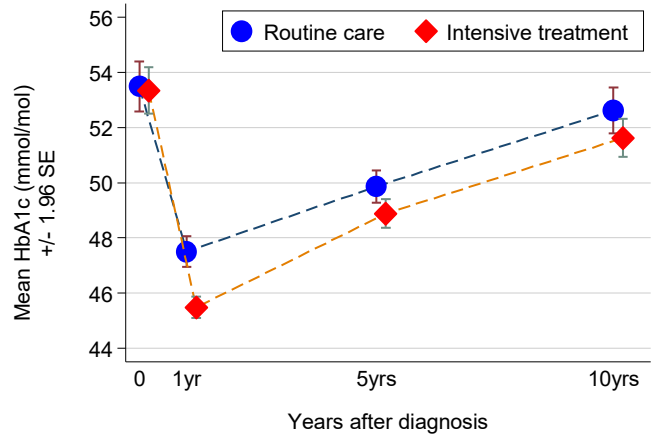
* Beta represents the baseline-adjusted difference (intensive treatment vs routine care) in the change in the characteristic between baseline and 10 year follow up, estimated from an ANCOVA model with adjustment for baseline value of the outcome. The ANCOVA models account for clustering within practice using robust standard errors, and are fit separately within each centre, with estimates then combined across centres using fixed effect meta-analysis. For continuous variables with a skewed distribution (creatinine, alb/creat ratio, eGFR), the ratio of geometric means (intensive treatment vs routine care) is presented, estimated from an ANCOVA model with adjustment for baseline value of the outcome, and using a log transformation of the variable at both baseline and 10 years. alb/creat ratio: urine albumin/creatinine ratio; eGFR: estimated glomerular filtration rate.

Table 2: Prescribed medication in the routine care and intensive treatment groups of the *ADDITION-Europe* trial at baseline and 10 year follow-up (values are n, %)

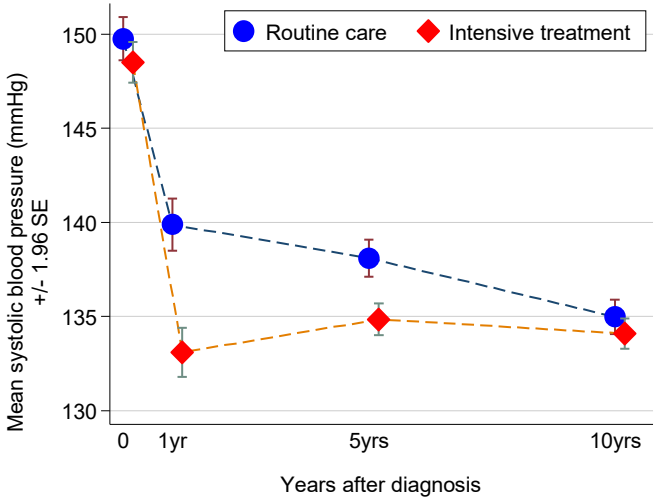
Characteristic	*ROUTINE CARE*						*INTENSIVE TREATMENT*						**Intensive Treatment vs Routine Care***	
	Baseline (n=1379)			***10 year follow up***			***Baseline (n=1678)***			***10 year follow up***				
	Total with data	N	%	Total with data	N	%	Total with data	N	%	Total with data	N	%	OR	95% CI
Any glucose lowering drug	1340	7	0.5	887	661	74.5	1609	8	0.5	1086	830	76.4	1.27	0.99 to 1.61
Metformin	1340	5	0.4	887	574	64.7	1609	6	0.4	1086	718	66.1	1.14	0.92 to 1.42
Sulphonylurea	1340	2	0.1	887	199	22.4	1609	2	0.1	1086	217	20.0	0.87	0.67 to 1.13
Thiazolidinedione	1340	0	0	887	15	1.7	1609	0	0	1086	24	2.2	1.44	0.63 to 3.32
Insulin	1340	0	0	887	98	11.0	1609	0	0	1086	134	12.3	1.12	0.83 to 1.52
Other glucose lowering drug	1340	0	0	887	137	15.4	1609	0	0	1086	193	17.8	1.11	0.82 to 1.52
Any antihypertensive drugs	1340	585	43.7	887	731	82.4	1609	752	46.7	1086	938	86.4	1.39	1.04 to 1.85
ACE inhibitor or ARB	1340	248	18.5	887	596	67.2	1609	345	21.4	1086	808	74.4	1.43	1.16 to 1.76
Beta-blocker	1340	252	18.8	887	265	29.9	1609	366	22.7	1086	401	36.9	1.23	0.97 to 1.55
Calcium channel blocker	1340	166	12.4	887	291	32.8	1609	202	12.6	1086	344	31.7	0.95	0.78 to 1.15
Diuretic	1340	330	24.6	887	376	42.4	1609	415	25.8	1086	519	47.8	1.22	0.98 to 1.53
Other antihypertensive drug	1340	23	1.7	887	29	3.3	1609	32	2.0	1086	50	4.6	1.60	0.92 to 2.79
Any lipid lowering drug	1340	206	15.4	887	698	78.7	1609	274	17.0	1086	864	79.6	1.06	0.83 to 1.34
Statin	1340	200	14.9	887	693	78.1	1609	271	16.8	1086	852	78.5	1.02	0.81 to 1.29
Aspirin	1340	169	12.6	887	270	30.4	1609	249	15.5	1086	459	42.3	1.76	1.35 to 2.31

***** The OR represents the odds ratio of being prescribed the medication at 10 year follow-up, comparing intensive treatment vs routine care, estimated from a logistic regression model with adjustment for baseline medication use. The logistic models account for clustering within practice using robust standard errors, and are fit separately within each centre, with estimates then combined across centres using fixed effect meta-analysis.

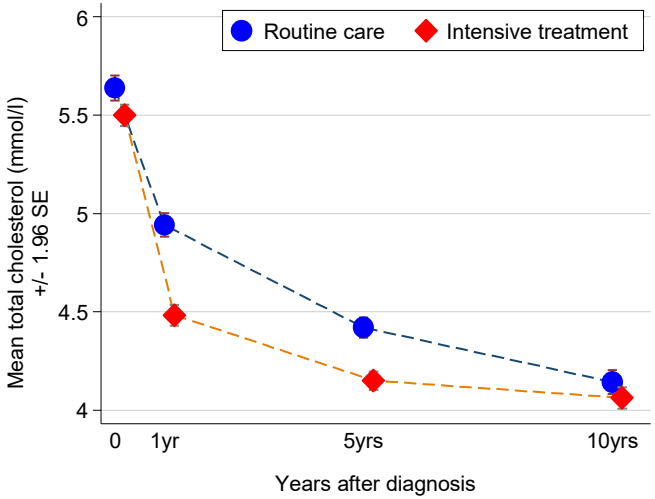
Figure 2: Comparison between routine care and intensive treatment groups in mean HbA_{1c}, systolic blood pressure, total cholesterol and weight values at baseline, one year, five years and 10 years after diagnosis



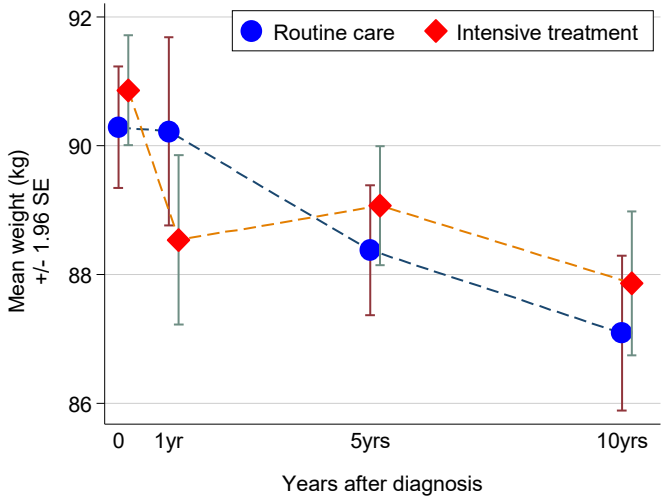
Routine Care	1298	1202	1226	954
Intensive Treatment	1591	1547	1514	1162



Routine Care	1346	642	1205	879
Intensive Treatment	1617	682	1518	1100



Routine Care	1300	1134	1226	950
Intensive Treatment	1593	1377	1524	1149



Routine Care	1344	585	1192	789
Intensive Treatment	1615	636	1491	1019

Table 3: Cardiovascular events and mortality in the *ADDITION-Europe* trial

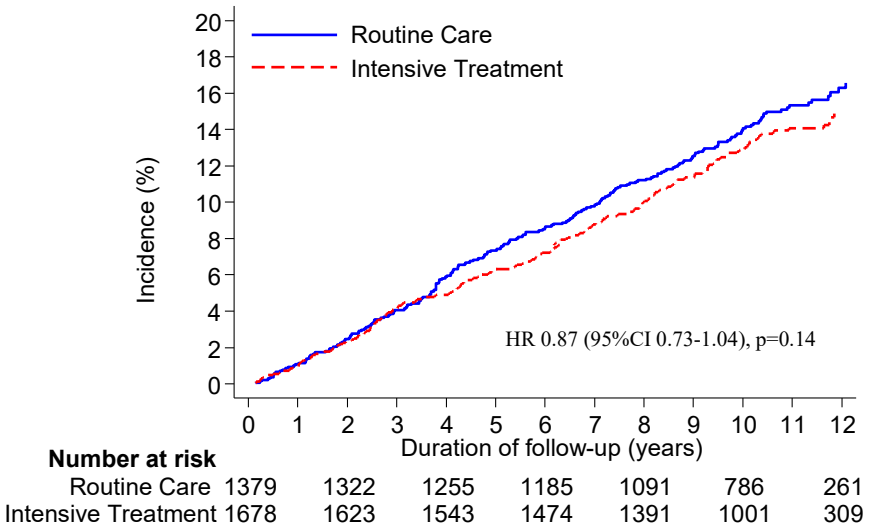
	Routine Care (n=1379) n (%)	**Intensive Treatment** (n=1678) n (%)	**Intensive Treatment vs Routine Care** Hazard Ratio	95% CI	I-squared (%)	p-value
Primary endpoint						
Composite cardiovascular events*	211 (15.3)	232 (13.8)	0.87	0.73, 1.04	0	0.14
Components of primary endpoint						
Cardiovascular death	47 (3.4)	60 (3.6)	0.97	0.69, 1.37	0	
Myocardial infarction	48 (3.5)	48 (2.9)	0.72	0.48, 1.08	59.8	
Stroke	43 (3.1)	38 (2.3)	0.74	0.48, 1.16	0	
Revascularisation	73 (5.3)	80 (4.8)	0.87	0.64, 1.17	24.5	
Amputation	0	6 (0.4)	-	-	-	
Total mortality	219 (15.9)	246 (14.7)	0.90	0.76, 1.07	0	
M*ortality by cause*						
Cardiovascular disease	47 (3.4)	60 (3.6)				
Malignant disease	99 (7.2)	112 (6.7)				
Suicide, violence or accident	4 (0.3)	5 (0.3)				
Infection	10 (0.7)	14 (0.8)				
Renal failure	3 (0.2)	4 (0.2)				
Hypoglycaemia	0 (0.0)	0 (0.0)				
Other non-CVD cause	36 (2.6)	32 (1.9)				
Non-classifiable/unknown death	20 (1.5)	19 (1.1)				

*Any of the following: CVD death, myocardial infarction, stroke, revascularisation, non-traumatic amputation

Hazard ratios are first estimated within each country using Cox regression with robust standard errors to allow for clustering within practice, and then combined across countries using fixed effects meta-analysis. I-squared is an estimate of the heterogeneity between countries. A p-value was calculated for primary endpoint only. Individual country specific estimates are displayed in forest plots

Figure 3: Cumulative incidence and relative risk of the composite cardiovascular endpoint
(A) Cumulative incidence curves in the routine care and intensive treatment groups. The p-value was calculated using Cox regression and fixed effects meta-analysis. (B) Hazard ratios of the development of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and revascularisation as a first event (secondary endpoints) and the composite cardiovascular endpoint (primary outcome), by country and overall, in the intensive treatment group compared with the routine care group. The size of each shaded box is inversely proportional to the country weight; the horizontal lines through each country's estimate are 95% CIs.

A


Routine Care
Intensive Treatment
Incidence (%)
0
2
4
6
8
10
12
14
16
18
20
HR 0.87 (95%CI 0.73-1.04), p=0.14
0 1 2 3 4 5 6 7 8 9 10 11 12
Duration of follow-up (years)
Number at risk
Routine Care 1379 1322 1255 1185 1091 786 261
Intensive Treatment 1678 1623 1543 1474 1391 1001 309

B

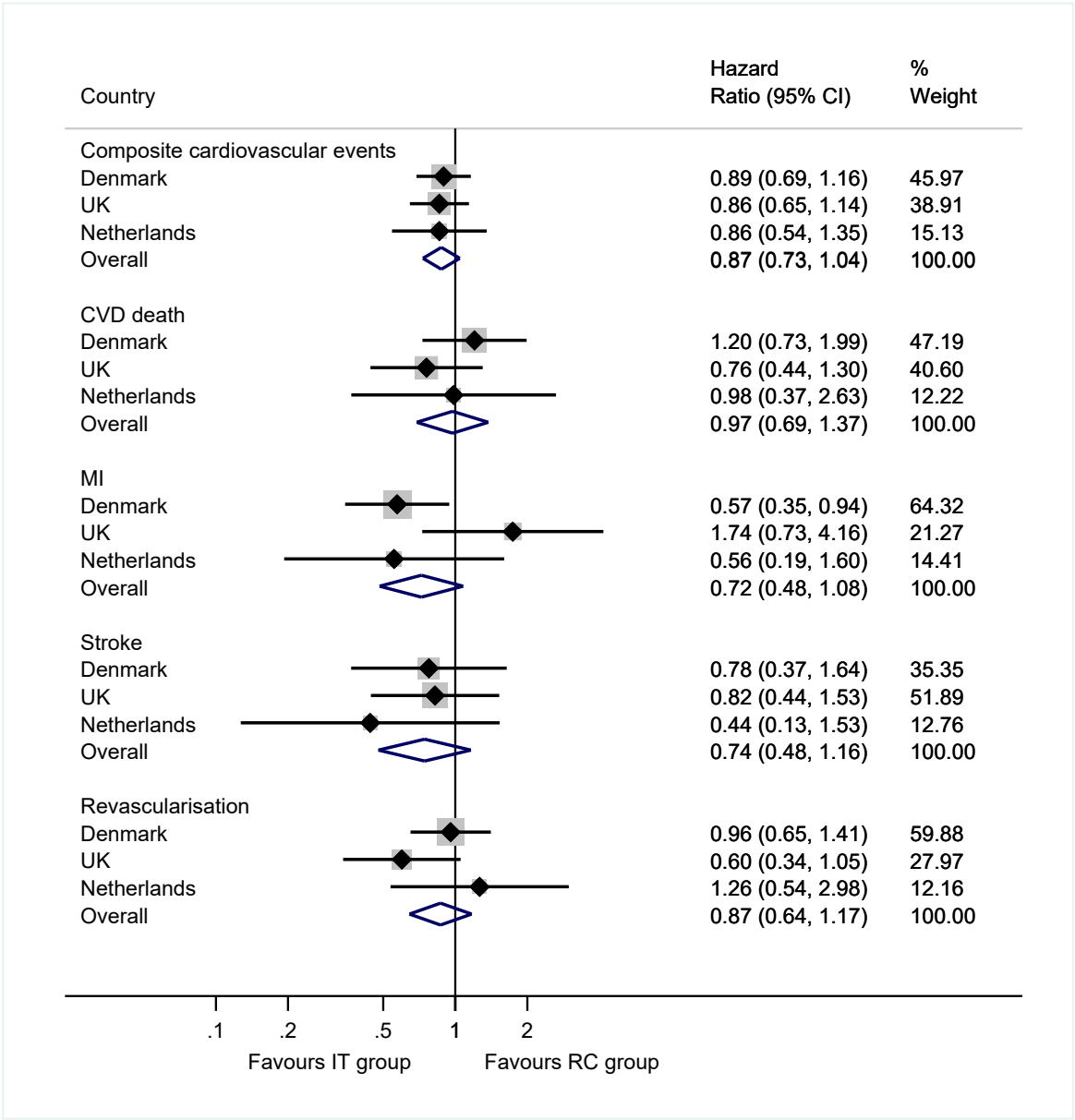
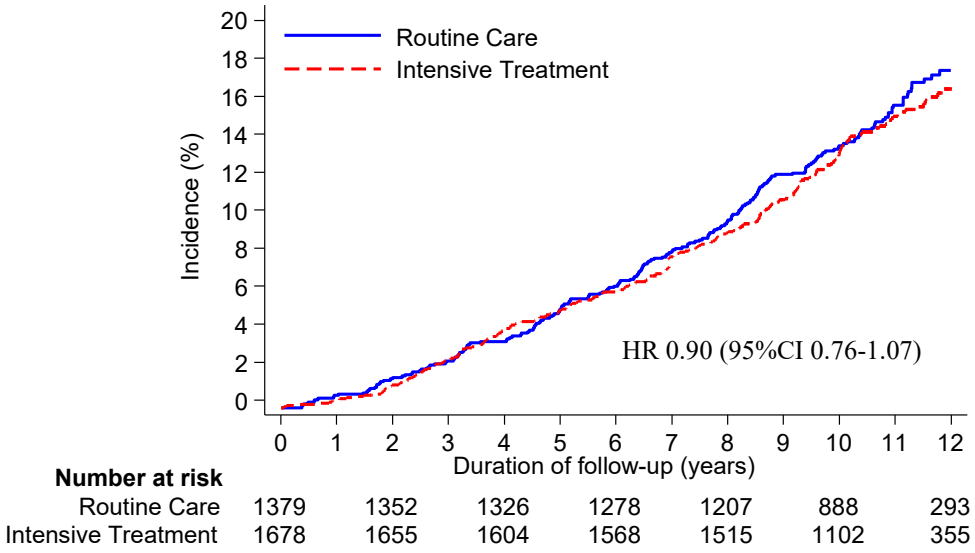
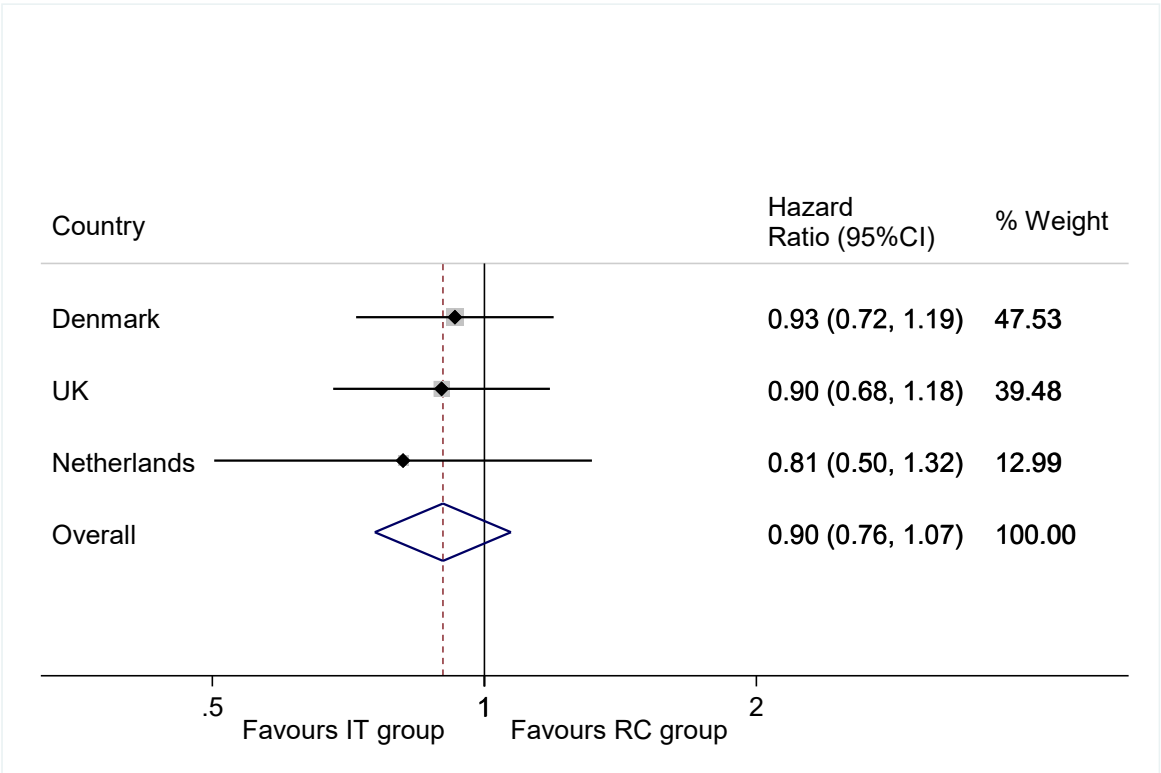

Country
Hazard Ratio (95% CI)
% Weight
Composite cardiovascular events
Denmark 0.89 (0.69, 1.16) 45.97
UK 0.86 (0.65, 1.14) 38.91
Netherlands 0.86 (0.54, 1.35) 15.13
Overall 0.87 (0.73, 1.04) 100.00
CVD death
Denmark 1.20 (0.73, 1.99) 47.19
UK 0.76 (0.44, 1.30) 40.60
Netherlands 0.98 (0.37, 2.63) 12.22
Overall 0.97 (0.69, 1.37) 100.00
MI
Denmark 0.57 (0.35, 0.94) 64.32
UK 1.74 (0.73, 4.16) 21.27
Netherlands 0.56 (0.19, 1.60) 14.41
Overall 0.72 (0.48, 1.08) 100.00
Stroke
Denmark 0.78 (0.37, 1.64) 35.35
UK 0.82 (0.44, 1.53) 51.89
Netherlands 0.44 (0.13, 1.53) 12.76
Overall 0.74 (0.48, 1.16) 100.00
Revascularisation
Denmark 0.96 (0.65, 1.41) 59.88
UK 0.60 (0.34, 1.05) 27.97
Netherlands 1.26 (0.54, 2.98) 12.16
Overall 0.87 (0.64, 1.17) 100.00
.1 .2 .5 1 2
Favours IT group
Favours RC group

Figure 4: Cumulative incidence and relative risk of all-cause mortality
(A) Cumulative incidence of mortality curves in the routine care and intensive treatment groups. (B) Hazard ratios of all-cause mortality, by country and overall, in the intensive treatment group compared with the routine care group. The size of each shaded box is inversely proportional to the country weight; the horizontal lines through each country's estimate are 95% CIs.

A


Routine Care
Intensive Treatment
Incidence (%)
20
18
16
14
12
10
8
6
4
2
0
HR 0.90 (95%CI 0.76-1.07)
0 1 2 3 4 5 6 7 8 9 10 11 12
Duration of follow-up (years)
Number at risk
Routine Care 1379 1352 1326 1278 1207 888 293
Intensive Treatment 1678 1655 1604 1568 1515 1102 355

B


Country
Hazard Ratio (95%CI)
% Weight
Denmark
0.93 (0.72, 1.19)
47.53
UK
0.90 (0.68, 1.18)
39.48
Netherlands
0.81 (0.50, 1.32)
12.99
Overall
0.90 (0.76, 1.07)
100.00
.5
1
2
Favours IT group
Favours RC group

Research in context

Evidence before this study

We searched PubMed for studies published between inception and June 2018 assessing the effect on cardiovascular disease and mortality of multifactorial interventions in patients with type 2 diabetes using the search terms “multifactorial intervention”, “cardiovascular disease”, “mortality” and “diabetes”. We placed no restriction on study quality. Risk of cardiovascular events and mortality was halved by intensive multifactorial treatment in the Steno-2 trial among 160 patients at high cardiovascular risk with longstanding diabetes and microalbuminuria. Similarly, in the J-DOIT3 trial which included 2542 patients who had been living with diabetes for 8.5 years, the risk of stroke was halved by intensive multifactorial treatment. However, apart from ADDITION, we did not identify any studies evaluating the impact of multifactorial treatment early in the course of the disease.

Added value of this study

We have shown that people with screen-detected diabetes have high levels of potentially modifiable cardiovascular risk factors and that achieving good control of these risk factors, including glycaemia, for ten years following diagnosis is both feasible in primary care and safe. Between-group differences in treatment in ADDITION were smaller than observed in the STENO-2 and J-DOIT3 trials and restricted to the first five years after diagnosis. Nevertheless, they were associated with a lower risk of cardiovascular events over 10 years among patients aged 60 or more years, suggesting a possible legacy effect of intensive treatment of risk factors early in the course of the disease.

Implication of all the available evidence

In the context of individualised treatment in primary care, patients and practitioners should be reassured that sustained reductions in glycaemia and related cardiovascular risk factors for ten years following detection by screening are achievable and safe. While there remains uncertainty about the cost-effectiveness of population-based screening, people with type 2 diabetes do appear to benefit from earlier detection and initiation of treatment of multiple risk factors.

Supplementary material

Table 1: Number and % of missing values at 10 years (excluding deaths from numerator and denominator) overall and by centre

	OVERALL						Denmark						Cambridge						Leicester						Netherlands					
	RC			IT			RC			IT			RC			IT			RC			IT			RC			IT		
	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n
Weight (kg)	1160	33.3	386	1432	30.6	438	514	40.9	210	764	42.8	327	344	11.9	41	385	6.8	26	93	93.5	87	59	89.8	53	209	23.0	48	224	14.3	32
HbA1c (mmol/mol)	1160	19.4	225	1432	20.5	293	514	24.5	126	764	30.8	235	344	11.3	39	385	5.5	21	93	17.2	16	59	6.8	4	209	21.1	44	224	14.7	33
Systolic blood pressure (mmHg)	1160	25.8	299	1432	25.0	358	514	26.5	136	764	33.9	259	344	10.5	36	385	4.9	19	93	92.5	86	59	91.5	54	209	19.6	41	224	11.6	26
Diastolic blood pressure (mmHg)	1160	25.8	299	1432	25.0	358	514	26.5	136	764	33.9	259	344	10.5	36	385	4.9	19	93	92.5	86	59	91.5	54	209	19.6	41	224	11.6	26
Total cholesterol (mmol/l)	1160	19.1	222	1432	21.4	306	514	24.7	127	764	31.8	243	344	10.8	37	385	6.2	24	93	20.4	19	59	8.5	5	209	18.7	39	224	15.2	34

Table 2: Participant baseline characteristics in those with/without specific data at 10 years

	HbA_{1c} at 10 years					Systolic blood pressure at 10 years					Total cholesterol at 10 years				
	Available N=2116		Missing, not dead N=518			Available N=1979		Missing, not dead N=657			Available N=2099		Missing, not dead N=528		
	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value
Age at diagnosis (years)	59.9	6.9	59.3	7.1	0.065	60.1	6.7	58.9	7.3	0.000	59.9	6.8	59.4	7.2	0.157
BMI (kg/m^2)	31.7	5.3	31.1	5.9	0.029	31.8	5.4	31.2	5.7	0.022	31.7	5.3	31.2	5.9	0.051
Weight (kg)	91.0	17.1	89.9	18.7	0.191	91.2	17.1	89.7	18.3	0.068	91.0	17.0	90.2	18.7	0.362
HbA1c (mmol/mol)	53.9	17.2	51.5	16.2	0.004	53.5	17.0	53.2	17.1	0.678	53.7	17.1	52.3	16.9	0.097
Systolic blood pressure (mmHg)	149.3	21.8	148.4	21.2	0.408	149.5	21.9	147.9	20.7	0.106	149.2	21.8	148.6	21.3	0.577
Diastolic blood pressure (mmHg)	86.5	11.2	86.7	10.3	0.750	86.3	11.2	87.5	10.5	0.021	86.5	11.2	86.8	10.6	0.617
Total cholesterol (mmol/l)	5.6	1.1	5.7	1.1	0.118	5.6	1.1	5.7	1.2	0.023	5.6	1.1	5.7	1.1	0.097
	%	n	%	n		%	n	%	n		%	n	%	n	
Women	42.3	896	45.9	238	0.151	42.7	845	43.8	288	0.617	42.5	892	45.3	239	0.258
Current smoker	24.1	503	31.9	161	0.000	24.2	470	30.8	199	0.001	24.4	505	30.2	156	0.008
History of MI	6.3	125	4.7	23	0.240	6.4	122	4.4	26	0.073	6.3	124	4.6	23	0.202
History of stroke	2.1	42	1.3	6	0.271	2.1	39	1.4	8	0.385	2.2	43	1.0	5	0.102
Any diabetes drug	0.3	7	0.8	4	0.137	0.4	7	0.6	4	0.479	0.3	7	0.8	4	0.241
Any antihypertensive drug	45.7	945	40.1	193	0.029	46.2	890	40.1	250	0.009	45.6	934	41.1	203	0.078
Any lipid-lowering drug	16.9	349	10.6	51	0.000	16.8	323	12.5	78	0.011	16.9	346	10.9	54	0.001

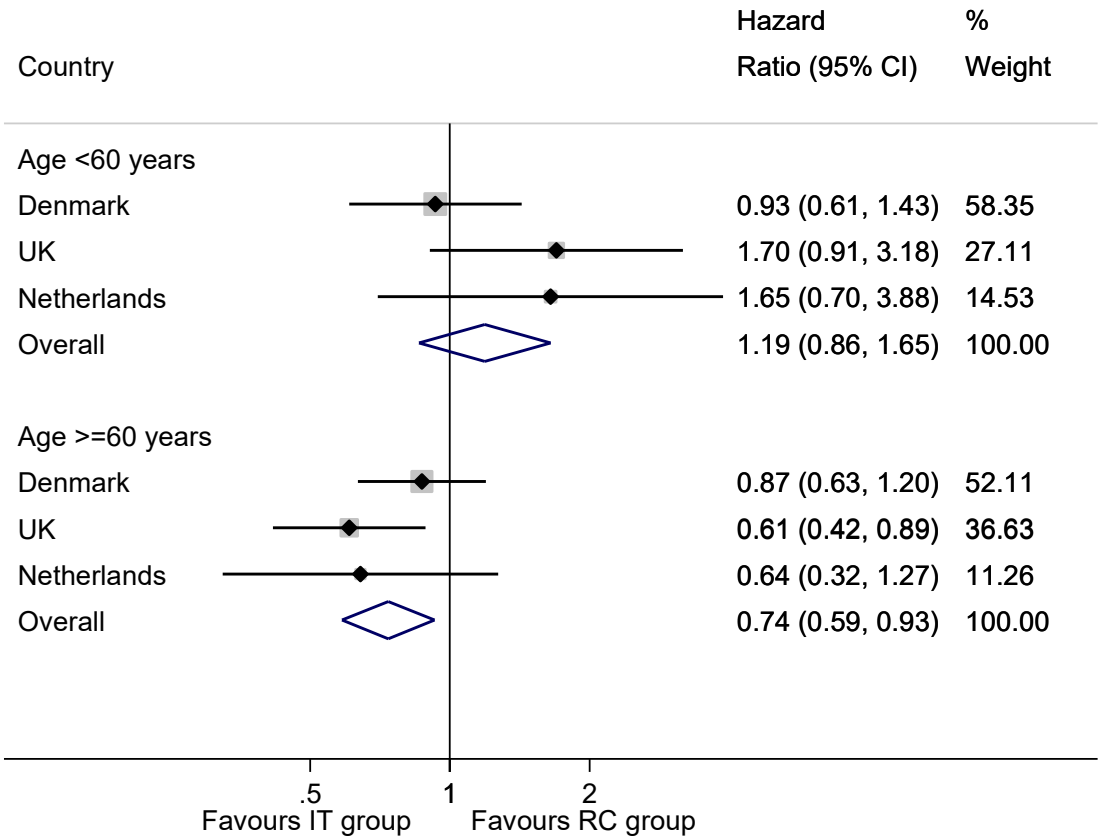
p-values are from 2-sample t-test (for continuous baseline characteristics) or Fisher exact test (for binary baseline characteristics) comparing available vs missing, not dead. The N values in the column headers reflect the number of individuals with available/missing data for the characteristic at 10 years. The summary statistics are then based on those within these groups who have available data at baseline; therefore these could be less than the N values in the column headers if some values at baseline are missing.

Table 3: Participant baseline characteristics in those with/without data at 10 years for variables with a skewed distribution

	HbA_{1c} at 10 years					**Systolic blood pressure at 10 years**					**Total cholesterol at 10 years**				
	Available N=2116		**Missing, not dead N=518**			**Available N=1979**		**Missing, not dead N=657**			**Available N=2099**		**Missing, not dead N=528**		
	Median	**IQR**	**Median**	**IQR**	**p-value**	**Median**	**IQR**	**Median**	**IQR**	**p-value**	**Median**	**IQR**	**Median**	**IQR**	**p-value**
Triglycerides (mmol/l)	1.6	1.2-2.4	1.7	1.2-2.4	0.268	1.6	1.2-2.4	1.7	1.2-2.5	0.082	1.7	1.2-2.4	1.7	1.2-2.4	0.426
Creatinine (µmol/L)	82.0	72.0-93.0	82.0	72.0-92.0	0.308	82.0	72.0-93.0	83.0	73.0-93.0	0.387	82.0	72.0-93.0	82.0	72.0-92.0	0.348
Alcohol (units/week)	4.0	1.0-12.0	6.0	1.0-13.0	0.009	4.0	0.0-12.0	6.0	2.0-13.0	0.000	4.0	1.0-12.0	5.0	1.0-12.-	0.063

p-values for continuous characteristics with a skewed distribution are from 2-sample Wilcoxon rank sum test comparing available vs missing, not dead. The N values in the column headers reflect the number of individuals with available/missing data for the characteristic at 10 years. The summary statistics are then based on those within these groups who have available data at baseline; therefore these could be less than the N values in the column headers if some values at baseline are missing.

Figure 1: Hazard ratios of the development of the composite cardiovascular endpoint (primary outcome), by country and overall, in the intensive treatment group compared with the routine care group, stratified by age (<60 years and ≥60 years). The size of each shaded box is inversely proportional to the country weight; the horizontal lines through each country's estimate are 95% CIs.



Hazard ratios are estimated within each age group and country using Cox regression with robust standard errors to allow for clustering within practice.

Table 4: Number of individuals in each age group (<60 years and ≥60 years) by country and randomised group

Denmark

Age	RC	IT	Total
<60 years	288 (46.2)	418 (45.9)	706 (46.1)
≥60 years	335 (53.8)	492 (54.1)	827 (54.0)
Total	623	910	1533

United Kingdom

Age	RC	IT	Total
<60 years	236 (46.0)	200 (39.0)	436 (42.5)
≥60 years	277 (54.0)	313 (61.0)	590 (57.5)
Total	513	513	1026

Netherlands

Age	RC	IT	Total
<60 years	117 (48.2)	123 (48.2)	240 (48.2)
≥60 years	126 (51.9)	132 (51.8)	258 (51.8)
Total	243	255	498

Table 5: Cardiovascular events by age group (<60 years and ≥60 years), country and randomised group

AGE<60	**DENMARK**				**UK**				**NETHERLANDS**			
	Routine Care (RC)		**Intensive Treatment (IT)**		**Routine Care (RC)**		**Intensive Treatment (IT)**		**Routine Care (RC)**		**Intensive Treatment (IT)**	
	N=288		**N=418**		**N=236**		**N=200**		**N=117**		**N=123**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Primary endpoint												
Composite cardiovascular events*	37	12.8	50	12.0	17	7.2	24	12.0	7	6.0	13	10.6
Components of primary endpoint												
CVD death	9	3.1	13	3.1	2	0.8	4	2.0	1	0.9	2	1.6
MI	9	3.1	7	1.7	1	0.4	9	4.5	3	2.6	0	0.0
Stroke	4	1.4	5	1.2	6	2.5	6	3.0	1	0.9	1	0.8
Revascularisation	15	5.2	24	5.7	8	3.4	5	2.5	2	1.7	10	8.1
Amputation	0	0.0	1	0.2	0	0.0	0	0.0	0	0.0	0	0.0

AGE≥60	**DENMARK**				**UK**				**NETHERLANDS**			
	Routine Care (RC)		**Intensive Treatment (IT)**		**Routine Care (RC)**		**Intensive Treatment (IT)**		**Routine Care (RC)**		**Intensive Treatment (IT)**	
	N=335		**N=492**		**N=277**		**N=313**		**N=126**		**N=132**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Primary endpoint												
Composite cardiovascular events*	64	19.1	82	16.7	60	21.7	44	14.1	26	20.6	19	14.4
Components of primary endpoint												
CVD death	12	3.6	24	4.9	17	6.1	11	3.5	6	4.8	6	4.5
MI	21	6.3	18	3.7	9	3.2	9	2.9	5	4.0	5	3.8
Stroke	11	3.3	12	2.4	14	5.1	11	3.5	7	5.6	3	2.3
Revascularisation	20	6.0	25	5.1	20	7.2	12	3.8	8	6.3	4	3.0
Amputation	0	0.0	3	0.6	0	0.0	1	0.3	0	0.0	1	0.8

Data sharing statement

A data dictionary, de-identified participant data, study protocol, statistical analysis plans and consent forms will be available to bona fide researchers with publication following review and approval of a proposal by investigators via the following website: https://epi-meta.mrc-epid.cam.ac.uk/.