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Abstract

A randomised trial of the effect and cost-effectiveness of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with screen-detected type 2 diabetes: the Anglo–Danish–Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (ADDITION-Europe) study

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Background: Intensive treatment (IT) of cardiovascular risk factors can halve mortality among people with established type 2 diabetes but the effects of treatment earlier in the disease trajectory are uncertain.

Objective: To quantify the cost-effectiveness of intensive multifactorial treatment of screen-detected diabetes.

Design: Pragmatic, multicentre, cluster-randomised, parallel-group trial.

Setting: Three hundred and forty-three general practices in Denmark, the Netherlands, and Cambridge and Leicester, UK.

Participants: Individuals aged 40–69 years with screen-detected diabetes.

Interventions: Screening plus routine care (RC) according to national guidelines or IT comprising screening and promotion of target-driven intensive management (medication and promotion of healthy lifestyles) of hyperglycaemia, blood pressure and cholesterol.

Main outcome measures: The primary end point was a composite of first cardiovascular event (cardiovascular mortality/morbidity, revascularisation and non-traumatic amputation) during a mean [standard deviation (SD)] follow-up of 5.3 (1.6) years. Secondary end points were (1) all-cause mortality; (2) microvascular outcomes (kidney function, retinopathy and peripheral neuropathy); and (3) patient-reported outcomes (health status, well-being, quality of life, treatment satisfaction). Economic analyses estimated mean costs (UK 2009/10 prices) and quality-adjusted life-years from an NHS perspective. We extrapolated data to 30 years using the UK Prospective Diabetes Study outcomes model [version 1.3; © Isis Innovation Ltd 2010; see www.dtu.ox.ac.uk/outcomesmodel (accessed 27 January 2016)].

Results: We included 3055 (RC, $n = 1377$; IT, $n = 1678$) of the 3057 recruited patients [mean (SD) age 60.3 (6.9) years] in intention-to-treat analyses. Prescription of glucose-lowering, antihypertensive and lipid-lowering medication increased in both groups, more so in the IT group than in the RC group. There were clinically important improvements in cardiovascular risk factors in both study groups. Modest but statistically significant differences between groups in reduction in glycated haemoglobin (HbA_{1c}) levels, blood pressure and cholesterol favoured the IT group. The incidence of first cardiovascular event [IT 7.2%, 13.5 per 1000 person-years; RC 8.5%, 15.9 per 1000 person-years; hazard ratio 0.83, 95% confidence interval (CI) 0.65 to 1.05] and all-cause mortality (IT 6.2%, 11.6 per 1000 person-years; RC 6.7%, 12.5 per 1000 person-years; hazard ratio 0.91, 95% CI 0.69 to 1.21) did not differ between groups. At 5 years, albuminuria was present in 22.7% and 24.4% of participants in the IT and RC groups, respectively [odds ratio (OR) 0.87, 95% CI 0.72 to 1.07), retinopathy in 10.2% and 12.1%, respectively (OR 0.84, 95% CI 0.64 to 1.10), and neuropathy in 4.9% and 5.9% (OR 0.95, 95% CI 0.68 to 1.34), respectively. The estimated glomerular filtration rate increased between baseline and follow-up in both groups (IT 4.31 ml/minute; RC 6.44 ml/minute). Health status, well-being, diabetes-specific quality of life and treatment satisfaction did not differ between the groups. The intervention cost £981 per patient and was not cost-effective at costs ≥ £631 per patient.

Conclusions: Compared with RC, IT was associated with modest increases in prescribed treatment, reduced levels of risk factors and non-significant reductions in cardiovascular events, microvascular complications and death over 5 years. IT did not adversely affect patient-reported outcomes. IT was not cost-effective but might be if delivered at a reduced cost. The lower than expected event rate, heterogeneity of intervention delivery between centres and improvements in general practice diabetes care limited the achievable differences in treatment between groups. Further follow-up to assess the legacy effects of early IT is warranted.

Trial registration: ClinicalTrials.gov NCT00237549.

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Contents

List of tables

List of figures

List of abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	angiotensin-converting enzyme
ACR	albumin–creatinine ratio
ADDITION-Europe	Anglo–Danish–Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care, a trial conducted in four centres: Denmark, the Netherlands, and Cambridge and Leicester (UK)
ADDQoL	Audit of Diabetes-Dependent Quality of Life
AF	atrial fibrillation
AIC	Akaike information criterion
ARB	angiotensin receptor blocker
aROC	area under the receiver operating characteristic
BIC	Bayesian information criterion
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CV	coefficient of variation
CVD	cardiovascular disease
DESMOND	Diabetes Education and Self-Management for Ongoing and Newly Diagnosed
DTSQ	Diabetes Treatment Satisfaction Questionnaire
eGFR	estimated glomerular filtration rate
EQ-5D	European Quality of Life-5 Dimensions
EQ-VAS	European Quality of Life visual analogue scale
ETDRS	Early Treatment Diabetic Retinopathy Study
GP	general practitioner
HbA_{1c}	glycated haemoglobin
HDL	high-density lipoprotein
HPS	Heart Protection Study
ICD-10	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Edition
ICER	incremental cost-effectiveness ratio
IGT	impaired glucose tolerance
IT	intensive treatment
ITT	intention to treat
LDL	low-density lipoprotein
MI	myocardial infarction
NIHR	National Institute for Health Research
OR	odds ratio
PROM	patient-reported outcome measure
PVD	peripheral vascular disease
QALY	quality-adjusted life-year
R&D	Research and Development
RC	routine care
SD	standard deviation
SE	standard error
SF-36	Short Form questionnaire-36 items
UKPDS	UK Prospective Diabetes Study
UKPDS-OM	UK Prospective Diabetes Study outcomes model
W-BQ12	12-item short form of the Well-Being Questionnaire
WHO	World Health Organization

Plain English summary

Diabetes is a common chronic condition associated with an increased risk of heart attack, stroke, amputation, eye disease and kidney damage. Many people have symptoms or a complication when diagnosed with diabetes; however, the true onset of the disease occurs several years earlier. Although it seems logical to propose that earlier detection would be beneficial, this has not been clearly established. We aimed to discover whether or not intensive treatment of people who have their diabetes detected early using preventative medication and lifestyle advice leads to health benefits at 5 years and in the longer term.

A total of 343 general practices in England, Denmark and the Netherlands took part. Following invitation to a screening programme, 3057 people were diagnosed with diabetes. General practices were allocated by chance to deliver either intensive treatment (a combination of medication and advice on lifestyle changes, e.g. diet and physical activity) or standard care according to national guidelines. After 5 years we re-examined participants to see whether or not intensive treatment reduced the risk of diabetes-related complications such as heart attack and stroke.

After 5 years, people receiving intensive treatment had slightly lower cholesterol levels, blood pressure and blood glucose levels than those receiving routine care. However, we cannot be sure that the small reductions in the number of heart attacks, strokes and premature deaths and in the level of visual impairment and kidney damage between the groups were not due to chance. Participants in both groups reported similar levels of well-being and quality of life and were equally satisfied with the treatment that they received. Intensive treatment is likely to be cost-effective only if it can be delivered at a reduced cost.

Scientific summary

Background

Type 2 diabetes represents a major global public health challenge. The UK NHS spends £7.7B per year on the complications of diabetes, mainly attributable to macrovascular disease. Intensive treatment (IT) of multiple cardiovascular risk factors can halve the rates of cardiovascular disease (CVD) and mortality among people with established type 2 diabetes. The effect of intensive multifactorial treatment earlier in the course of the disease is unknown. Resolving this uncertainty is important in assessing the costs and benefits of screening for diabetes.

Objectives

We aimed to examine the effectiveness of intensive multifactorial treatment among patients with type 2 diabetes detected by screening for 5-year macrovascular, microvascular and patient-reported outcomes. We also aimed to estimate the short- and long-term cost-effectiveness of IT compared with routine care (RC) in terms of mean costs and quality-adjusted life-years (QALYs) accrued.

Methods

We undertook a pragmatic, multicentre, cluster-randomised, parallel-group trial with a concurrent economic evaluation of intensive multifactorial treatment among individuals with screen-detected diabetes. A total of 343 general practices in Denmark, the Netherlands, and Cambridge and Leicester, UK, were independently randomised to screening plus RC of diabetes according to national guidelines or screening and promotion of target-driven IT of multiple risk factors. We undertook population-based stepwise screening among people aged 40–69 years (50–69 years in the Netherlands) without known diabetes between April 2001 and December 2006. Individuals were diagnosed with diabetes according to 1999 World Health Organization criteria. General practitioners (GPs) assessed patients against exclusion criteria: having an illness with a life expectancy of < 12 months; being housebound; being pregnant or lactating; or having psychological or psychiatric problems that might invalidate informed consent.

In IT practices, GPs, practice nurses and participants were educated in target-driven management (using medication and promotion of a healthy lifestyle) of hyperglycaemia, blood pressure and cholesterol. The intervention delivered was practice based, except in Leicester, where patients also had access to individualised community clinics every 2 months. Treatment targets and algorithms were based on trial data demonstrating the benefits of IT of CVD risk factors among those with type 2 diabetes. Practitioners were advised to treat to the following targets: glycated haemoglobin (HbA_{1c}) of < 53 mmol/l (7.0%) if $HbA_{1c} > 6.5\%$; blood pressure of $\leq 135/85$ mmHg if $\geq 120/80$ mmHg; cholesterol of < 5 mmol/l without ischaemic heart disease or < 4.5 mmol/l with ischaemic heart disease; and prescription of aspirin to those treated with antihypertensive medication. The treatment algorithm included a recommendation to prescribe a statin to all patients with a cholesterol level of ≥ 3.5 mmol/l following results from the Heart Protection Study. Individuals in the RC group received the standard pattern of diabetes care according to current recommendations in each centre. Group allocation was concealed from those assessing and adjudicating outcomes.

The primary end point 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 during a mean [standard deviation (SD)] follow-up of 5.3 (1.6) years. In each centre participants' medical records or national registers were searched for potential end points. For each possible end point, packs containing relevant clinical information were prepared and sent to two members of the expert committees, who were unaware of group allocation, for independent adjudication according to an agreed protocol using standardised case report forms.

Secondary end points were (1) all-cause mortality; (2) microvascular outcomes, including kidney function [microalbuminuria, macroalbuminuria and estimated glomerular filtration rate (eGFR)], retinopathy (retinal photos) and peripheral neuropathy (questionnaire data) at 5 years; and (3) patient-reported outcomes, including health status (European Quality of Life-5 Dimensions) at baseline and 5 years and health status [Short Form questionnaire-36 items (SF-36), European Quality of Life visual analogue scale (EQ-VAS)], well-being (12-item short form of the Well-Being Questionnaire), diabetes-specific quality of life (Audit of Diabetes-Dependent Quality of Life) and satisfaction with diabetes treatment (Diabetes Treatment Satisfaction Questionnaire) at 5 years.

An individually randomised trial would have required a total of 2700 individuals (1350 per group) to detect a 30% reduction in cumulative risk of the primary end point at a 5% significance level and with 90% power, allowing for 10% loss to follow-up and assuming an event rate in the RC group of 3% per year [based on results from the UK Prospective Diabetes Study (UKPDS)]. We expected a minimal effect of clustering within general practices, with an estimated intracluster correlation coefficient of 0.01; assuming an average of 10 participants per general practice, the design effect was 1.09 and thus we inflated the estimated sample size for this cluster trial to 3000.

An economic evaluation of the intervention in the UK was undertaken from a UK payer (NHS) perspective using trial data to estimate the mean costs and QALYs gained per patient for the IT and RC interventions. We report short-term (within-trial) and long-term (10–30 years based on decision modelling) incremental cost-effectiveness ratios (ICERs) and associated decision uncertainty.

Results

We recruited 3057 (RC, $n = 1379$; IT, $n = 1678$) participants between 2001 and 2006. Two participants from the RC group withdrew consent in the first few months of the study and hence data were included for 1377 RC participants. Prescription of glucose-lowering, antihypertensive and lipid-lowering medication increased in both groups, with more patients in the IT group than in the RC group prescribed cardioprotective medication at follow-up. Clinically important improvements in cardiovascular risk factors and modelled cardiovascular risk were observed in both study groups between baseline and 5 years' follow-up. Modest differences between groups in the reduction in levels of HbA_{1c}, blood pressure, cholesterol and modelled cardiovascular risk favoured the IT group. In the whole trial cohort, 10-year modelled CVD risk was 27.3% (SD 13.9%) at baseline and 21.3% (SD 13.8%) at 5 years' follow-up. The incidence of first cardiovascular event [IT 7.2%, 13.5 per 1000 person-years; RC 8.5%, 15.9 per 1000 person-years; hazard ratio 0.83, 95% confidence interval (CI) 0.65 to 1.05] and all-cause mortality (IT 6.2%, 11.6 per 1000 person-years; RC 6.7%, 12.5 per 1000 person-years; hazard ratio 0.91, 95% CI 0.69 to 1.21) did not differ significantly between groups.

Five years after diagnosis any kind of albuminuria was present in 22.7% of participants in the IT group and 24.4% of participants in the RC group [odds ratio (OR) 0.88, 95% CI 0.72 to 1.07). Retinopathy was present in 10.2% of the IT group and 12.1% of the RC group (OR 0.84, 95% CI 0.64 to 1.10); eight patients had severe retinopathy ($n = 1$ IT; $n = 7$ RC). Neuropathy was present in 4.9% and 5.9% of the IT and RC groups, respectively (OR 0.95, 95% CI 0.68 to 1.34). The eGFR increased between baseline and follow-up in both groups (IT 4.31 ml/minute; RC 6.44 ml/minute).

Health status, well-being, diabetes-specific quality of life and treatment satisfaction did not differ significantly between the IT group and the RC group after 5 years' follow-up. There was some heterogeneity between centres [I^2 between 13% (SF-36 physical functioning) and 73% (EQ-VAS)].

The incremental cost to the NHS of the IT intervention was £285, £935, £1190 and £1745 over a 1-, 5-, 10- and 30-year time horizon, respectively (discounted at 3.5%). Incremental QALYs were 0.0000, –0.0040, 0.0140 and 0.0465 over the same time horizons. Point estimate ICERs suggested that the intervention was not cost-effective although the ratio improved over time: the ICER over 10 years was £82,250, falling to £37,500 over 30 years. The ICER fell below £30,000 only when the intervention cost was below £631 per patient; we estimated the cost of the intervention at £981.

Conclusions

Compared with RC, IT was associated with modest increases in prescribed treatment and reduced levels of cardiovascular risk factors, but reductions in the incidence of cardiovascular events, microvascular complications and death over 5 years were not statistically significant. Despite increasing age and diabetes duration there was a decline in modelled CVD risk in the whole trial cohort in the 5 years following diagnosis. The IT intervention did not adversely affect patient-reported outcomes. Given conventional thresholds for cost-effectiveness, the IT intervention was not cost-effective compared with RC for screen-detected diabetes patients in the UK. The intervention may be cost-effective if it can be delivered at a reduced cost.

The lower than expected CVD event rate means that the 5-year duration of follow-up may be insufficient to detect a potential difference between groups. The apparent divergence of event rates from 4 years suggests that further follow-up of this trial is justified to test whether or not IT reduces cardiovascular risk in the long term as seen in the UKPDS.

Intensive treatment by lifestyle intervention and prescription of cardioprotective medication led to clinically important reductions in CVD risk factors and modelled CVD risk in the trial cohort. Furthermore, IT was not associated with adverse patient-reported outcomes. As such, health practitioners might consider treating multiple cardiovascular risk factors early and intensively in the diabetes disease trajectory, when the rate of CVD risk progression may be slowed.

Trial registration

This trial is registered as NCT00237549.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction

Burden of diabetes

Type 2 diabetes is a common chronic disease, which affected 382 million people worldwide in 2013.[1] It is estimated that there will be 592 million individuals living with diabetes by 2035. Diabetes is a major cause of premature death. Global mortality attributable to known diabetes in adults aged 20–79 years in the year 2013 is estimated at 5.1 million deaths, which is 8.4% of total world mortality.[1] Diabetes is ranked among the leading causes of blindness, renal failure and lower limb amputation in virtually every developed society. People with diabetes have an increased risk of cardiovascular, cerebrovascular and peripheral vascular disease (PVD) and have a reduced risk of survival after suffering from silent ischaemia and myocardial infarction (MI) (compared with those without diabetes). Around 65% of individuals with type 2 diabetes die of cardiovascular disease (CVD). Diabetes is a very expensive chronic condition. It imposes a huge burden on national economies and health-care systems, as well as costs for individuals with diabetes and their families. Expenditure related to diabetes in 2010 was estimated to be approximately 10% of total health-care budgets in the UK and is projected to rise to 17% in 2035.[2]

Preventing diabetes

The high social and economic cost of diabetes makes a compelling case for prevention of the disease. But where should governments and health services focus their attention? Most research has been completed on the tertiary prevention of diabetes, that is, the treatment of people with established disease. There have been significant improvements in the treatment of individuals with diabetes[3] and there is good evidence that the development of long-term complications of diabetes can be significantly decreased by intensive treatment (IT) (see *Screening and early treatment for early diabetes*). We also have long-term evidence that diabetes can be prevented among those at high risk of developing the disease (primary prevention).[4] Intensive lifestyle and pharmacological interventions reduce the rate of progression of type 2 diabetes among people with impaired glucose tolerance (IGT). In a meta-analysis of published diabetes prevention trials, Gillies *et al.*[4] reported pooled hazard ratios of 0.51 [95% confidence interval (CI) 0.44 to 0.60] for lifestyle interventions compared with standard advice and 0.70 (95% CI 0.62 to 0.79) for oral diabetes drugs compared with the control. Longer-term follow-up of these trials provides evidence of the sustained prevention of diabetes.[5–7] Delaying or preventing diabetes in this way also reduces the risk of microvascular complications and reduces cardiovascular and all-cause mortality.[8,9]

Secondary prevention strategies (i.e. earlier detection, e.g. by screening) have received little attention in the past. The current evidence base for the recommendation of screening and early treatment for diabetes is limited.

Screening and early treatment for diabetes

Type 2 diabetes meets many of the formal criteria for a disease for which screening is justified.[10] The condition is an important health problem associated with a substantial burden of suffering and health service cost. The natural history of the disease is well characterised.[11,12] The condition is frequently asymptomatic,[13] with the true onset occurring several years before diagnosis.[11,14] Although detection of the condition may be improving in some parts of the world,[15] nearly half of all people with diabetes remain undiagnosed.[1] When patients are diagnosed, many already have complications, such as CVD, chronic kidney disease and heart failure, retinopathy and neuropathy.[16–18] This suggests a potential window for earlier detection and treatment. Furthermore, there are a number of screening tests that are simple, safe and

validated and that perform reasonably well when evaluated against recommended diagnostic criteria.[19] Modelling studies suggest that a programme of screening for diabetes would reduce both all-cause and diabetes-related mortality.[20–22] However, these estimates depend on a number of key assumptions. The only published trial of screening to date did not show an effect of population-based screening on mortality over 10 years of follow-up.[23]

The National Screening Committee states that there should be an effective treatment for individuals identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.[10] A screening programme for diabetes is most likely to seek to prevent CVD, the leading cause of premature death and disability among patients with diabetes. There is good evidence that the development of long-term complications of diabetes can be significantly decreased by IT. Results from the UK Prospective Diabetes Study (UKPDS) and the Kumamato trials have demonstrated the benefits of tight glycaemic[24,25] and blood pressure control,[26] whereas several trials, including the Collaborative Atorvastatin Diabetes Study[27] and the Heart Protection Study (HPS),[28] have confirmed the benefits of lipid-lowering drugs. The Steno study is one of the few trials to compare the benefits of targeted intensive multifactorial treatment with those of routine care (RC) for risk factors for CVD in individuals with established diabetes.[29] After 13 years of follow-up, patients receiving the IT had a 59% (95% CI 0.25% to 0.67%) lower risk of a CVD event and a 46% (95% CI 0.32% to 0.89%) lower risk of all-cause mortality than those receiving RC. When we started our research in 2010, there was no trial evidence that intensive multifactorial treatment improved CVD outcomes when commenced in the lead time between detection by screening and diagnosis in routine clinical practice.

In terms of preventing microvascular complications, treatment of individual risk factors such as blood pressure and glucose level reduces the risk of microvascular complications among clinically diagnosed patients.[24,30–32] IT of multiple risk factors in the Steno study was associated with a 61% (95% CI 13% to 83%) lower risk of nephropathy, a 58% (95% CI 14% to 79%) lower risk of retinopathy and a 63% (95% CI 21% to 82%) lower risk of autonomic neuropathy.[33] However, the effects on microvascular outcomes of starting multifactorial treatment earlier in the course of the disease are uncertain. Data from trials of IT of hyperglycaemia suggest that beneficial effects can be seen for microvascular outcomes in the short term, whereas cardiovascular benefits are evident only with longer follow-up. However, there remains some uncertainty about the merits of tight glycaemic control.[34,35]

Little research has been completed on the potential effects of intensive multifactorial treatment on patient-reported outcome measures (PROMs) early in the course of the disease. For largely asymptomatic patients, such a treatment regime might be burdensome. Health practitioners might be reluctant to offer IT including the prescription of several medications and recommendations to change several lifestyle behaviours; this might lead to psychosocial stress and reduced satisfaction with treatment.[36] When assessing the effectiveness of early treatment, PROMs are a valuable complement to hard outcomes such as mortality and cardiovascular events. They are also increasingly being used as key performance indicators in chronic illness. PROMs reflect a patient's assessment of his or her own health and well-being and involve questions about physical and social functioning and mental well-being. They may include both generic and disease-specific questions. The reliability of PROMs is similar to that of clinical measures such as blood pressure or blood glucose monitoring.[37] The use of PROMs has been recommended in the evaluation of health-care services and in regulatory decision-making.[38] Their use provides an opportunity to help drive changes in how health care is organised and delivered.[37]

Evidence from the UKPDS study suggests that IT of blood pressure and blood glucose among newly diagnosed type 2 diabetes patients is not associated with adverse effects on quality of life.[39] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial of intensive glycaemic control in US patients with long-standing type 2 diabetes was associated with modest improvements in satisfaction with diabetes treatment and did not lead to an increase in health-related quality of life.[40] The effects of intensive multifactorial treatment on PROMs among people with type 2 diabetes detected by screening are not known.

In addition to a lack of information on the effects of intensive multifactorial intervention on macrovascular, microvascular and PROMs early in the diabetes disease trajectory, little is known about the cost-effectiveness of such treatment. It is expected that increasing numbers of new patients will be identified as governments introduce national assessment programmes, such as the NHS Health Checks programme.[41] The balance of benefits, harms and costs of IT may not be the same for screen-detected individuals as for those with clinically diagnosed and long-standing diabetes.

The ADDITION-Europe trial

In 2001 a group of colleagues from Cambridge in the UK, Utrecht in the Netherlands and Copenhagen and Aarhus in Denmark came together to answer some of the outstanding questions about screening and early treatment for diabetes. Colleagues in Leicester were later invited to join the collaboration. The main aim of the Anglo–Danish–Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (ADDITION-Europe) was to investigate whether or not intensive multifactorial treatment improves outcomes compared with RC when commenced in the lead time between detection by screening and clinical diagnosis. This was a two-phase study consisting of a screening phase and a pragmatic, cluster-randomised, parallel-group trial. Results from the screening phase of the study have previously been reported.[42–46] This report concerns the results from the 5-year follow-up of the trial, which was funded in the UK by the National Institute for Health Research (NIHR) Health Technology Assessment programme.

Aims

To examine the effect of intensive multifactorial treatment compared with RC on (1) cardiovascular outcomes, (2) microvascular outcomes and (3) self-reported health status, well-being, diabetes-specific quality of life and treatment satisfaction after 5 years' follow-up. A further aim was to assess the cost-effectiveness of intensive multifactorial treatment compared with RC in the UK setting.

Chapter 2 Trial design and methods

Design

The ADDITION-Europe trial was set up to evaluate the effectiveness of intensive multifactorial treatment with regard to macrovascular, microvascular and PROMs among individuals with screen-detected diabetes. It consisted of two phases – a screening phase and a pragmatic cluster-randomised parallel-group trial – in four centres (Denmark, Cambridge, UK, the Netherlands and Leicester, UK). This report concerns the results of the treatment trial (see *Chapter 3*). The main trial was supplemented with an economic evaluation to consider the cost-effectiveness of the intervention in the UK (see *Chapter 4*). A description of the trial protocol has already been published.[47]

Ethical approval and research governance

The study was approved by local ethics committees in each centre and participants provided informed consent.

Randomisation, concealment and blinding

Of 1312 general practices invited to participate, 379 (29%) agreed and 343 clusters (26%) were randomised. Practices were randomly assigned by statisticians independent of the measurement teams to screening plus routine diabetes care or screening followed by intensive multifactorial treatment in a 1 : 1 ratio. Randomisation included stratification by county and number of full-time family physicians in Denmark and by single-handed or group status in the Netherlands. In Cambridge, randomisation included minimisation for the local district hospital and the number of patients per practice with diabetes. In Leicester, randomisation included minimisation for practice demographics, deprivation status and prevalence of type 2 diabetes.

Population-based stepwise screening took place between April 2001 and December 2006 among people aged 40–69 years (50–69 years in the Netherlands) without known diabetes, as previously described.[43,48–50] Screening programmes, which varied by centre (*Table 1*), consisted of a risk score[51] (Cambridge) or self-completion questionnaires (Denmark[52] and the Netherlands[54]) followed by capillary glucose testing or an invitation to attend an oral glucose tolerance test without prior risk assessment (Leicester). Individuals were diagnosed with diabetes according to the World Health Organization (WHO)'s 1999 criteria,[56] including the requirement for confirmatory tests on separate occasions.

TABLE 1 Characteristics of the ADDITION-Europe screening programmes, intervention delivery and outcome ascertainment by study centre

Centre	Screening programme	Intervention delivery	Outcome ascertainment
Cambridge, UK	• Electronic medical records of patients aged 40–69 years were searched for routinely collected information to allow the calculation of the Cambridge diabetes risk score[51] • Individuals with a score of ≥ 0.17 were invited by their GP to attend a stepwise screening programme including capillary RBG, FBG and HbA_{1c} tests	• Practice-based educational meetings with GPs 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 were provided with educational materials for patients • Small financial incentives for GPs	• Participants were tagged for mortality with the Office for National Statistics • Sensitive electronic searches of general practice records were undertaken between March 2009 and February 2010. If a possible event was highlighted copies were made of medical records. Additional information was obtained from hospital medical records and coroners' offices as required
Denmark	(a) Patients aged 40–69 years were sent a letter including questions from the Danish Diabetes Risk Score Questionnaire[52] and advising those with a score of ≥ 5 to arrange an appointment with their GP to enter a stepwise screening programme including capillary RBG, FBG and HbA_{1c} testing (b) Patients aged 40–69 years were asked to fill in the Danish Diabetes Risk Score Questionnaire[52] when attending their GP surgery. Those at high risk entered the same stepwise screening programme	• Small group or practice-based educational meetings with GPs and nurses to discuss treatment targets, algorithms and lifestyle advice • Audit and feedback included in follow-up group meetings up to twice a year or co-ordinated by post • Practice staff were provided with educational materials for patients • Small financial incentives for GPs • Patients were sent reminders if annual measures were overdue	• The national patient register was searched on 31 December 2009 for deaths and for ICD-10 codes for cardiovascular events (I08–I77) and surgical procedures concerning amputations and revascularisations. For possible events, information was obtained from hospital medical records and coroners' offices as required
Leicester, UK	• Patients aged 40–69 years were invited directly for an OGTT in a local testing facility	• Patients were referred to the DESMOND structured education programme[53] • Patients were offered 2-monthly appointments with a diabetes nurse or physician in a community peripatetic clinic for 1 year and 4-monthly appointments thereafter • Clinic staff were prompted to contact patients defaulting from appointments • Small financial incentives for GPs	• Participants were tagged for mortality with the Office for National Statistics • Sensitive electronic searches of general practice records were undertaken between March 2009 and February 2010. If a possible event was highlighted copies were made of medical records. Additional information was obtained from hospital medical records and coroners' offices as required

TABLE 1 Characteristics of the ADDITION-Europe screening programmes, intervention delivery and outcome ascertainment by study centre (*continued*)

Centre	Screening programme	Intervention delivery	Outcome ascertainment
The Netherlands	(a) Patients aged 50–69 years were sent a letter from their GP including the Hoorn study Symptom Risk Questionnaire[54] and advising those with a score of ≥ 4 to enter a stepwise screening programme including capillary RBG and FBG testing in a local testing facility (b) Patients aged 50–69 years were sent a letter from their GP including the Hoorn study Symptom Risk Questionnaire[54] and advising those with a score of ≥ 6 to enter a stepwise screening programme including capillary FBG testing in a local testing facility	• Small group or practice-based educational meetings with GPs and nurses to discuss treatment targets, algorithms and lifestyle advice • Audit and feedback included in follow-up meetings up to twice a year or co-ordinated by post • Patients were seen by diabetes nurses who were authorised to prescribe medication and adjust doses under GP supervision • Patients were sent reminders if annual measures were overdue • Small financial incentives for GPs	• General practice records were hand-searched and end point and vital status information was extracted onto standardised forms. For patients who had moved practice, end-point data were obtained by telephone interview with their current GP

DESMOND, Diabetes Education and Self-Management for Ongoing and Newly Diagnosed; FBG, fasting blood glucose; GP, general practitioner; HbA_{1c}, glycated haemoglobin; ICD-10, *International Statistical Classification of Diseases and Related Health Problems*, Tenth Edition; OGTT, oral glucose tolerance test; RBG, random blood glucose.
Source: reproduced open access from Griffin *et al.*[55]

Inclusion and exclusion criteria

All patients newly diagnosed with type 2 diabetes were eligible to participate in the treatment study unless their family physician indicated that they had contraindications to the proposed study medication, an illness with a life expectancy of < 12 months or psychological or psychiatric problems that were likely to invalidate informed consent. Overall, 3057 eligible participants with screen-detected diabetes agreed to take part (Denmark, $n = 1533$; Cambridge, $n = 867$; the Netherlands, $n = 498$; Leicester, $n = 159$).

Intervention

The characteristics of the interventions to promote IT in each centre have been described previously[47–49,57] and are summarised in *Table 1*. We aimed to educate and support general practitioners (GPs) and practice nurses in target-driven management (using medication and promotion of a healthy lifestyle) of hyperglycaemia, blood pressure and cholesterol, based on the stepwise regimen used in the Steno-2 study.[29] Treatment targets and algorithms (*Table 2*) based on trial data in people with type 2 diabetes[24,26,29,58,59] were the same for the IT groups in all centres. GPs were advised to consider prescribing an angiotensin-converting enzyme (ACE) inhibitor for patients with blood pressure ≥ 120/80 mmHg or a previous cardiovascular event[58] and 75 mg of aspirin daily to patients without specific contraindications. Although treatment targets were specified and classes of medication recommended, prescribing decisions, including choice of individual drugs, were made by practitioners and patients. Following publication of the results of the HPS,[28] the treatment algorithm included a recommendation to prescribe a statin to all patients with a cholesterol level of ≥ 3.5 mmol/l.

TABLE 2 Treatment recommendations and targets in the IT group of the ADDITION-Europe trial

	Treatment target	Treatment threshold	Baseline	Review 1	Review 2	Review 3
HbA_{1c}	< 7.0%	> 6.5%	Diet	If HbA_{1c} > 6.5%, prescribe metformin	If HbA_{1c} > 6.5%, increase metformin dose/add a second medication (PGR or SU or TZD)	If HbA_{1c} > 6.5%, add a third medication (PGR or SU or TZD) and consider adding insulin
BP	≤ 135/85 mmHg[a]	≥ 120/80 mmHg	If BP > 120/80 mmHg or CVD+, prescribe an ACE inhibitor titrated to the maximum dose	If BP > 135/85 mmHg, add a thiazide diuretic or calcium antagonist	If BP > 135/85 mmHg, add a thiazide diuretic or calcium antagonist	If BP > 135/85 mmHg, add a beta-blocker or alpha-blocker
Cholesterol IHD–	< 5.0 mmol/l	≥ 3.5 mmol/l	If TC ≥ 3.5 mmol/l, prescribe a statin	If TC > 5.0 mmol/l, increase statin dose up to the maximum	If TC > 5.0 mmol/l, increase statin dose up to the maximum	Consider adding a fibrate if TC > 5.0 mmol/l
Cholesterol IHD+	< 4.5 mmol/l	≥ 3.5 mmol/l	If TC ≥ 3.5 mmol/, prescribe a statin	If TC > 4.5 mmol/l, increase statin dose up to the maximum	If TC > 4.5 mmol/l, increase statin dose up to the maximum	Consider adding a fibrate if TC > 4.5 mmol/l
Aspirin	75/80 mg of aspirin daily to all patients treated with antihypertensive medication and without specific contraindications					

BP, blood pressure; CVD+, previous cardiovascular event or presence of cardiovascular risk factor other than diabetes; HbA_{1c}, glycated haemoglobin; IHD–, no history of ischaemic heart disease; IHD+, history of ischaemic heart disease; PGR, prandial glucose regulator; SU, sulphonylurea; TC, total cholesterol; TZD, thiazolidinedione.
a ≤ 130/80 mmHg in Leicester.
Source: reproduced open access from Griffin *et al.*[55]

Intensive treatment was promoted through the addition of several features to existing diabetes care. Small group or practice-based educational meetings were arranged with GPs and nurses to discuss the treatment targets and algorithms and lifestyle advice, including supporting evidence. Audit and feedback were included in follow-up meetings up to twice per year (the total number of practice meetings ranged from 2 to 10) or co-ordinated by post. In the Netherlands patients were seen in general practice by diabetes nurses who were authorised to prescribe medication and adjust doses under GP 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 additional funding to support the delivery of care (up to the equivalent of three 10-minute consultations with a GP and three 15-minute consultations with a nurse per patient per year for 3 years). Leicester patients were referred to the Diabetes Education and Self-Management for Ongoing and Newly Diagnosed (DESMOND) structured education programme[53] and were offered 2-monthly appointments with a diabetes nurse or physician in a community peripatetic clinic for 1 year and 4-monthly appointments thereafter. Clinic staff were prompted to contact patients defaulting from appointments.

In the RC group, GPs were provided only with the diagnostic test results. Patients with screen-detected diabetes received the standard pattern of diabetes care according to the recommendations applicable in each centre.[60–63]

Data collection

Centrally trained staff undertook health assessments at baseline and after 5 years, including biochemical and anthropometric measures, and administered questionnaires, following standard operating procedures. Staff were unaware of study group allocation. Follow-up examinations took place from September 2008 until the end of December 2009. The mean [standard deviation (SD)] follow-up period was 5.3 (1.6) years. All biochemical measures were analysed in five regional laboratories at baseline and follow-up. Standardised self-report questionnaires were used to collect information on education, employment, ethnicity, lifestyle habits (smoking status, alcohol consumption), prescribed medication and health status. Questionnaires were completed at the same health assessment visit as the anthropometric and biochemical measurements. If participants did not complete follow-up questionnaires or measurements then the most recent values were obtained from general practice records along with information on prescribed medication.

Primary end point

The primary end point was a composite of first cardiovascular event, including cardiovascular mortality, cardiovascular morbidity (non-fatal MI and non-fatal stroke), revascularisation and non-traumatic amputation. All-cause mortality and each of the individual components of the primary end point were secondary outcomes. In each centre participants' medical records or national registers were searched for potential end points by staff unaware of group allocation. For each possible end point, packs containing relevant clinical information (such as a death certificate, post-mortem report, medical records, hospital discharge summary, electrocardiographs and laboratory results) were prepared and sent to two members of the expert committees, who were unaware of group allocation, for independent adjudication according to an agreed protocol using standardised case report forms. Committee members met to reach consensus over discrepancies. The date of completion of follow-up for the primary end point was deemed to be the date of the first primary end point, the date of remeasurement at 5 years if no end point occurred or the date that the end-point search was undertaken if the participant did not experience an event or attend follow-up.

Secondary end points

Microvascular outcomes

Prespecified secondary outcomes included measures of kidney function, retinopathy and peripheral neuropathy.

Nephropathy was assessed by the urinary albumin–creatinine ratio (ACR) and the estimated glomerular filtration rate (eGFR). The urinary ACR was measured on spot urine and analysed at Aarhus Hospital (Aarhus, Denmark) and Steno Diabetes Centre (Gentofte, Denmark) using a Hitachi 912 Chemistry Analyzer (Tokyo, Japan); at Addenbrooke's Hospital (Cambridge, UK) and Leicester Royal Infirmary (Leicester, UK) using an Olympus AU400 Chemistry Analyzer (Tokyo, Japan); and at the SHL Centre for Diagnostic Support in Primary Care (Etten-Leur, the Netherlands) using a Roche Hitachi Modular P Chemistry Analyzer (Basel, Switzerland). Repeated analyses of standardised trial control samples for urine creatinine during follow-up confirmed the reliability and precision of the laboratory methods with coefficients of variation (CVs) $< 3.4\%$ in all laboratories. Analyses of trial and external quality control samples of urine albumin revealed CVs between 2.0% and 9.8% in the Etten-Leur, Leicester and Gentofte laboratories and CVs of 4.9% for low concentrations and 3.4% for high concentrations in the Addenbrooke's laboratory in Cambridge during the period of trial testing. Microalbuminuria was defined as an ACR of ≥ 2.5 mg/mmol for men and ≥ 3.5 mg/mmol for women and macroalbuminuria was defined as an ACR of ≥ 25 mg/mmol. Nephropathy was defined as the presence of either microalbuminuria or macroalbuminuria. The eGFR was calculated using data on serum creatinine, age, sex and ethnicity for each individual using the Modification of Diet in Renal Disease formula[64] at baseline and follow-up. Change between the two time points was analysed as a continuous variable. Plasma creatinine was analysed with kinetic colourimetric methods at all laboratories at baseline and follow-up except in the Netherlands where an enzymatic method was used at follow-up. Repeated analyses of standardised control samples for creatinine during follow-up the confirmed reliability and precision of the laboratory methods, with CVs between 1.3% and 6.4%.

Retinopathy was assessed using gradable digital images taken using a retinal camera (two from each eye, one with the fovea in the centre and one with the macula in the centre). In the Netherlands and Leicester all retinal images were taken as part of the follow-up examination. In Denmark 81% of the images were taken as part of the study follow-up, with the remainder being obtained from routine health service records. All retinal images in Cambridge were retrieved from routine medical records. Only images taken in the 2 years preceding the follow-up visit were included in this analysis. Information on retinal photography devices used at the four centres is available on the study website [see www.addition.au.dk/ (accessed 30 June 2014)]. Retinal images were graded by three certified graders, who were unaware of the participants' study group allocation, using a quantitative grading system and subsequently categorised according to the Early Treatment Diabetic Retinopathy Study (ETDRS) semiquantitative scale.[65] Two binary end points were then defined: (1) any retinopathy compared with no retinopathy and (2) severe or proliferative retinopathy compared with no, mild or moderate retinopathy.

Peripheral neuropathy was assessed using the self-administered Michigan Neuropathy Screening Instrument,[66] which includes 13 questions about neuropathic symptoms. Responses to the questions are summed to calculate the total score. Responses of 'yes' to items 1–3, 5, 6, 8, 9, 11, 12, 14 and 15 each score 1 point and 'no' responses on items 7 and 13 each score 1 point. Item 10 is not included in the calculation of a score for neuropathy. Participants were defined as having peripheral neuropathy if they had a score of ≥ 7. The peripheral neuropathy scores were considered missing if categorisation was not possible because of unanswered items.[67]

Patient-reported outcomes

As the participants were screen detected, no diabetes-specific measures were obtained at baseline. At follow-up, questionnaires were used to cover both generic and diabetes-specific measures.

Health status was assessed using the European Quality of Life-5 Dimensions (EQ-5D), a generic health-related quality of life questionnaire consisting of a classification system (EQ-5D profile) and a visual analogue scale [European Quality of Life visual analogue scale (EQ-VAS)]. The EQ-5D profile was completed by participants at baseline and follow-up; the EQ-VAS was completed at follow-up only. The EQ-5D profile covers five domains of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each with three levels of functioning: level 1, no problems; level 2, some problems; level 3, severe problems. This results in 243 health states, which are converted to a single index ('utility') using a population-specific algorithm. The standard UK value set gives utilities ranging from –0.594 to +1.00 (full health).[68] A value of 0 represents death; negative values imply a health state worse than death. The EQ-VAS is a graded, vertical line, anchored at 0 (worst imaginable health state) and 100 (best imaginable health state). Patients were asked to mark a point on the EQ-VAS that best reflected their actual health state.[69]

The Short Form questionnaire-36 items (SF-36)[70] generates a profile of scores on eight dimensions of health: (1) physical functioning; (2) role limitations because of physical problems; (3) social functioning; (4) bodily pain; (5) general mental health; (6) role limitations because of emotional problems; (7) vitality; and (8) general health perceptions. Two summary scales can be calculated: the physical component summary score and the mental component summary score. For all dimensions an average score can be calculated, with a range from 0 (least favourable health state) to 100 (most favourable health state). The SF-36 was completed at follow-up.

General well-being was assessed using the previously validated 12-item short form of the Well-Being Questionnaire (W-BQ12),[71] which measures different aspects of the well-being of individuals, including diabetes patients. It can be scored as three subscales: negative well-being (a higher score means more negative well-being), energy (a higher score means more energy) and positive well-being (a higher score means more positive well-being). Each subscale consists of four items with a score range of 0–12. Furthermore, a score for general well-being can be calculated;[72] this has a score range of 0–36 and a higher score indicates better well-being. The W-BQ12 was completed at follow-up.

Diabetes-specific quality of life was assessed using the previously validated Audit of Diabetes-Dependent Quality of Life (ADDQoL),[73] a measure of patients' perceived importance of diabetes and its treatment and its impact on quality of life. We used the ADDQoL 19, which includes 19 diabetes-specific items. For each item patients are asked how things would be without diabetes, with scores ranging from –3 (a great deal better) to 1 (worse), and to rate each item, with scores ranging from 3 (very important) to 0 (not at all important). A weighted rating per item can be calculated by multiplying the unweighted rating by the importance rating. The total ADDQoL score is the mean of all weighted ratings of applicable domains and ranges from –9 (maximum negative impact of diabetes) to 3 (maximum positive impact of diabetes). The ADDQoL was completed at follow-up.

Satisfaction with diabetes treatment was assessed using the previously validated Diabetes Treatment Satisfaction Questionnaire (DTSQ).[74] It consists of a six-item scale assessing treatment satisfaction and two items assessing the perceived frequency of hyperglycaemia and hypoglycaemia. The treatment satisfaction score ranges from 0 (very dissatisfied) to 36 (very satisfied). The DTSQ was completed at follow-up.

Sample size

An individually randomised trial would have required a total of 2700 individuals (1350 per group) to detect a 30% reduction in the cumulative risk of the primary end point at a 5% significance level and with 90% power, allowing for 10% loss to follow-up and assuming an event rate in the RC group of 3% per year (based on results from the UKPDS[24]). We expected a minimal effect of clustering within general practices, with an estimated intracluster correlation coefficient of 0.01; assuming an average of 10 participants per general practice, the design effect was 1.09 and so we inflated the estimated sample size for this cluster trial to 3000.

Statistical analysis

The analysis and reporting of this trial were undertaken in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines [see www.consort-statement.org/ (accessed 27 January 2016)]. Statistical analysis was undertaken in Stata 11.1 (StataCorp LP, College Station, TX, USA), SAS v9.2 (SAS Institute Inc., Cary, NC, USA) and Review Manager v5.1 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark), following a predefined analysis plan, which was finalised before preparation of the end-point data set, agreed with the Trial Steering Committee and deposited on the study website (see www.addition.au.dk/). The primary comparative analyses between the randomised groups were conducted on an intention-to-treat (ITT) basis without imputation of missing data.

Preliminary analyses

We summarised the baseline characteristics of individuals and general practices within each randomised group, by centre and overall.

Changes in mean values or percentages of other clinical and medication variables from baseline to follow-up were summarised in each randomised group and intervention effects and 95% CIs for these changes were estimated using the methods described in the primary and secondary analysis sections. We also calculated 10-year modelled CVD risk using the UKPDS model (version 3)[75] at 5 years post diagnosis. This is a diabetes-specific risk assessment tool that estimates the absolute risk of fatal or non-fatal CVD within a defined time frame. The variables include age, sex, ethnicity, smoking status, glycated haemoglobin (HbA_{1c}) level, systolic blood pressure, total to high-density lipoprotein (HDL) cholesterol ratio, atrial fibrillation (AF), previous MI or stroke, macroalbuminuria (ACR $\geq$ 30 mg/mmol), microalbuminuria (ACR $\geq$ 2.5 mg/mmol in men or $\geq$ 3.5 mg/mmol in women), duration of diagnosed diabetes and body mass index. We did not have data on AF in ADDITION-Europe participants and so all individuals were coded as zero (no AF). Centre-specific estimates of the difference in modelled CVD risk between treatment groups were combined using fixed-effects meta-analysis. Odds ratios (ORs) of meeting each of three treatment targets [HbA_{1c} < 53 mmol/l (7.0%) if HbA_{1c} > 6.5%; blood pressure $\leq$ 135/85 mmHg if $\geq$ 120/80 mm Hg; cholesterol < 5 mmol/l without ischaemic heart disease or < 4.5 mmol/l with ischaemic heart disease) comparing IT with RC were also estimated.

Primary analyses: cardiovascular outcomes

We plotted the cumulative probability of the primary end point. To assess intervention effects we used Cox regression to estimate a hazard ratio and 95% CI within each centre. As there were few participants and hence events in the Leicester centre, data for the primary end point and its components were grouped with data from Cambridge, the other UK centre. Because randomisation was at the practice level, robust standard errors (SEs) were calculated that take into account the two-level structure of the data (individuals clustered within practices) and any potential correlation between individuals within practices. We calculated the intracluster correlation coefficient for the primary end point. We combined centre-specific log-hazard ratios and SEs using fixed-effects meta-analysis and calculated the I^2-statistic, which represents the proportion of variability (in log-hazard ratios) between centres that is due to heterogeneity. We tested the proportional hazards assumption by including a parameter for treatment × time interaction in each centre-specific Cox regression model. We analysed continuous intermediate end points within each centre using normal errors regression, with adjustment for the baseline value of the end point, excluding individuals who died or who were lost to follow-up. We combined the estimated differences in mean change from baseline across centres using fixed-effects meta-analysis. In the regression models we included individuals with a missing value of the outcome at baseline using the missing indicator method;[76] variables with a skewed distribution were log-transformed. We estimated the effect of the intervention on prescribing end points using logistic regression within each centre and combined the estimated ORs across centres using fixed-effects meta-analysis. We undertook sensitivity analyses by excluding follow-up clinical

data obtained from general practice records and prespecified subgroup analyses for the primary end point by including interaction terms between the intervention group and patient age and self-reported history of CVD, which were then pooled across centres. The cumulative incidence of the composite cardiovascular end point was calculated using the method for competing risks described by Gooley *et al.*,[77] with the competing events here being the primary end point and death from non-cardiovascular causes.

Secondary analyses: all-cause mortality

All-cause mortality data were analysed using the method described in the previous section for the composite CVD end point. Kaplan–Meier estimates of cumulative incidence were calculated.

Secondary analyses: microvascular outcomes

Binary end points (any albuminuria and any retinopathy) were analysed using a logistic regression model estimating the OR and 95% CI for the comparison between IT and RC separately within each centre. The continuous end points (ACR, eGFR) were analysed using a normal errors regression model with adjustment for baseline.

In both logistic and normal errors regression models, given the cluster-randomised design, SEs were adjusted using the cluster option in Stata to allow for correlation between patients within practices. The estimated ORs and differences in means from the four centres were pooled using fixed-effects meta-analysis and a forest plot was used to display the results. The I^2-statistic, representing the proportion of variability between centres that is due to heterogeneity, was calculated. Intracluster correlation coefficient values were estimated for all of the microvascular outcomes.

Prespecified analyses of potential interactions between randomised groups and subgroups defined by the following baseline variables were undertaken: age (< 60 and ≥ 60 years), sex, HbA_{1c} [$< 6.6\%$ (< 49 mmol/mol) and $\geq 6.6\%$ (≥ 49 mmol/mol), which was the median value] and the presence of albuminuria. For ACR and eGFR, those participants with a missing baseline value of the variable were included in the analysis using the missing indicator method.[76] A sensitivity analysis using multiple imputation was used to investigate the impact of missing data on the retinopathy and peripheral neuropathy end points.

Secondary analyses: patient-reported outcomes

We presented mean scores and SDs for all PROMs at follow-up by centre and by randomised group. We used linear mixed-effects regression models to estimate the difference in each PROM at follow-up and 95% CI, comparing the IT group with the RC group. A random effect per general practice was included to account for intracluster correlation. All PROMs were left skewed. As an alternative to transformation, we wished to control for baseline levels of PROMs. These were not available for all measures so we included baseline EQ-5D score as a proxy for baseline quality of life; correction for baseline EQ-5D score greatly improved the normality of the residuals. The estimated differences in means from the four centres were then pooled using random-effects meta-analysis and a forest plot was used to display the estimated mean differences and 95% CIs for each centre and overall. We calculated the I^2-statistic to represent the proportion of variability between centres attributable to heterogeneity.

Individuals who were lost to follow-up or who did not complete both the baseline and the follow-up questionnaires were excluded. Patients with missing data may be those who experienced more serious illness and greater disability and therefore these missing data are unlikely to be 'missing completely at random' but will rather be 'missing at random'. Simply excluding these patients may lead to selection bias and therefore we used multiple imputation[78] to perform a sensitivity analysis, imputing five data sets using patient characteristics at baseline and at 5 years' follow-up and including all patients who were alive at follow-up.

Patient and public involvement

In the development of the ADDITION-Cambridge study, patients were involved in two pilot studies. The first was to assess the feasibility and uptake of the diabetes screening programme and to examine the effects of invitation to diabetes screening on anxiety, self-rated health and illness perceptions.[79] The second was a qualitative study of patients' experiences of being screened for diabetes.[80] Further qualitative work was undertaken exploring practitioners' experiences of taking part in the main ADDITION-Cambridge study.[81] In terms of patient involvement during the 5-year follow-up phase of the trial, we sent a newsletter to all ADDITION-Cambridge participants in 2008 outlining the results to date and informing them of our intention to invite them back for the 5-year follow-up assessment. We said to participants: '[a]ny ideas that you may have on the conduct and planning of the 5-year follow-up health check would be welcomed – please get in touch if you have any comments'. Responses fed into our 5-year planning. We also sent participants a newsletter in May 2012 with the 5-year study results and invited them and a guest to attend a local meeting during June/July 2012 where they had the chance to meet with ADDITION staff and hear about the results of the study. The five meetings were very well received and gave this special group of patients a chance to ask questions about the study and their diabetes treatment. Comments ranged from 'very informative' and 'the content was useful and excellent' to 'the results of the study will motivate me to work harder at controlling my diabetes'. There was very strong support for being involved with a 10-year follow-up study. Similar feedback to study participants took place in the Netherlands and Denmark.

In ADDITION-Leicester, the intervention model was particularly suited to patient and public involvement, with ongoing contact with the clinical care team facilitating continuity and dialogue. IT participants were consulted and offered continued post-trial care delivered in a setting of their choice (primary or secondary care). A number of participants have become members of the local patient and public involvement group and are actively involved in steering local research. A newsletter describing the final results and thanking participants for their involvement was sent following completion of the 5-year outcome ascertainment for the entire cohort (July 2014). A significant number of participants were identified as being at high risk of diabetes during the ADDITION-Leicester study and have subsequently been involved with other studies aimed at the prevention of diabetes. We have also developed a black and minority ethnic panel that has contributed more widely to diabetes research in hard-to-reach groups.

Chapter 3 Trial results

Of the 343 general practices that were randomised, 318 (RC, $n = 157$; IT, $n = 161$) completed screening and included eligible participants. Participating practices in the Netherlands and the UK have been described previously.[43,48,49] All four centres had a diabetes prevalence of 3.5% and a nationally representative mean patient list of ≈7000 individuals ($n = 7378$ RC group, $n = 7160$ IT group). Baseline sociodemographic, biochemical, clinical and treatment characteristics of individuals in the two randomised groups were well matched overall (see *Table 3*). However, more patients were identified in IT than in RC practices in Denmark ($n = 910$ and 623, respectively) and more IT than RC participants had a previous history of ischaemic heart disease [*International Statistical Classification of Diseases and Related Health Problems*, Tenth Edition (ICD-10) codes I20–25: 11.2% vs. 8.5%, respectively] or other cardiac diagnoses (ICD-10 codes I30–I52: 8.4% vs. 4.5%, respectively). The mean age of ADDITION-Europe participants was 60 years and 58% were male, 94% were Caucasian and 41% were employed. Levels of CVD risk factors among participants at diagnosis were high and many participants were not receiving treatment for these risk factors.[50] Participant and practice flows are shown in *Figure 1* (CONSORT diagram).

Of those who were still alive in 2009, 2400 (84%) individuals returned to a clinical research facility for a 5-year follow-up health assessment. We obtained biochemical and clinical data from GP records for a further 328 (11.5%) participants. Compared with those with follow-up data, participants with missing data were more likely to be from an ethnic minority group (10.2% vs. 5.7%; $p = 0.04$) and to have higher cholesterol (5.9 mmol/l vs. 5.6 mmol/l; $p = 0.004$) and low-density lipoprotein (LDL) cholesterol values (3.7 mmol/l vs. 3.4 mmol/l; $p = 0.009$) at baseline.

Changes in biochemical, clinical and treatment variables in the two trial groups are shown in *Table 3*. Prescription of antihypertensive, glucose-lowering and lipid-lowering medication increased in both groups. At follow-up, compared with the RC group, approximately 10% more participants were prescribed glucose-lowering, antihypertensive and lipid-lowering medication in the IT group. In addition, 15% more IT patients were prescribed ACE inhibitors or angiotensin receptor blockers (ARBs) and 30% more IT patients were prescribed aspirin at follow-up. Cardiovascular risk factors in both groups improved over 5 years of follow-up. The modest but statistically significant between-group differences in change from baseline for total and LDL cholesterol, systolic and diastolic blood pressure and HbA_{1c} favoured the IT group.

The 10-year modelled CVD risk was 27.3% (SD 13.9%) at baseline in the whole trial cohort and 21.3% (SD 13.8%) at 5 years. Across all four centres there was a reduction in modelled CVD risk from baseline to 5 years in both the RC group (–5.0%, SD 12.2%) and the IT group (–6.9%, SD 9.0%). *Figure 2* shows the distribution of CVD risk at baseline and follow-up by treatment group; the distribution of modelled CVD risk shifted to the left for both groups.

TABLE 3 Clinical and biochemical values and prescribed medication in the RC and IT groups of the ADDITION-Europe trial at baseline and mean follow-up of 5.3 years[a]

	RC						IT						Between-group difference in change from baseline to follow-up	
	Baseline			Follow-up			Baseline			Follow-up				
Characteristic	% missing	*n*	%	% missing	*n*	%	% missing	*n*	%	% missing	*n*	%	Beta/OR	95% CI
Demographic variables														
Male sex	0	790	57.3	–	–	–	0	981	58.5	–	–	–	–	–
Age at diagnosis (years), mean (SD)	0	60.2	6.8	–	–	–	0	60.3	6.9	–	–	–	–	–
White ethnicity	3	1246	93.4	–	–	–	4	1539	95.8	–	–	–	–	–
Employed	27	425	42.0	–	–	–	29	482	40.3	–	–	–	–	–
Clinical variables														
History of MI	7	79	6.1	–	–	–	5	109	6.8	–	–	–	–	–
History of stroke	8	24	1.9	–	–	–	7	45	2.9	–	–	–	–	–
Current smokers	2	375	27.8	21	187	18.4	2	444	26.9	18	261	20.2	1.06	0.77 to 1.45
Units of alcohol per week, median (IQR)	14	4.0	1 to 13	22	3.0	0 to 10	11	4.0	1 to 13	19	3.0	0 to 10	–0.24	–0.77 to 0.29
BMI (kg/m^2), mean (SD)	3	31.6	5.6	14	31.0	5.6	4	31.6	5.6	11	31.1	5.7	0.03	–0.17 to 0.22
Weight (kg), mean (SD)	3	90.3	17.6	7	88.4	17.8	4	90.9	17.5	5	89.1	18.2	–0.02	–0.58 to 0.55
Waist circumference (cm), mean (SD)	2	106.8	13.5	17	105.3	13.6	4	107.1	13.5	13	105.4	13.6	–0.30	–1.01 to 0.42
HbA_{1c} (%), median (IQR)	6	6.6	6.1 to 7.3	5	6.5	6.1 to 7.1	5	6.5	6.1 to 7.3	4	6.4	6.0 to 6.9	–0.08	–0.14 to –0.02
HbA_{1c} (%), mean (SD)	6	7.0	1.5	5	6.7	0.95	5	7.0	1.6	4	6.6	0.95	–0.08	–0.14 to –0.02
Systolic blood pressure (mmHg), mean (SD)	2	149.8	21.3	6	138.1	17.6	4	148.5	22.1	4	134.8	16.8	–2.86	–4.51 to –1.20

Characteristic	RC						IT						Between-group difference in change from baseline to follow-up	
	Baseline			Follow-up			Baseline			Follow-up				
	% missing	*n*	%	% missing	*n*	%	% missing	*n*	%	% missing	*n*	%	Beta/OR	95% CI
Diastolic blood pressure (mmHg), mean (SD)	2	86.5	11.3	7	80.7	10.8	4	86.1	11.1	4	79.5	10.7	–1.44	–2.30 to –0.58
Total cholesterol (mmol/l), mean (SD)	6	5.6	1.2	5	4.4	0.9	5	5.5	1.1	3	4.2	0.9	–0.27	–0.34 to –0.19
HDL cholesterol (mmol/l), median (IQR)	7	1.2	1.0 to 1.5	7	1.3	1.1 to 1.6	7	1.2	1.0 to 1.5	4	1.2	1.0 to 1.5	0.00	–0.03 to 0.02
LDL cholesterol (mmol/l), mean (SD)	10	3.5	1.0	9	2.3	0.8	10	3.4	1.0	6	2.1	0.8	–0.20	–0.26 to –0.13
Triglycerides (mmol/l), median (IQR)	6	1.7	1.2 to 2.4	6	1.6	1.1 to 2.3	6	1.6	1.2 to 2.3	4	1.5	1.0 to 2.1	–0.05	–0.12 to 0.01
Creatinine (µmol/l), mean (SD)	8	84.9	18.6	6	79.8	29.9	7	83.4	17.1	5	81.0	30.5	1.81	0.10 to 3.53
Self-reported medication														
Any glucose-lowering drug	3	7	0.5	6	681	56.4	4	8	0.5	3	990	65.0	1.53	1.25 to 1.89
Number of glucose-lowering drugs, median (IQR)	3	0	0 to 0	6	1	0 to 1	4	0	0 to 0	3	1	0 to 1	–	–
Metformin	3	5	0.4	6	583	48.3	4	6	0.4	3	835	54.8	–	–
Sulphonylurea	3	2	0.1	6	215	17.8	4	2	0.1	3	291	19.1	–	–
Thiazolidinedione	3	0	0	6	50	4.1	4	0	0	3	69	4.5	–	–
Insulin	3	0	0	6	43	3.6	4	0	0	3	96	6.3	–	–
Other glucose-lowering drugs	3	0	0	6	31	2.6	4	0	0	3	81	5.3	–	–

continued

TABLE 3 Clinical and biochemical values and prescribed medication in the RC and IT groups of the ADDITION-Europe trial at baseline and mean follow-up of 5.3 years[a] (*continued*)

	RC						IT						Between-group difference in change from baseline to follow-up	
	Baseline			Follow-up			Baseline			Follow-up				
Characteristic	% missing	*n*	%	% missing	*n*	%	% missing	*n*	%	% missing	*n*	%	Beta/OR	95% CI
Any antihypertensive drugs	3	585	43.7	6	911	75.4	4	752	46.7	3	1274	83.6	1.61	1.27 to 2.04
Number of antihypertensive drugs, median (IQR)	3	0	0 to 1	6	2	1 to 3	4	0	0 to 2	3	2	1 to 3		
ACE inhibitor or ARB	3	248	18.5	6	721	59.7	4	345	21.4	3	1126	73.9	1.84	1.52 to 2.22
Beta-blocker	3	252	18.8	6	285	23.6	4	366	22.7	3	462	30.3	–	–
Calcium antagonist	3	166	12.4	6	326	27.0	4	202	12.6	3	446	29.3	–	–
Diuretic	3	330	24.6	6	529	43.8	4	415	25.8	3	767	50.3	–	–
Other antihypertensive drugs	3	23	1.7	6	49	4.1	4	32	2.0	3	70	4.6	–	–
Any cholesterol-lowering drugs	3	206	15.4	6	889	73.6	4	274	17.0	3	1241	81.4	–	–
Statins	3	200	14.9	6	864	71.5	4	271	16.8	3	1217	79.9	1.46	1.20 to 1.78
Aspirin	3	169	12.6	6	504	41.7	4	249	15.5	3	1078	70.7	–	–

ARB, angiotensin receptor blocker; BMI, body mass index; IQR, interquartile range; LDL, low-density lipoprotein.
a Values shown are *n* (%) unless specified otherwise.
Source: reproduced open access from Griffin *et al.*[55]

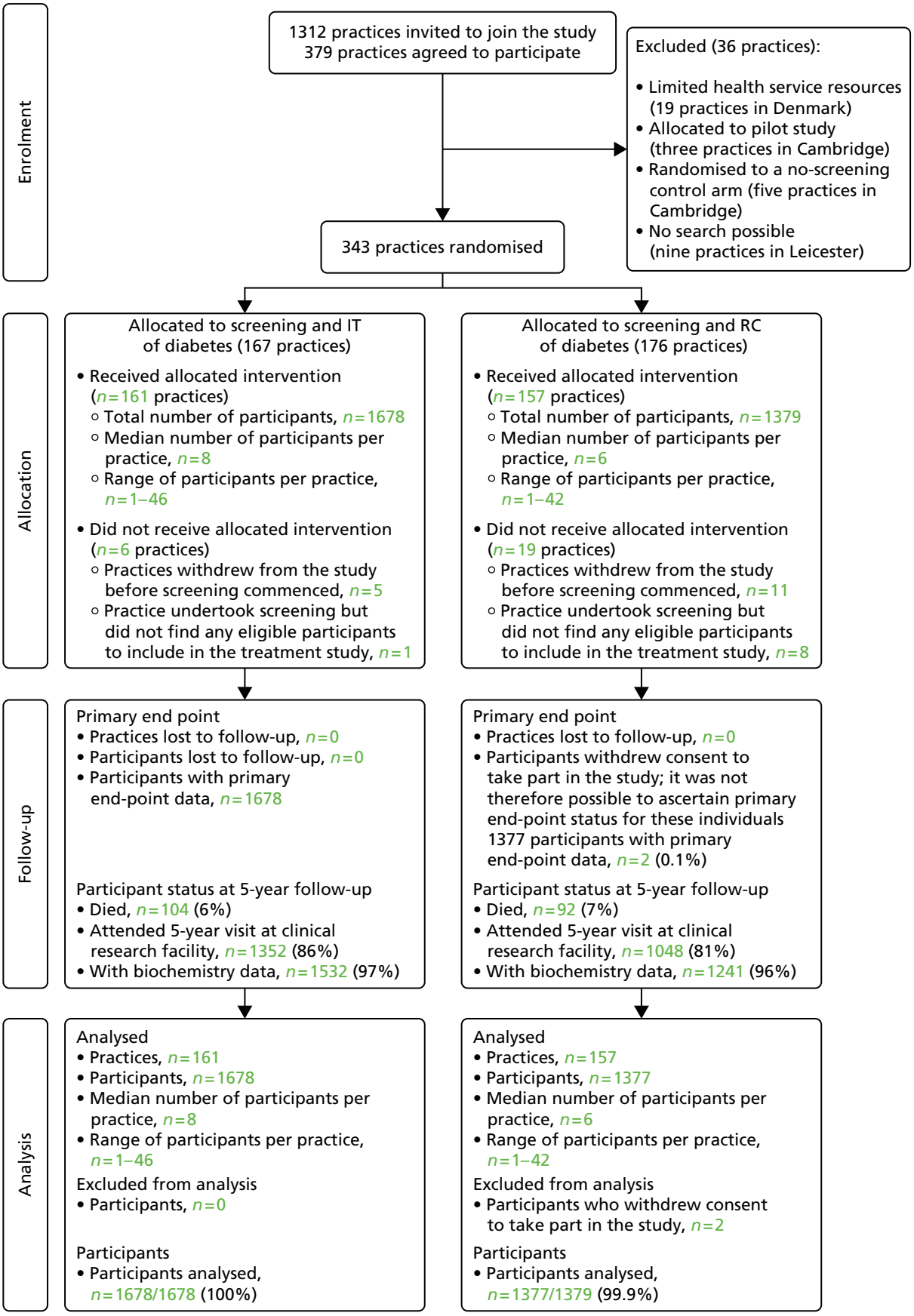

FIGURE 1 Practice and participant flows in the ADDITION-Europe trial. Source: reproduced open access from Griffin *et al.*[55]

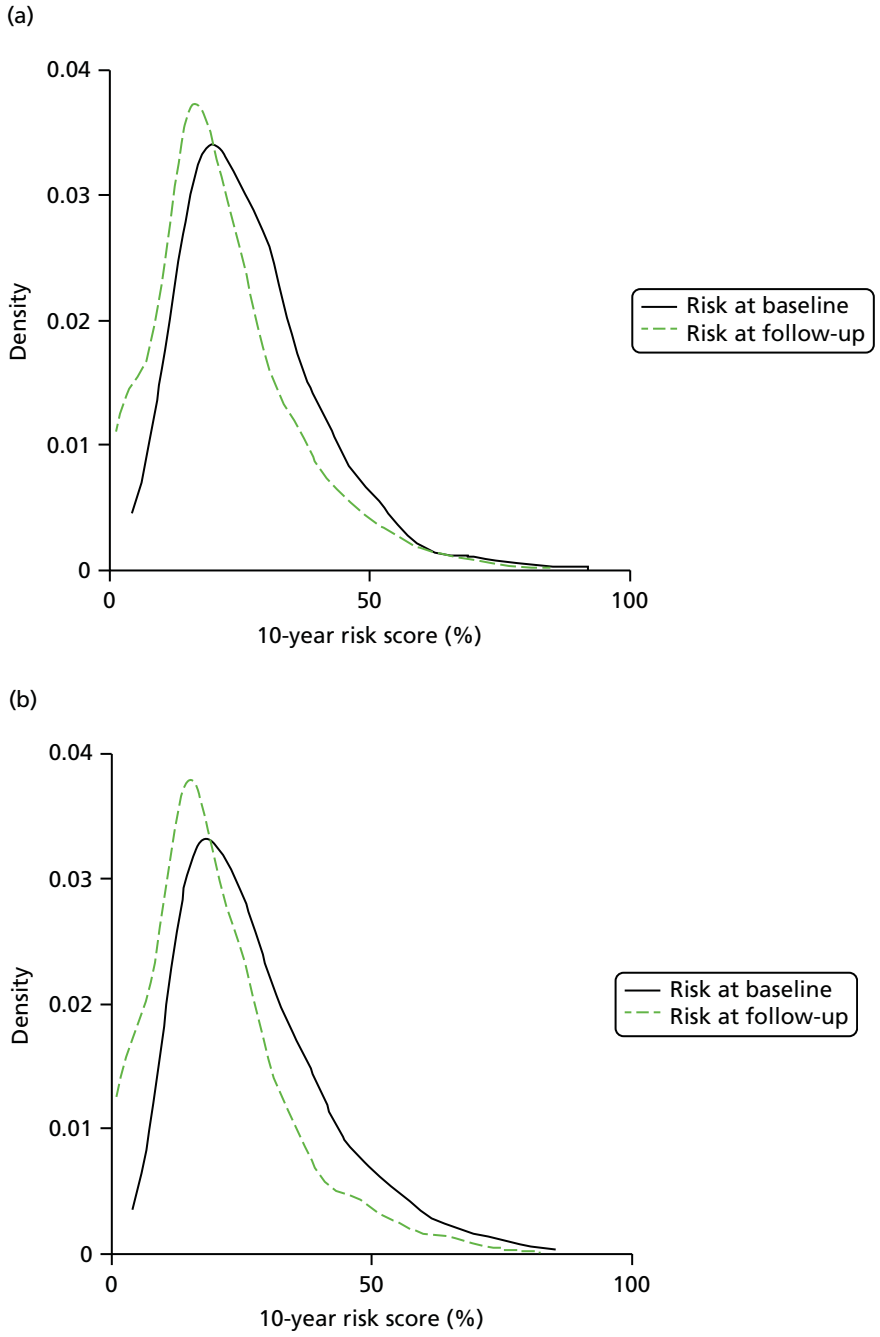

FIGURE 2 Distribution of the UKPDS (version 3) modelled CVD risk score at baseline and 5 years' follow-up in the ADDITION-Europe trial cohort by treatment group. (a) RC; and (b) IT. Source: reproduced open access from Black *et al.*[82]

Within all four centres the modelled CVD risk was lower in the IT group than in the RC group at 5 years (*Figure 3*). The difference between the groups varied from –0.9% (95% CI –3.6% to 1.7%) in Cambridge to –4.8% (95% CI –8.4% to –1.3%) in the Netherlands. There was moderate variation between centres ($I^2 = 53.6\%$). For all centres combined, the 10-year modelled CVD risk was significantly lower (–2.0%, 95% CI –3.1% to –0.9%) in the IT group after adjustment for baseline cardiovascular risk and clustering by general practice.

Figure 4 shows the percentage of participants meeting treatment targets for cholesterol, HbA_{1c} and blood pressure in each group at baseline and follow-up. More patients met treatment targets at follow-up than at baseline in both groups. The proportion meeting the targets was higher in the IT group than in the RC group. There was no difference between groups in the percentage of those reporting hypoglycaemia ($\chi^2 = 4.44$; $p = 0.62$).[74] The results were the same when excluding participants with follow-up clinical data obtained from GP records.

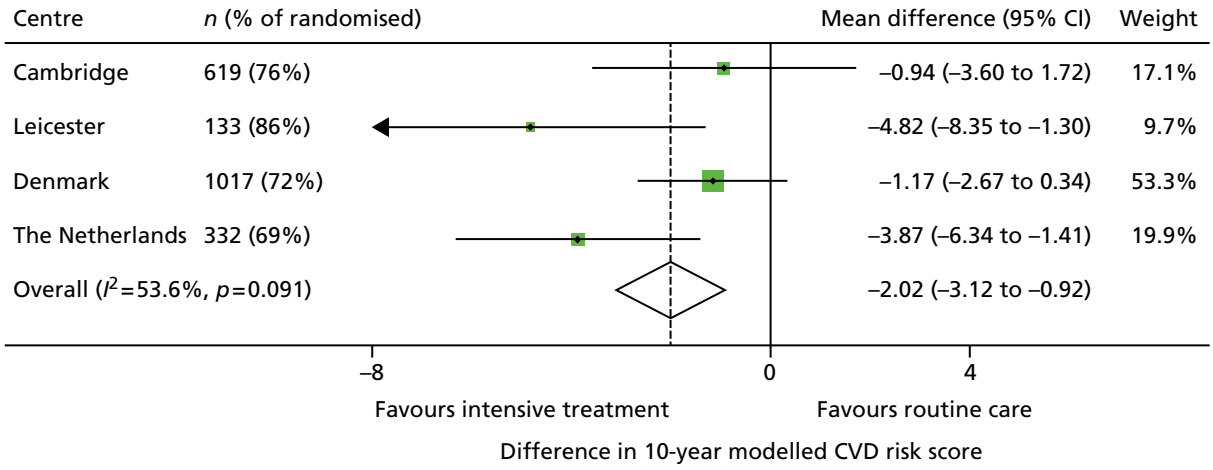

FIGURE 3 Difference in the UKPDS (version 3) modelled CVD risk score between treatment groups at 5 years' follow-up in the ADDITION-Europe trial cohort, adjusted for baseline risk and accounting for clustering by general practice. Source: reproduced open access from Black *et al.*[82]

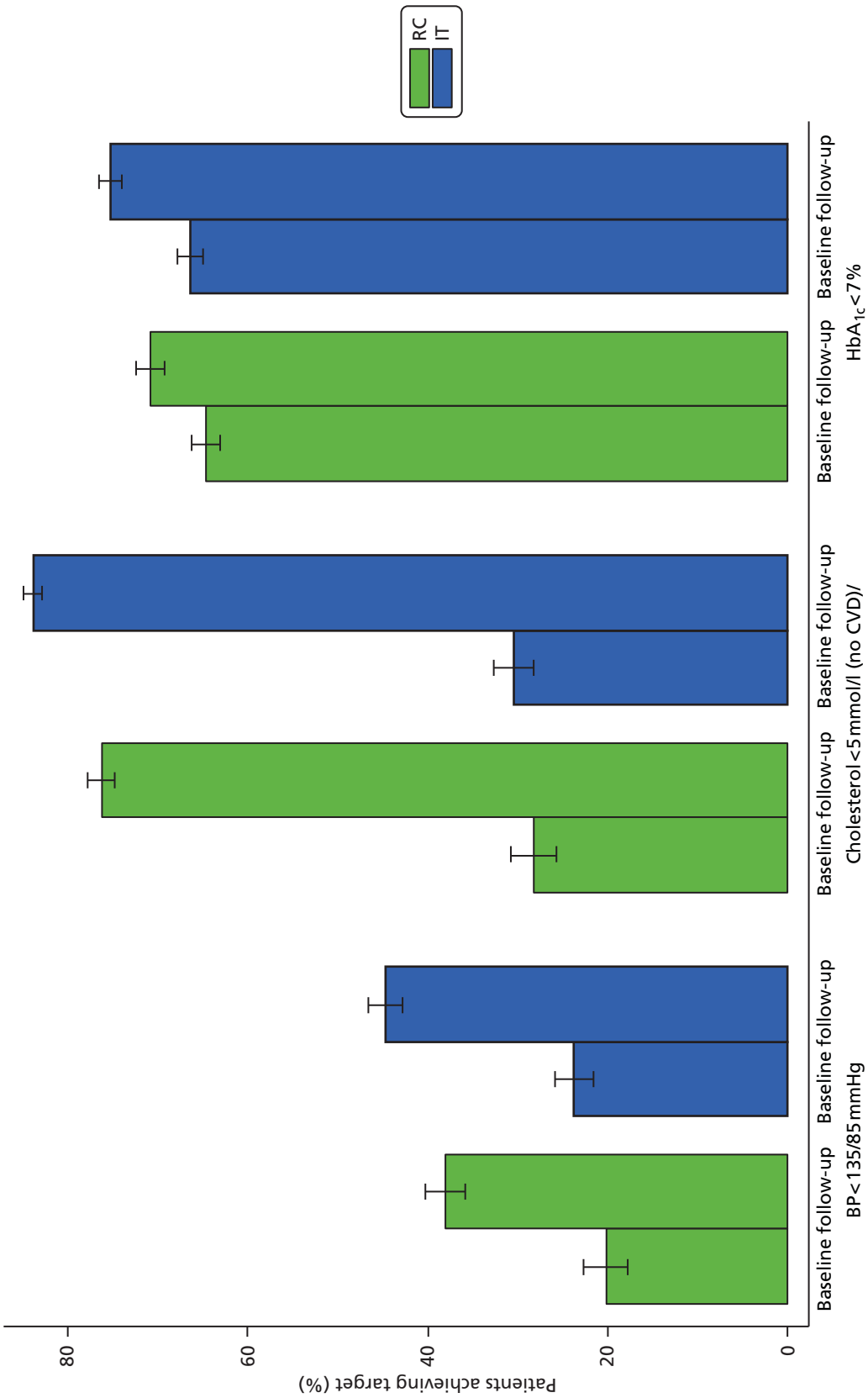

FIGURE 4 Percentage of participants in each group of the ADDITION-Europe trial (±1 SE) for whom the treatment targets were met at baseline and follow-up at a mean of 5.3 years. BP, blood pressure. Source: reproduced open access from Griffin *et al.*[55]

Primary analyses: cardiovascular outcomes

Primary end-point data were available for 99.9% (3055/3057) of participants. In total, 238 first cardiovascular events occurred during a mean (SD) follow-up period of 5.3 (1.6) years (*Table 4*). There were 121 events among 1678 participants (7.2%) in the IT group (incidence 13.5, 95% CI 11.3 to 16.1 per 1000 person-years) and 117 events among 1377 participants (8.5%) in the RC group (incidence 15.9, 95% CI 13.3 to 19.1 per 1000 person-years). The hazard ratio for the IT group compared with the RC group was 0.83 (95% CI 0.65 to 1.05; $p = 0.12$). The cumulative probability for the primary CVD end point appeared to diverge after 4 years of follow-up (*Figure 5*). In predefined subgroup analyses there were no interactions between the intervention and age or previous cardiovascular event ($p > 0.1$). The *p*-value was calculated using Cox regression and fixed-effects meta-analysis.

However, estimated hazard ratios were 0.70 (95% CI 0.52 to 0.95) in those aged ≥ 60 years and 1.12 (95% CI 0.70 to 1.79) in those aged < 60 years. Hazard ratios for individual components of the composite end point all favoured the IT group (see *Table 4*), although none achieved statistical significance (*Figure 6*). There were no amputations as first events. The intracluster correlation coefficient for the primary end point was 0.002 (Denmark 0.014, UK 0.0000016, the Netherlands 0.025). This suggests that the cluster design had little effect on study power.

In total, there were 196 deaths ($n = 60$ cardiovascular, $n = 97$ cancer and $n = 39$ other), 104 (6.2%) in the IT group (mortality rate 11.6, 95% CI 9.6 to 14.0 per 1000 person-years) and 92 (6.7%) in the RC group (mortality rate 12.5, 95% CI 10.2 to 15.3 per 1000 person-years) (see *Table 4*). The combined mortality hazard ratio for the IT group compared with the RC group was 0.91 (95% CI 0.69 to 1.21). A Kaplan–Meier plot is shown in *Figure 7* and country-specific hazard ratios in *Figure 8*. The heterogeneity of results between countries was not statistically significant. In the UK there were significantly fewer deaths in the IT group, whereas in Denmark there was a non-significant reduction in cumulative risk in the RC group.

TABLE 4 Cardiovascular events and all-cause mortality in the ADDITION-Europe trial

End point	RC ($n = 1377$), *n* (%)	IT ($n = 1678$), *n* (%)	IT vs. RC			
			Hazard ratio[a]	95% CI	I^2 (%)[b]	*p*-value[c]
Primary end point: composite cardiovascular events[d]	117 (8.5)	121 (7.2)	0.83	0.65 to 1.05	0	0.12
Components of primary end point						
CVD death	22 (1.6)	26 (1.5)	0.88	0.51 to 1.51	52	
MI	32 (2.3)	29 (1.7)	0.70	0.41 to 1.21	0	
Stroke	19 (1.4)	22 (1.3)	0.98	0.57 to 1.71	0	
Revascularisation	44 (3.2)	44 (2.6)	0.79	0.53 to 1.18	0	
Amputation	0	0	–	–	–	
Total mortality	92 (6.7)	104 (6.2)	0.91	0.69 to 1.21	55	

a Hazard ratios are first estimated within each country using Cox regression with Huber–White adjustment of SEs for clustering within practice and are then combined across countries using fixed-effects meta-analysis.
b I^2 is an estimate of the heterogeneity between countries.
c A *p*-value was calculated for the primary end point only.
d Any of the following: CVD death, MI, stroke, revascularisation or amputation.

Note
Individual country-specific estimates are displayed in forest plots (see *Figure 6*).
Source: reproduced open access from Griffin *et al.*[55]

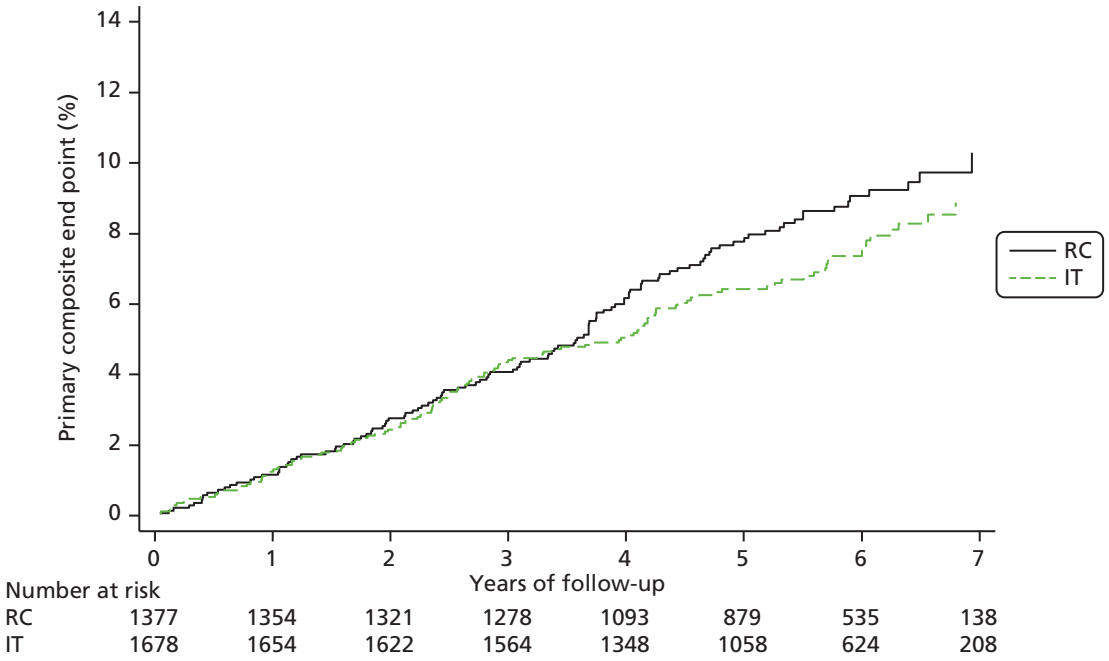

FIGURE 5 Cumulative incidence of the composite cardiovascular end point in the RC and IT groups of the ADDITION-Europe trial ($p = 0.12$). Source: reproduced open access from Griffin *et al.*[55]

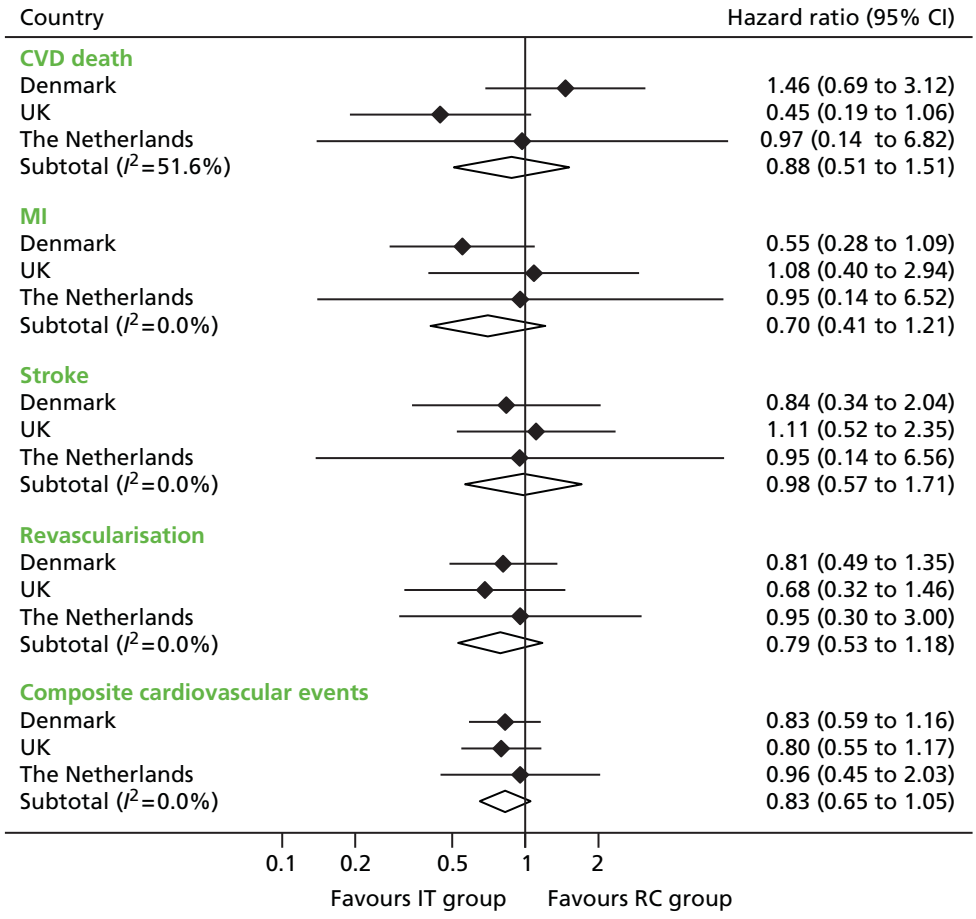

FIGURE 6 The relative risk of the development of cardiovascular death, non-fatal MI, non-fatal stroke and revascularisation as a first event and the composite cardiovascular end point by country and overall in the IT group compared with the RC group. Source: reproduced open access from Griffin *et al.*[55]

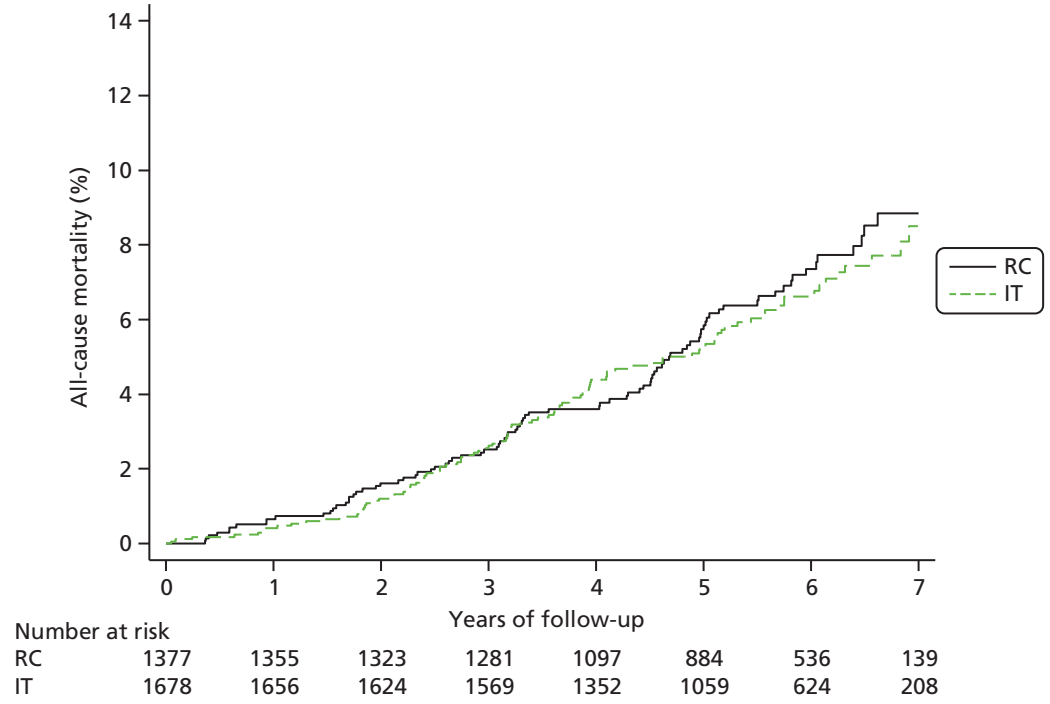

FIGURE 7 Kaplan–Meier estimates of all-cause mortality in the RC and IT groups in the ADDITION-Europe trial. Source: reproduced open access from Griffin *et al.*[55]

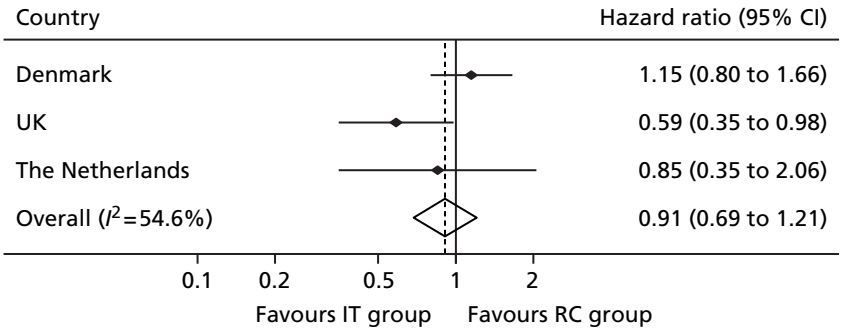

FIGURE 8 The relative risk of all-cause mortality by country and overall in the IT group compared with the RC group in the ADDITION-Europe trial. Source: reproduced open access from Griffin *et al.*[55]

Secondary analyses: microvascular outcomes

Of the 2861 patients still alive at 5 years, 2493 (87.1%), 2710 (94.7%) and 2312 (80.8%) had data for urinary ACR, eGFR and peripheral neuropathy, respectively. Retinal photographs were retrieved for 2190 (76.5%) participants.

At 5 years' follow-up any albuminuria was present in 316 (22.7%) participants in the IT group and 269 (24.4%) participants in the RC group. Macroalbuminuria was present in 56 (4.0%) and 37 (3.4%) participants in the IT and RC groups, respectively. Centre-specific ORs for any albuminuria favoured the IT group, but the pooled OR was not statistically significant (0.88, 95% CI 0.72 to 1.07; *Figure 9*). The pooled OR for macroalbuminuria was 1.15 (95% CI 0.76 to 1.74). In both groups the urinary ACR increased between baseline and follow-up. In the IT group the mean (SD) increase was 1.45 (SD 0.60) mg/mmol and in the RC group the mean (SD) increase was 1.30 (0.66) mg/mmol. The overall difference in means was –0.02 (95% CI –0.96 to 0.91) mg/mmol. There were no significant interactions between study group and any of the subgroups.

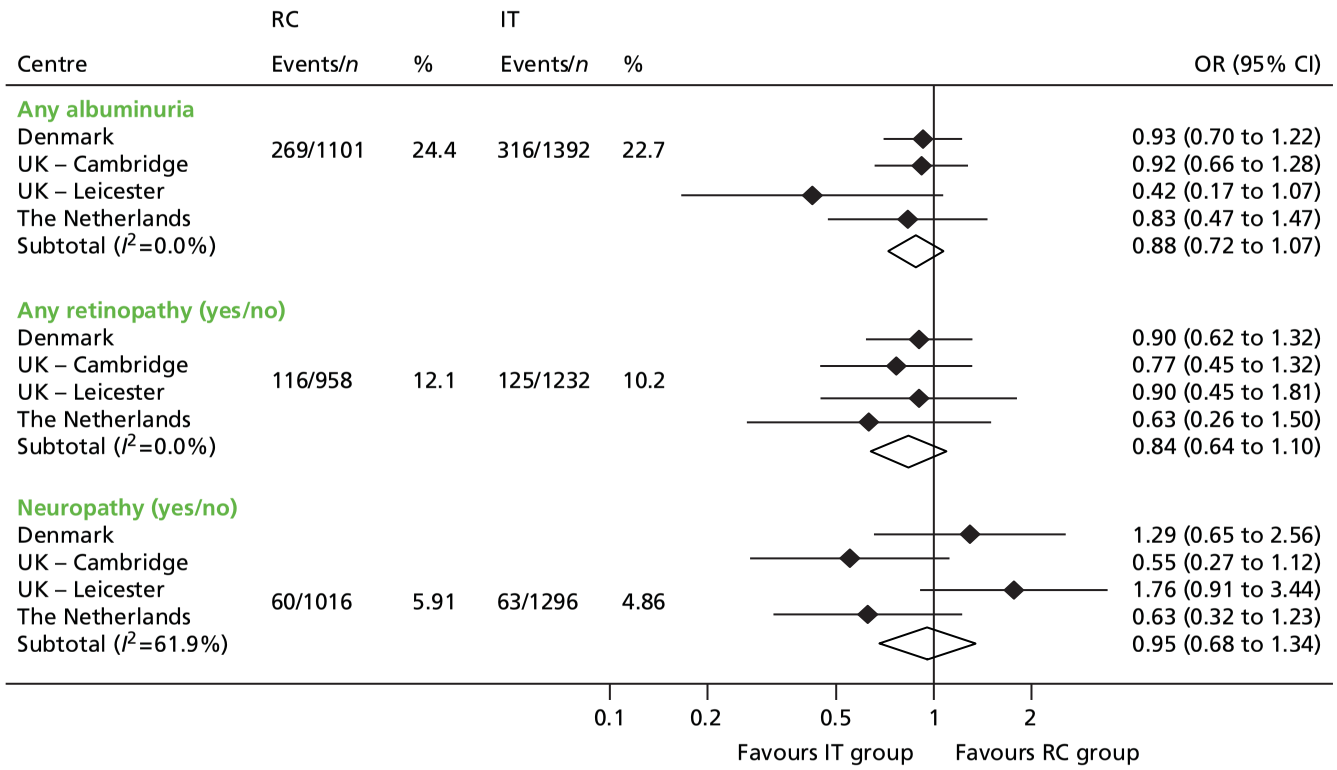

FIGURE 9 Odds ratios and frequencies of any retinopathy, any peripheral neuropathy and any albuminuria at follow-up by study group in the ADDITION-Europe trial. Source: reproduced from Sandbæk *et al.*,[83] under the Creative Commons Attribution-NonCommercial-NoDerivs 3.0 licence (CC BY-NC-ND 3.0).

The mean (SD) eGFR increased between baseline and follow-up in both the IT group and the RC group [IT 4.31 (0.49) ml/minute, RC 6.44 (0.90) ml/minute; difference in means –1.39 (95% CI –2.97 to 0.19) ml/minute]. There were no significant interactions between treatment group and any of the subgroups concerning eGFR. The number of missing data was equally distributed between the two groups.

Retinopathy was present in 125 (10.1%) participants in the IT group and 116 (12.1%) patients in the RC group. Centre-specific ORs favoured the IT group but the pooled OR was not statistically significant (0.84, 95% CI 0.64 to 1.10) (see *Figure 9*). Imputation of missing values did not affect the estimates.

Individuals without retinal images at follow-up had significantly higher baseline mean HbA_{1c} levels than individuals with retinal data [7.18% (55 mmol/mol) vs. 6.99% (53 mmol/mol), respectively; $p = 0.044$]. However, there was no difference between randomised groups (interaction p-value = 0.78). There was a significant interaction between retinopathy, randomised group and baseline HbA_{1c} level ($p = 0.007$). IT appeared to be more effective among individuals with $HbA_{1c} \geq 6.6\%$ (≥ 49 mmol/mol) at baseline (OR 0.65, 95% CI 0.45 to 0.93) than among individuals with $HbA_{1c} < 6.6\%$ (< 49 mmol/mol) at baseline (OR 1.17, 95% CI 0.75 to 1.82). There was no evidence of an interaction with either age or sex. Severe retinopathy was present in one participant in the IT group and in seven participants in the RC group.

Peripheral neuropathy was present in 63 (4.9%) participants in the IT group and 60 (5.9%) participants in the RC group (pooled OR 0.95, 95% CI 0.68 to 1.34) (see *Figure 9*). Non-responders to the neuropathy questionnaire had a higher body mass index ($p = 0.055$) and were more likely to be from a ethnic minority group ($p = 0.004$) than responders. Imputation of missing values did not affect the estimates.

The overall intracluster correlation coefficient values were as follows: retinopathy 0.014 (95% CI 0.00017 to 0.55), albuminuria 0.025 (95% CI 0.0066 to 0.091) and neuropathy 0.011 (95% CI 4.6×10^{-7} to 1). These results indicate that the impact of clustering on study power was small.

Secondary analyses: patient-reported outcomes

Data from 2861 participants were included in the multiple imputation analyses. Patients who completed questionnaires at baseline and follow-up ($n = 2217$) were more likely than those who did not complete questionnaires ($n = 644$) to be male (59.5% vs. 50.8%), of white ethnicity (95.2% vs. 89.9%) and employed (44.8% vs. 32.7%). Questionnaire completers were also less likely to smoke (24.3% vs. 34.0%), had higher levels of alcohol consumption (median 5 units per week vs. 3 units per week) and had higher EQ-5D scores (median 0.85 vs. 0.81) at baseline. They also had lower systolic blood pressure levels (148.5 mmHg vs. 151.4 mmHg). Other characteristics were comparable between treatment groups (data not shown).

Table 5 shows the PROM scores at follow-up, separately for each centre and by randomised group. EQ-5D values did not change between diagnosis and follow-up: the median (interquartile range) score was 0.85 (0.73 to 1.00) at baseline and 0.85 (0.73 to 1.00) at 5 years' follow-up.

The mean differences in PROMs comparing the IT group with the RC group are shown in *Figures 10–13*. There were no statistically significant differences in health status (see *Figure 10*), well-being (see *Figure 11*), diabetes-specific quality of life (see *Figure 12*) and satisfaction with diabetes treatment (see *Figure 13*) between the two groups. There was some heterogeneity between centres. The I^2-statistic varied between 41% (W-BQ-positive) and 73% (EQ-VAS).

Multiple imputation analyses resulted in slightly different point estimates. However, the overall patterns remained the same and there were no statistically significant differences in any of the PROMs (results not shown).

TABLE 5 Patient-reported outcome measures at follow-up by centre and by randomised group in the ADDITION-Europe trial[a]

	Centre															
	Denmark				Cambridge				Leicester				The Netherlands			
	IT		RC		IT		RC		IT		RC		IT		RC	
Measure	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
SF-36																
PCS score	665	46.7 (10.0)	428	46.7 (9.6)	350	43.9 (11.6)	310	44.6 (11.3)	59	44.3 (11.4)	84	43.4 (10.5)	177	46.8 (10.4)	144	47.0 (10.5)
MCS score	665	55.3 (9,1)	428	54.9 (8.5)	350	53.4 (9.0)	310	54.6 (8.4)	59	50.9 (10.1)	84	52.2 (9.8)	177	54.3 (8.2)	144	53.7 (7.4)
EQ-5D score	695	0.85 (0.21)	463	0.84 (0.22)	351	0.81 (0.23)	312	0.83 (0.22)	60	0.75 (0.31)	85	0.79 (0.23)	176	0.86 (0.18)	144	0.82 (0.26)
EQ-VAS	691	76.9 (16.9)	462	76.4 (18.5)	355	76.1 (18.0)	316	78.4 (16.4)	60	78.3 (16.3)	88	74.8 (18.4)	175	76.5 (13.7)	144	75.3 (15.6)
W-BQ12 score																
General	680	28.5 (5.9)	447	28.1 (6.3)	346	25.5 (6.5)	310	26.4 (5.9)	58	25.3 (6.7)	78	25.0 (6.3)	171	27.6 (6.3)	141	27.4 (5.7)
Negative	689	1.1 (2.0)	458	1.1 (1.8)	351	1.7 (2.4)	314	1.4 (2.1)	59	1.9 (2.5)	86	2.1 (2.5)	175	1.1 (1.9)	143	1.1 (1.8)
Energy	691	8.1 (2.7)	453	8.0 (2.8)	352	7.0 (2.7)	315	7.3 (2.6)	58	7.1 (2.7)	82	7.1 (2.3)	174	8.5 (2.6)	142	8.5 (2.3)
Positive	692	9.4 (2.5)	456	9.2 (2.8)	352	8.2 (2.8)	315	8.4 (2.7)	59	8.2 (2.6)	85	8.0 (2.9)	177	8.0 (3.1)	144	8.1 (2.6)
ADDQoL score	552	–0.73 (1.15)	348	–0.69 (1.07)	315	–0.84 (1.29)	271	–0.87 (1.30)	50	–1.20 (1.78)	76	–2.39 (2.52)	169	–0.55 (0.86)	135	–0.55 (0.92)
DTSQ score	648	30.9 (6.2)	405	30.1 (6.7)	344	31.5 (4.9)	305	31.2 (5.4)	60	33.0 (3.8)	85	29.1 (7.3)	174	31.2 (5.6)	140	31.0 (5.6)

MCS, mental component summary; PCS, physical component summary.

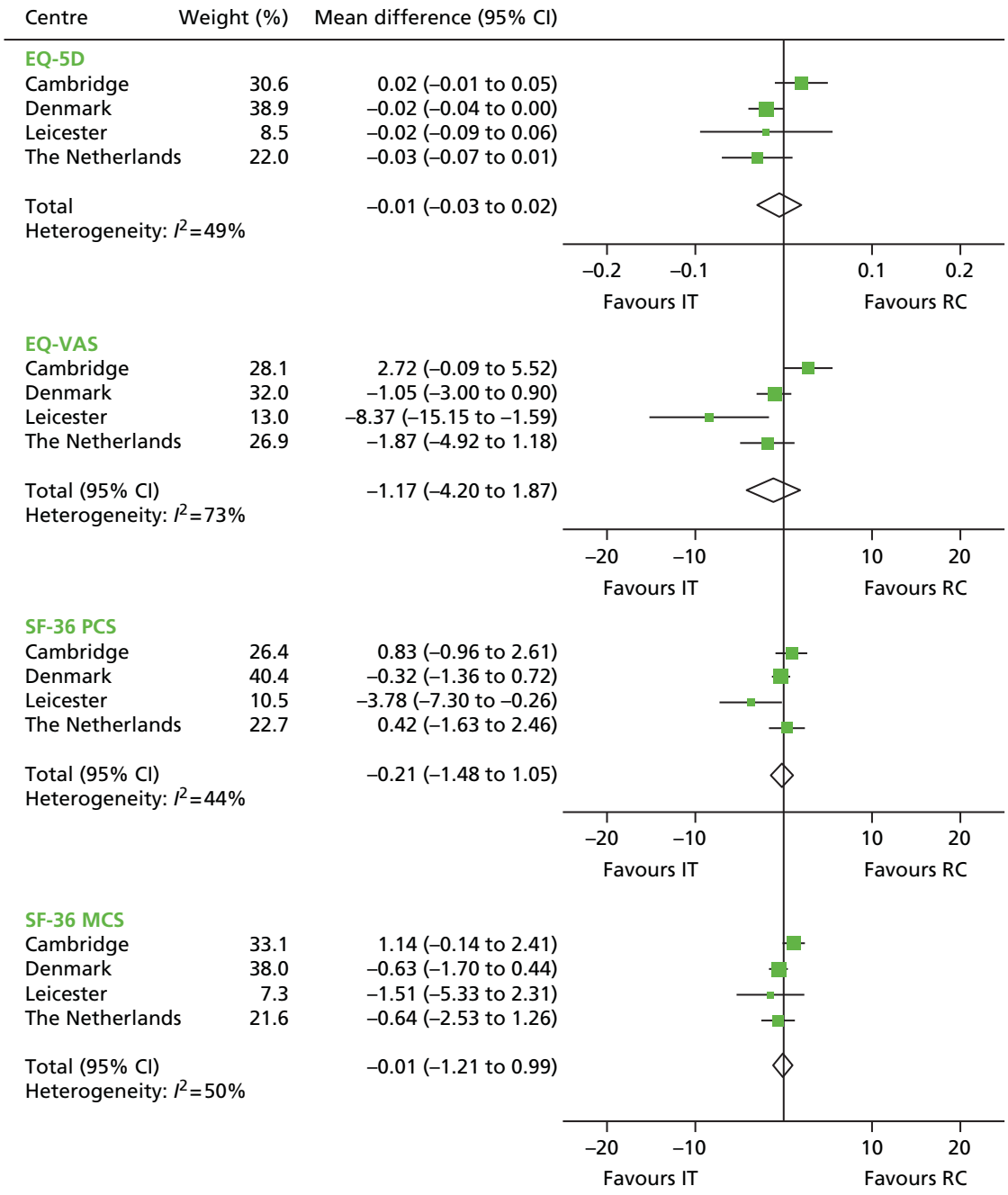

FIGURE 10 Mean difference in health status between the IT group and the RC group by centre (boxes) after 5 years' follow-up in the ADDITION-Europe trial and pooled estimates (diamonds) calculated by random-effects meta-analysis. Horizontal bars and diamond widths denote 95% CIs and box sizes indicate relative weight in the analysis. MCS, mental component summary; PCS, physical component summary. Source: reproduced from van den Donk *et al.*,[84] under the Creative Commons Attribution Noncommercial licence.

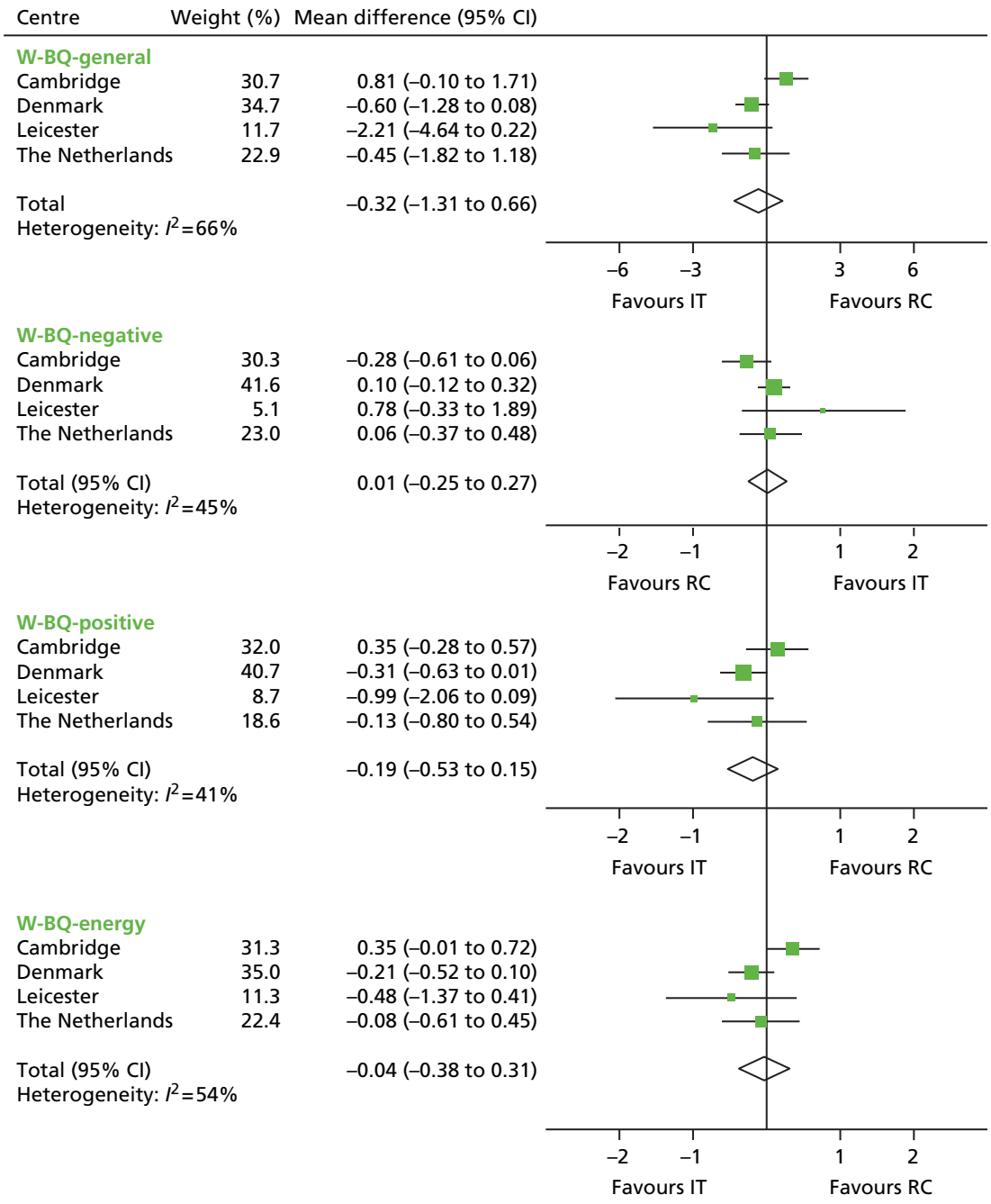

FIGURE 11 Mean difference in W-BQ12 scores between the IT group and the RC group by centre (boxes) after 5 years' follow-up in the ADDITION-Europe trial and pooled estimates (diamonds) calculated by random-effects meta-analysis. Horizontal bars and diamond widths denote 95% CIs and box sizes indicate relative weight in the analysis. Source: reproduced from van den Donk *et al.*,[84] under the Creative Commons Attribution Noncommercial licence.

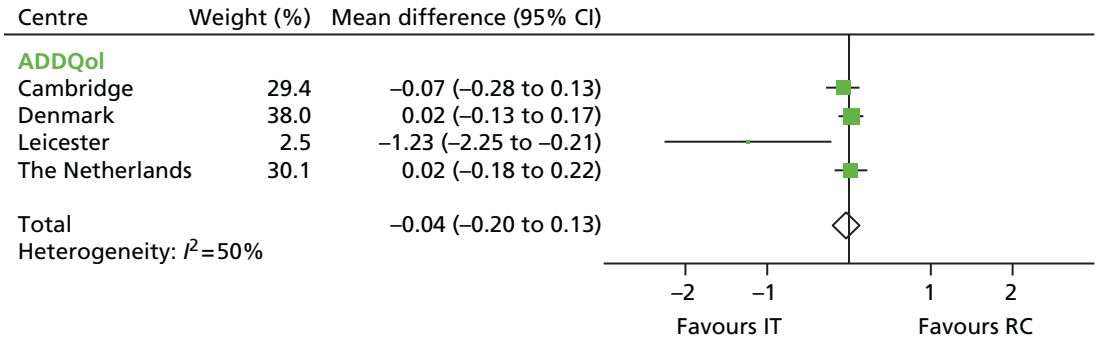

FIGURE 12 Mean difference in ADDQoL scores between the IT group and the RC group by centre (boxes) after 5 years' follow-up in the ADDITION-Europe trial and pooled estimates (diamonds) calculated by random-effects meta-analysis. Horizontal bars and diamond widths denote 95% CIs and box sizes indicate relative weight in the analysis. Source: reproduced from van den Donk *et al.*,[84] under the Creative Commons Attribution Noncommercial licence.

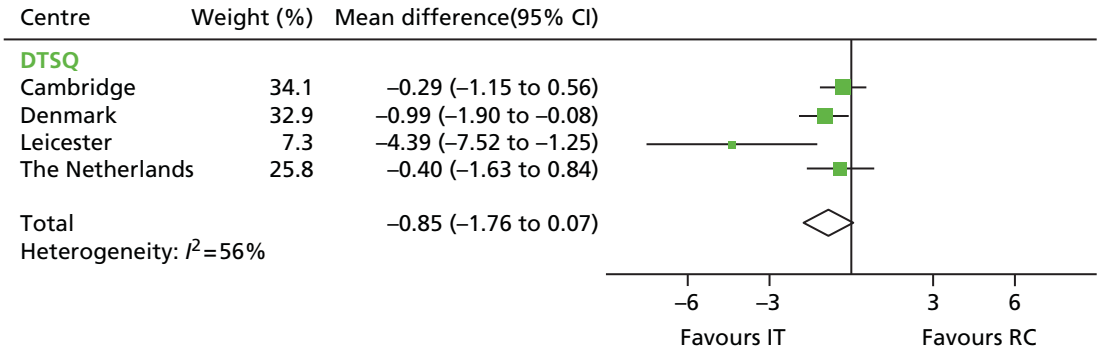

FIGURE 13 Mean difference in DTSQ scores between the IT group and the RC group by centre (boxes) after 5 years' follow-up in the ADDITION-Europe trial and pooled estimates (diamonds) calculated by random-effects meta-analysis. Horizontal bars and diamond widths denote 95% CIs and box sizes indicate relative weight in the analysis. Source: reproduced from van den Donk *et al.*,[84] under the Creative Commons Attribution Noncommercial licence.

Chapter 4 Economic evaluation

This chapter reports two analyses related to the cost-effectiveness of early IT of type 2 diabetes. First, we assessed the performance of the UKPDS outcomes model [UKPDS-OM, version 1.3; © Isis Innovation Ltd 2010; see www.dtu.ox.ac.uk/outcomesmodel (accessed 27 January 2016)][85] in predicting CVD risk in the ADDITION-Europe population; we wanted to investigate its suitability for modelling longer-term outcomes and costs for the ADDITION-Europe cohort. The second analysis concerns the short-term (1–6 years within-trial analysis) and long-term (10–30 years based on decision modelling) cost-effectiveness of the ADDITION intervention in the UK from a UK payer (NHS) perspective.

Validating the UK Prospective Diabetes Study outcomes model

Accurate prediction of cardiovascular risk among individuals with diabetes is important for providing prognostic information and targeting treatment to those at highest risk. It is also a key component of economic evaluations of interventions aimed at reducing the disease burden of diabetes and improving the quality and length of life for those with this chronic condition.

The UKPDS-OM is a cost-effectiveness analysis tool. It was derived from the UKPDS, a multicentre randomised controlled trial among 5102 individuals with newly diagnosed type 2 diabetes.[85] Participants were recruited from 23 UK centres.[86] The UKPDS-OM has been validated for the prediction of CVD and other complications in internal and external cohorts of people with clinically diagnosed diabetes. The observed and predicted cumulative incidence of CVD complications from diagnosis to 12 years' follow-up were very similar when using an internal cohort.[85] Results varied from poor to moderate in terms of discrimination, calibration and absolute risk for external cohorts,[87,88] with the UKPDS-OM tending to overestimate CVD risk.[89]

The UKPDS-OM was developed using data from individuals recruited between 1977 and 1997. The treatment and costs of diabetes and related complications have changed since this time. The variables assessed by the model are also likely to vary over time and between countries. As such, we aimed to evaluate the performance of the UKPDS-OM in the ADDITION-Europe study, which included a multinational contemporary cohort of individuals with screen-detected diabetes.

Methods

The 5-year accumulated absolute risks of MI and stroke were estimated for each participant in the ADDITION-Europe study using the UKPDS-OM.[85] The model includes information on age at diagnosis, sex, ethnicity, duration of diabetes, weight, height, smoking status, presence or absence of AF, PVD, systolic blood pressure, HbA_{1c}, total cholesterol, HDL cholesterol and years since pre-existing CVD events. Values for smoking status, systolic blood pressure, HbA_{1c}, total cholesterol and HDL cholesterol were included at both baseline and 5 years' follow-up.

As information on AF and PVD were not collected at baseline in the ADDITION-Europe study, and given that all patients had newly diagnosed diabetes, these variables were set to 0. The number of years since pre-existing ischaemic heart disease, congestive heart failure, amputation, blindness and renal failure were also set to 0 as this information was also not collected at baseline. Data on the number of years since any previous MI or stroke were collected in the ADDITION-Europe study and entered as appropriate into the model. As revascularisation is not a component of the UKPDS-OM and only a single case of amputation was reported during follow-up in the ADDITION-Europe study, only MI and stroke events were examined in this analysis.

Statistical analysis

We calculated the observed and predicted risk of non-fatal MI and non-fatal stroke by country and trial group using the UKPDS-OM. We employed multiple imputation to deal with missing data[90] using the Markov chain Monte Carlo method and assuming an arbitrary missing pattern. A multivariate normal distribution was used to impute missing values for age, sex, weight, height, smoking status, total cholesterol, HDL cholesterol, systolic blood pressure and HbA_{1c}. It has been previously demonstrated that multivariate normal imputation is less biased than complete-case analysis[91] and produces similar results to other approaches despite the presence of binary and ordinal variables that do not follow a normal distribution. If the imputed HDL cholesterol value was greater than the total cholesterol value (five cases at baseline; one case at final follow-up), we assumed that HDL cholesterol (mmol/l) = total cholesterol – 0.1. For each patient with missing data we undertook five imputations and computed the average of the five risk estimates.[92]

In the UKPDS-OM the categories of the variable ethnicity were white-Caucasian, Afro-Caribbean, and Asian-Indian. In the ADDITION-Europe cohort there were some unknown or unclassifiable values, for example mixed white + African, mixed white + Asian or others. These cases were unavoidably excluded from the analysis as ethnicity is improper for multiple imputation (156 cases).

We examined the discrimination of the UKPDS-OM by computing the area under the receiver operating characteristic (aROC) curve and assessed goodness of fit using the Hosmer–Lemeshow chi-square test. The same methods have been employed in previous studies for the validation of the UKPDS and Framingham risk engines.[87,88,93]

In the UKPDS-OM, both MI and stroke are assigned a particular Weibull regression equation with age, sex, HbA_{1c} and other variables as covariates.[85] To examine which distribution was the best fit for baseline risk of MI and stroke, we performed a number of survival regression analyses including exponential, log-normal, log-logistic, Weibull and generalised gamma. We computed minimal Bayesian information criterion (BIC) and Akaike information criterion (AIC) values to assess global model fit.[94] We then analysed the covariates with the best fit distribution to determine if they were significantly associated with MI and stroke. A *p*-value of < 0.10 was defined as statistically significant.[95] As risk factor values were not available for every year of follow-up in the ADDITION-Europe trial cohort, the average of the baseline and final follow-up values was used.

We also conducted a complete-case sensitivity analysis to examine whether or not the results were replicated after excluding patients for whom there were missing data ($n = 781/2899$; 26.9%). Statistical analyses were performed with SAS v9.3.

Results

Of the 3055 ADDITION-Europe participants, 156 were excluded as a result of unclassifiable or unknown ethnicity. Baseline values for age, sex, treatment group and HbA_{1c} did not differ significantly between the included and excluded patients.

Observed and predicted risk of non-fatal myocardial infarction and stroke

The non-fatal MI and stroke rates for the ADDITION-Europe participants were 0.0228 and 0.0152, respectively. The observed risks of MI and stroke were lower than the predicted risks using the UKPDS-OM. When the data were broken down by country, overestimation was greater in the Dutch population than in the Danish and UK populations for both non-fatal MI and non-fatal stroke (*Table 6*).

Examination of the absolute event rates between intervention groups represents the impact of IT compared with RC. For non-fatal MI, the difference between intervention groups was higher than that predicted by the UKPDS-OM, suggesting that the UKPDS-OM underestimated the effect of IT. For non-fatal stroke, the difference was much smaller between the observed and predicted data, indicating only a slight overestimation (see *Table 6*).

TABLE 6 Observed and predicted risk of non-fatal MI and stroke by country and intervention group in the ADDITION-Europe trial

Event	Centre	Intervention	Total *n*	Number of events	Observed risk (95% CI) (%)	Average predicted risk (%)
Non-fatal MI	All	RC	1314	39	2.97 (2.12 to 4.04)	6.86
		IT	1585	27	1.70 (1.13 to 2.47)	6.77
	Denmark	RC	601	25	4.16 (2.71 to 6.08)	6.46
		IT	851	14	1.65 (0.90 to 2.74)	6.16
	The Netherlands	RC	212	2	0.94 (0.11 to 3.37)	8.45
		IT	236	2	0.85 (0.10 to 3.03)	8.74
	UK	RC	501	12	2.40 (1.24 to 4.15)	6.67
		IT	498	11	2.21 (1.12 to 3.92)	6.87
Non-fatal stroke	All	RC	1314	19	1.45 (0.87 to 2.25)	2.30
		IT	1585	25	1.58 (1.02 to 2.32)	2.34
	Denmark	RC	601	8	1.33 (0.58 to 2.61)	2.24
		IT	851	12	1.41 (0.73 to 2.45)	2.05
	The Netherlands	RC	212	2	0.94 (0.11 to 3.37)	3.00
		IT	236	2	0.85 (0.10 to 3.03)	3.63
	UK	RC	501	9	1.80 (0.82 to 3.38)	3.08
		IT	498	11	2.21 (1.11 to 3.92)	2.21

Source: reproduced open access from Tao *et al.*[96]

Discrimination analysis

The aROC curve was 0.72 (95% CI 0.66 to 0.79) for non-fatal MI and 0.70 (95% CI 0.64 to 0.77) for non-fatal stroke, suggesting that the UKPDS-OM had moderate discriminatory ability. The Netherlands had the lowest aROC curve for MI (0.69) and the highest for stroke (0.79). Results from the Hosmer–Lemeshow test were non-significant in the overall trial cohort and in each country, suggesting that the goodness of fit was acceptable (*Table 7*).

Survival regression analysis

Following survival analysis, an exponential distribution was the best for baseline risk for both MI and stroke based on BIC values. For AIC values, log-normal and exponential distributions provided the best fit for MI and stroke, respectively. As such, we used the exponential distribution in survival regression analysis with a selection of different covariates: age, sex, treatment group, smoking status, body mass index, HbA_{1c} level, systolic blood pressure and ln(total cholesterol/HDL) for MI or total cholesterol/HDL for stroke. Age, sex and HbA_{1c} level were significantly associated with non-fatal MI; age and sex were significantly associated with non-fatal stroke (*Table 8*).

Complete-case analysis

In total, 2118 (out of 2899) participants were included in the complete-case analysis. Compared with participants excluded because of missing data, the included participants had a slightly lower mean age (60.09 vs. 60.84 years) and a higher mean HbA_{1c} value (7.06% vs. 6.96%); there was also a higher proportion of men (59.0% vs. 55.3%) among the included participants. The results were generally similar to the results of the main imputed analysis in terms of observed and predicted risk and best fit distribution. The one exception was for the survival analysis, for which sex no longer remained significantly associated with stroke and HbA_{1c} became significant.

TABLE 7 Discrimination and calibration analysis results for the UKPDS-OM using ADDITION-Europe trial cohort data

Event	Centre	aROC curve (95% CI)	Chi-square value from the Hosmer–Lemeshow test	*p*-value from the Hosmer–Lemeshow test
MI	All centres	0.72 (0.66 to 0.79)	9.79	0.28
	Denmark	0.76 (0.66 to 0.85)	7.61	0.47
	The Netherlands	0.69 (0.45 to 0.94)	7.11	0.53
	UK	0.70 (0.59 to 0.81)	8.01	0.43
Stroke	All centres	0.70 (0.64 to 0.77)	9.10	0.33
	Denmark	0.76 (0.68 to 0.84)	7.59	0.47
	The Netherlands	0.79 (0.55 to 1.00)	7.17	0.52
	UK	0.65 (0.54 to 0.76)	6.07	0.64

Source: reproduced open access from Tao *et al.*[96]

TABLE 8 Goodness of fit of baseline risk and covariates of survival regression analysis using ADDITION-Europe trial cohort data

Event	Distribution	BIC	AIC	Covariates significant ($p > 0.10$) from the exponential distribution
MI	Gamma	656.12	585.50	Age, sex, HbA_{1c}
	Exponential	641.45	583.43	
	Log-logistic	648.95	585.13	
	Log-normal	646.98	583.16	
	Weibull	649.24	585.43	
Stroke	Gamma	434.02	364.41	Age, sex
	Exponential	418.54	360.50	
	Log-logistic	426.21	362.39	
	Log-normal	426.27	362.45	
	Weibull	426.21	362.40	

Source: reproduced open access from Tao *et al.*[96]

Cost-effectiveness analysis

In our second analysis we aimed to examine the short- and long-term cost-effectiveness of IT compared with RC among people with screen-detected type 2 diabetes.

Methods

This analysis used data from the two UK centres (Cambridge and Leicester) in the ADDITION-Europe trial.

Costs

These included the cost of delivering the intervention and the routine cost to the NHS of treating diabetes and diabetes-related events observed during trial follow-up. All costs were calculated in UK pounds and monetary values were transformed to the 2009/10 UK national level using the Hospital and Community Health Services Pay and Prices Index,[97,98] which coincided with the census date for outcome assessment.

Cost of delivering the ADDITION intervention

The cost of delivering the intervention included the costs of (1) the design of the materials, and consultation meetings with health professionals regarding development and production; (2) practitioner and patient meetings, which included the costs of delivering the meetings, the time of consultants and educators and the time of doctors and nurses; and (3) extra patient consultations and treatment (including prescription of cardioprotective medication and glucometers with strips) (*Table 9*). The unit costs for the time of doctors, nurses and other health professionals were obtained from standard UK unit cost references.[97,98] The volume of resources used was obtained from the ADDITION study protocol[47] and relevant trial documents. Some costs were estimated from internal accounting during the trial. The cost for extra prescriptions in the IT group (compared with the RC group) was established in treatment algorithms in 2001 at the beginning of the ADDITION study and was transformed to 2009/10 prices. Intervention costs were different in Cambridge and Leicester and were averaged for the purposes of the cost-effectiveness analysis. For the long-term analysis we assumed that the additional prescription costs in the intervention arm would continue to be incurred each year.

Cost of the treatment of diabetes and diabetes-related complications

Unit treatment costs were obtained from published literature (*Table 10*). We collected the annual treatment cost of type 2 diabetes without complications and type 2 diabetes-related complications in the year of the event and in subsequent years. We extracted both inpatient costs (costs of admissions to hospital either as a day case or as an inpatient for ≥ 1 night) and non-inpatient costs (costs of all home, clinic and telephone contacts with GPs, nurses, podiatrists, opticians and dieticians and with eye and other hospital outpatient clinics) from the UKPDS,[100] from where the majority of treatment costs used in this study were taken. In the short-term within-trial cost-effectiveness analysis and the long-term modelling analysis we used an additive method to sum the annual costs of multiple complications.[85]

Utility decrement

We collected published utility decrement data to calculate quality-adjusted life-years (QALYs) as the health outcome measurement for diabetes without complications and diabetes with complications, including ischaemic heart disease, MI, heart failure, stroke, revascularisation, amputation, blindness and renal failure (see *Table 10*).[102] The majority of these utility data were taken from the UKPDS study based on EQ-5D measurement.[104] The same value was assigned to the year of the event and to subsequent years. For patients with multiple events the additive method was used in which we summed utility decrements for each event. Thus, the health state of patients diagnosed with diabetes with no complications was assigned a utility of $1 - 0.22 = 0.78$. Those with diabetes and a history of MI were assigned a value of $1 - 0.22 - 0.055 = 0.725$. Utility decrements were applied until death; thus, a patient experiencing a MI would experience a 0.055 decrement to their utility in the year of the infarction and for every subsequent year.

Short-term cost-effectiveness analysis

We calculated the accumulated costs and QALYs for every year from diabetes diagnosis based on observed events (MI, stroke, revascularisation and amputation) in the ADDITION trial. Both costs and QALYs incurred after the first year were discounted at 3.5% per annum in line with current UK guidelines.[105] To adjust for baseline imbalances we used ordinary least squares regression analyses to calculate costs and QALYs as a function of intervention group (RC/IT), treatment centre (Cambridge/Leicester), age at diagnosis, sex and HbA_{1c} level at baseline. Adjusted incremental treatment costs and QALYs were reported as means and 95% CIs.

Long-term modelling analysis

We used the UKPDS-OM (version 1.3) to perform long-term modelling analysis[85] as it is derived from a UK population and focuses on cardiovascular complications. Our validation analysis described earlier[96] concluded that the model provided a reasonable prediction of the incremental event rate although it tended to overestimate the absolute event rates.

TABLE 9 Costs of delivering IT in the UK in the 5 years following diagnosis (2009/10 £, discounted at 3.5%)

Category	Category	Category	Personnel/item	Time	Other	Unit cost (£)	Cost (£)	Remark
Delivery	Materials	Design	2 associated health professionals	8 hours	–	44[a]	704	
		Practitioner folders	118 doctors and 52 nurses	–	–	8.2	1394	Internal accounting
		Patient folders	513 patients (IT group)	–	–	5.8	2975	Internal accounting
		Handouts	–	–	–	–	446	Internal accounting
		Consultation meeting	1 associated health professional (and 6 patients)	2 hours	£5 for travel	44[a]	93	Patient cost excluded
		Focus group meeting	3 consultants	3 hours	£5 for travel	121[b]	1104	
			3 nurses	3 hours	£5 for travel	44[a]	411	
	Preparatory meetings	Cambridge (in general practices)	2 consultants	3 hours × 100		121[b]	72,600	
			4.5 doctors	1.5 hours × 100		121[b]	81,675	
			2 nurses	1.5 hours × 100		30[c]	9000	
		Leicester (in hospitals)	2 educators	6 hours × 6	£54.1 for logistics × 6	44[a]	3493	
Subtotal							173,895	
Extra consultations		Cambridge ($n = 452$)	10-minute GP visit	3 visits × 3 years		185[d]	121,091	Annual discount rate 3.5%
			10-minute nurse visit	3 visits × 3 years		30[c]	19,637	
		Leicester ($n = 61$)	GP initial visit + GP extra visits + annual review visit	60 minutes + 20 minutes × 4 + 30 minutes		165[e,f]	28,534	
			2 visits + annual review visit	(20 minutes + 30 minutes) × 4		165[e,f]	20,748	

Category	Category	Category	Personnel/item	Time	Other	Unit cost (£)	Cost (£)	Remark
Subtotal							190,010	
Extra treatments		Cambridge ($n = 452$)	Extra prescription of SUs, ACE inhibitors and statins		Total cost = £262.5 per patient	262.5	118,650	Internal accounting
		Leicester ($n = 61$)	Extra prescription of SUs, ACE inhibitors and statins					Cost = £262.5 per patient
	262.5		16,013	Internal accounting				
	95% of participants issued with a glucometer and box of 50 strips at diagnosis		Glucometer cost = £1438; strips cost = £2968	4406	4406	Internal accounting		
Subtotal							139,069	
Total							502,974	
Cost per person							980	

SU, sulphonylurea.

a Cost of advanced nurse time (includes lead specialist, clinical nurse specialist and senior specialist) per hour: £44 (source: per hour of advanced nurse time, with qualification costs; table 10.7[98]).

b Cost of health professional or consultant per hour: £121 (source: per hour of General Medical Services activity, with qualification costs; table 10.8b[98]).

c Cost per GP nurse or research assistant hour: £30 (source: per hour of nurse (GP practice), with qualification costs; table 10.6[98]).

d Cost per GP patient contact hour: £185 (source: per hour of GP patient contact, with qualification costs; table 10.8b[98]).

e Cost per hour of hospital nurse: £52 (source: per hour of nurse 24-hour (includes staff nurse, registered nurse, registered practitioner) patient contact, with qualification costs; table 14.4[98]).

f Cost per hospital doctor patient contact hour: £169 (source: per hour of consultant medical patient contact, with qualification costs; table 15.5[98]).

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TABLE 10 Unit costs (2009/10 £) and utility decrements for diabetes and diabetes-related complications

Event	Cost, year of event (£)		Cost, subsequent years (£)	Source	Utility decrement	Source
	Fatal	Non-fatal				
Type 2 diabetes	–	494.5	494.5	Clarke *et al.*[100]	–0.220	Schwarz *et al.*[101]
Ischaemic heart disease	–	3558.4	1175.2	Clarke *et al.*[100]	–0.090	Clarke *et al.*[102]
MI	2295.6	6861.8	1129.8	Clarke *et al.*[100]	–0.055	Clarke *et al.*[102]
Heart failure	3968.4	3968.4	1391.1	Clarke *et al.*[100]	–0.108	Clarke *et al.*[102]
Stroke	5786.8	4196.9	793.4	Clarke *et al.*[100]	–0.164	Clarke *et al.*[102]
Revascularisation	–	4943.1	316.3	Valentine *et al.*[103]	–0.059	Valentine *et al.*[103]
Amputation	13,664.2	13,664.2	788.7	Clarke *et al.*[100]	–0.280	Clarke *et al.*[102]
Blindness	–	1791.7	758.9	Clarke *et al.*[100]	–0.074	Clarke *et al.*[102]
Renal failure	30,599.2	30,599.2	30,599.2	Schwarz *et al.*[101]	–0.263	Clarke *et al.*[102]
CVD death	3724.3	–	–	Valentine *et al.*[103]	–	

Costs extracted from the UKPDS study were based on participant hospital records and a survey of 3488 UKPDS participants in 1996–7 from which inpatient and outpatient costs were predicted. From this a representative cost per patient per year was estimated for each complication/event. The cost estimates incorporate an expected length of stay in secondary care and home, clinic and telephone contacts with GPs, nurses and allied health professionals.
Source: reproduced from Tao *et al.*,[99] under the Creative Commons Attribution 4.0 International licence (CC BY 4.0).

Information from ADDITION trial participants at baseline was entered into the UKPDS-OM, including age at diagnosis, sex, ethnicity, duration of diabetes, weight, height, smoking status, systolic blood pressure, HbA_{1c}, total cholesterol, HDL cholesterol and years since pre-existing CVD events. Values for smoking status, systolic blood pressure, HbA_{1c}, total cholesterol and HDL cholesterol were also included from measurements taken at 1 and 5 years' follow-up. For the years in between (2, 3 and 4 years) and for future years, the risk factor values were simulated by the UKPDS outcomes risk equations, that is, left to propagate through the long-term model. Data on AF, PVD, ischaemic heart disease, congestive heart failure, amputation, blindness and renal failure at diagnosis were not collected in the ADDITION study. Given that all participants were newly diagnosed, all values were set to zero for these variables.

To deal with missing data, multiple imputation was applied using the Markov chain Monte Carlo method assuming an arbitrary missing pattern.[90,106] A multivariate normal distribution was used to impute missing values of weight, height, smoking status, cholesterol, HDL cholesterol, systolic blood pressure and HbA_{1c}. In the UKPDS-OM the required ethnicity categories were white Caucasian, Afro-Caribbean and Asian-Indian. There were some unknown or unclassifiable values, for example mixed white + African, mixed white + Asian, etc., in the ADDITION-UK trial. It was not suitable to replace these using multiple imputation and so we excluded these participants from the analysis ($n = 25$). After imputation, if the imputed HDL cholesterol value was higher than the cholesterol value (which was logically impossible), we assumed that HDL cholesterol (mmol/l) = cholesterol – 0.1 (five cases at baseline; one case at final follow-up). Five imputations were taken for each participant and we combined the results with Rubin's rules.[90,92]

Using the UKPDS-OM we performed a patient-level modelling analysis on time horizons of 10, 20 and 30 years with a discount rate of 3.5%. We report the 30-year simulation as the main result. For each time horizon, 1000 inner loops and 100 bootstraps were conducted.[107] Means and CIs at the patient level were used to conduct a further bootstrap analysis, adjusting for centre, age at diagnosis, sex and HbA_{1c} at baseline as per the short-term analysis. Incremental cost-effectiveness ratios (ICERs) for the 10-, 20- and 30-year simulations are reported.

Analysis of uncertainty

Decision uncertainty is illustrated with a scatterplot of incremental cost–QALY pairs and the cost-effectiveness acceptability curve.[108] One-way sensitivity analyses were performed on treatment costs for events (±10%), utility decrements (±10%) and the discount rate (0%, 5%) using the 30-year simulation data with the results shown as a tornado diagram.[109] We also explored two scenarios with intervention costs of £750 (three-quarters of the cost) and £500 (half of the cost) to represent lower set-up costs (e.g. making use of previously designed materials).

Statistical analyses of within-trial data were performed using SAS v9.3. Analysis of long-term modelled scenarios was conducted using the UKPDS model and Microsoft Excel® 2013 (Microsoft Corporation, Redmond, WA, USA).

Results

Of 1026 participants in the ADDITION-UK study, two withdrew from the study and 25 were excluded from the modelling analysis because of unknown or unclassifiable ethnicity. Thus, 1024 participants were included in the short-term cost-effectiveness analysis and 999 were included in the long-term modelling analysis.

The total cost of delivering the IT intervention in ADDITION-UK was £502,974. This equates to £981 per person (£339 for materials and preparatory meetings, £370 for extra patient consultations and £272 for extra treatments) (see *Table 9*). The cost by centre was £90,379 (£1482 per person) in Leicester and £412,595 (£913 per person) in Cambridge.

Short-term cost-effectiveness analysis

There were no differences in cumulative QALYs over any time horizon from 1 to 5 years (*Table 11*). The cumulative incremental cost to the NHS (intervention cost and other expenditure incurred as a result of cardiovascular complications) ranged from £285 over a 1-year time horizon to £935 over 5 years (discounted at 3.5%). As IT was more costly and led to virtually no incremental health gains compared with RC over the first 5 years, we estimate that IT of people with screen-detected diabetes is, on average, not cost-effective in the short term.

Long-term cost-effectiveness analysis

Intensive treatment was associated with positive incremental QALYs in the long term (0.0465 by 30 years, statistically significant at 20 years and beyond). The incremental cost of IT compared with RC at 10, 20 and 30 years also increased over time to £1745 at 30 years, yielding a point estimate ICER of £82,250 at 10 years, which fell to £35,000 at 20 years and rose slightly to £37,500 at 30 years (see *Table 11*). The unadjusted results suggest a lower point estimate QALY gain in the IT arm, which is reversed once adjustment is made for baseline differences. The result suggests that, although cost-effectiveness improves over time, it is still above commonly accepted thresholds in the UK (defined as reaching an ICER of £30,000 per QALY gained),[105] even over a 30-year time horizon (*Figure 14*).

Analysis of uncertainty

Uncertainty and sensitivity analyses were performed on the predicted 30-year results. The cost-effectiveness plane based on bootstrap sampling shows the scatterplot of cost and QALY pairs under the base case (intervention cost of £981 per person) and two alternative scenarios with lower IT intervention costs (*Figure 15*) (£750 and £500 per person). Under these scenarios, 30-year point estimate ICERs are £37,503, £32,550 and £27,178. The cost at which the ICER falls to £30,000 is £631. If the intervention could be delivered ≤ £631 per patient, it may be considered cost-effective.

TABLE 11 Cumulative cost and QALYs in years following diabetes diagnosis, adjusted by centre, age, sex and HbA_{1c}[a]

	RC			IT						
Time horizon	*n*	Cost, mean (SE) (£)	QALYs, mean (SE)	*n*	Cost, mean (SE) (£)	QALYs, mean (SE)	Adjusted incremental cost (95% CI) (£)	Adjusted incremental QALYs (95% CI)	ICER (£)	*P*(ICER < £30,000) (%)[b]
1	511	536.6 (0.8)	0.779 (0.000)	513	826.4 (1.7)	0.778 (0.000)	285.3 (199.3 to 371.3)	0.0000 (–0.002 to 0.002)	ICER was infinite or IT group was dominated at all years	
2	511	1138.7 (2.0)	1.531 (0.000)	513	1426.0 (2.0)	1.530 (0.000)	278.8 (151.4 to 406.2)	0.0000 (–0.004 to 0.004)		
3	511	1705.8 (2.9)	2.256 (0.000)	513	2298.7 (3.0)	2.254 (0.000)	578.3 (388.6 to 768)	0.0000 (–0.006 to 0.006)		
4	501	2239.3 (3.4)	2.955 (0.000)	509	3014.9 (3.6)	2.954 (0.000)	754.2 (531.5 to 976.9)	–0.0012 (–0.009 to 0.007)		
5	451	2804.4 (4.7)	3.631 (0.000)	455	3772.7 (4.7)	3.627 (0.000)	934.9 (653.6 to 1216.2)	–0.0040 (–0.016 to 0.008)		
10	501	6156.52 (20.02)	6.450 (0.138)	498	7435.86 (11.83)	6.400 (0.140)	1189.80 (1126.26 to 1244.96)	0.0140 (–0.0013 to 0.0291)	82,251.60	1.0
20	501	11,174.53 (31.27)	9.324 (0.243)	498	12,683.64 (20.70)	9.157 (0.243)	1495.66 (1368.31 to 1624.84)	0.0428 (0.0013 to 0.0846)	34,934.23	36.9
30	501	13,181.37 (22.38)	10.076 (0.293)	498	14,768.63 (29.19)	9.818 (0.290)	1745.31 (1564.44 to 1929.12)	0.0465 (0.0014 to 0.0929)	37,503.41	31.4

a Results for time horizon of 1–5 years are based on within-trial data. Results for time horizon of 10, 20 and 30 years are based on results extrapolated using the UKPDS model.
b Probability that the ICER is < £30,000 per QALY gained.
Source: reproduced from Tao *et al.*,[99] under the Creative Commons Attribution 4.0 International licence (CC BY 4.0).

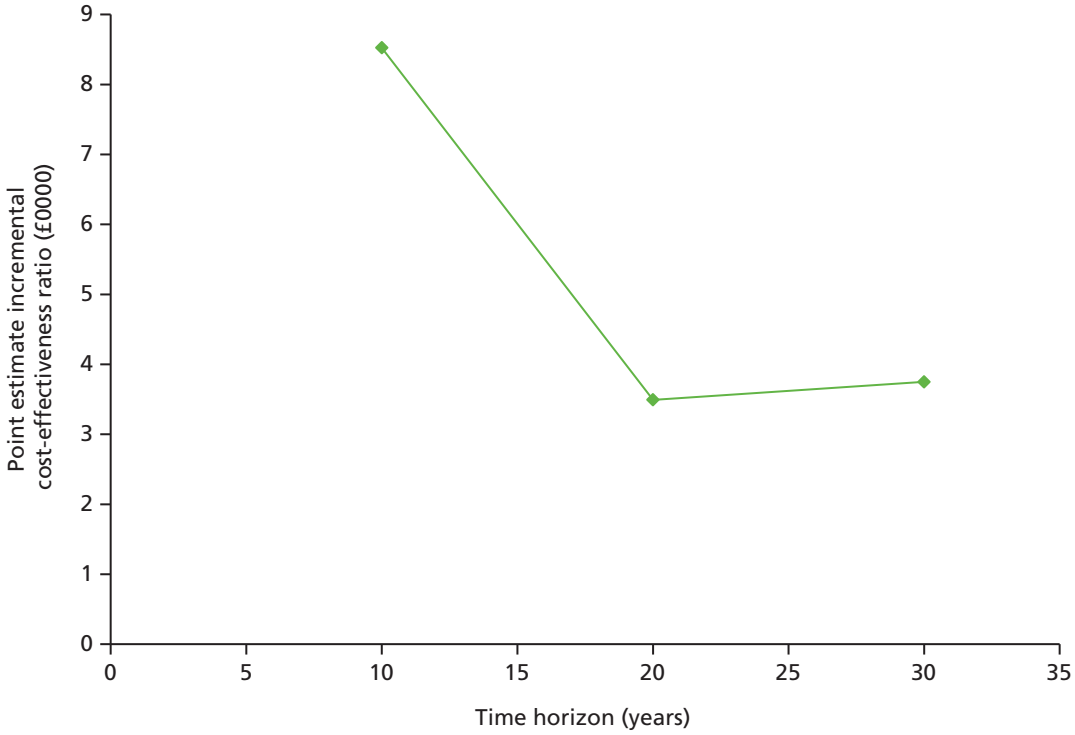

FIGURE 14 Broken line chart showing the simulated ICERs at 10, 20 and 30 years for the ADDITION-Europe intervention. Source: reproduced from Tao *et al.*,[99] under the Creative Commons Attribution 4.0 International licence (CC BY 4.0).

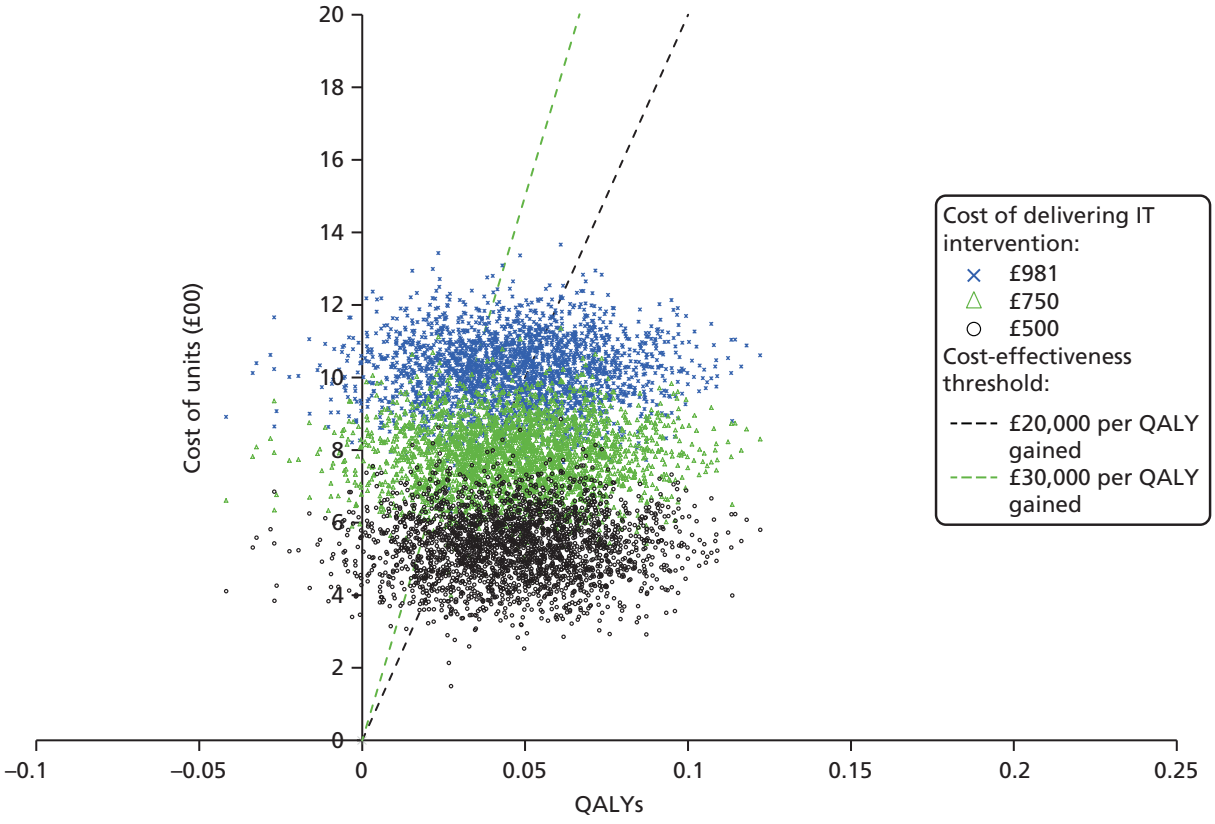

FIGURE 15 Cost-effectiveness plane showing pairs of incremental costs and QALYs from bootstrap samples using three different costs of delivering the IT intervention. The points to the right of the lines are cost-effective. Source: reproduced from Tao *et al.*,[99] under the Creative Commons Attribution 4.0 International licence (CC BY 4.0).

Under all three scenarios, the majority of points are in the north-east quadrant, suggesting that IT is nearly always both more expensive and more effective (generates more QALYs) than RC, although the proportion of the probability mass in the north-west quadrant suggests that there is greater uncertainty around whether or not incremental QALYs are positive. The probability of cost-effectiveness according to the three different treatment costs (£981, £750 and £500) is 51.1%, 60.9% and 70.4% at a £20,000 per QALY gained threshold and 65.1%, 71.1% and 77.0% at a £30,000 per QALY gained threshold, respectively (*Figure 16*).

One-way sensitivity analyses varying unit treatment costs, utility decrements and the discount rate showed that the discount rate had the biggest impact on the ICER, with the impact of variations in utility decrements and treatment costs being minimal (*Figure 17*).

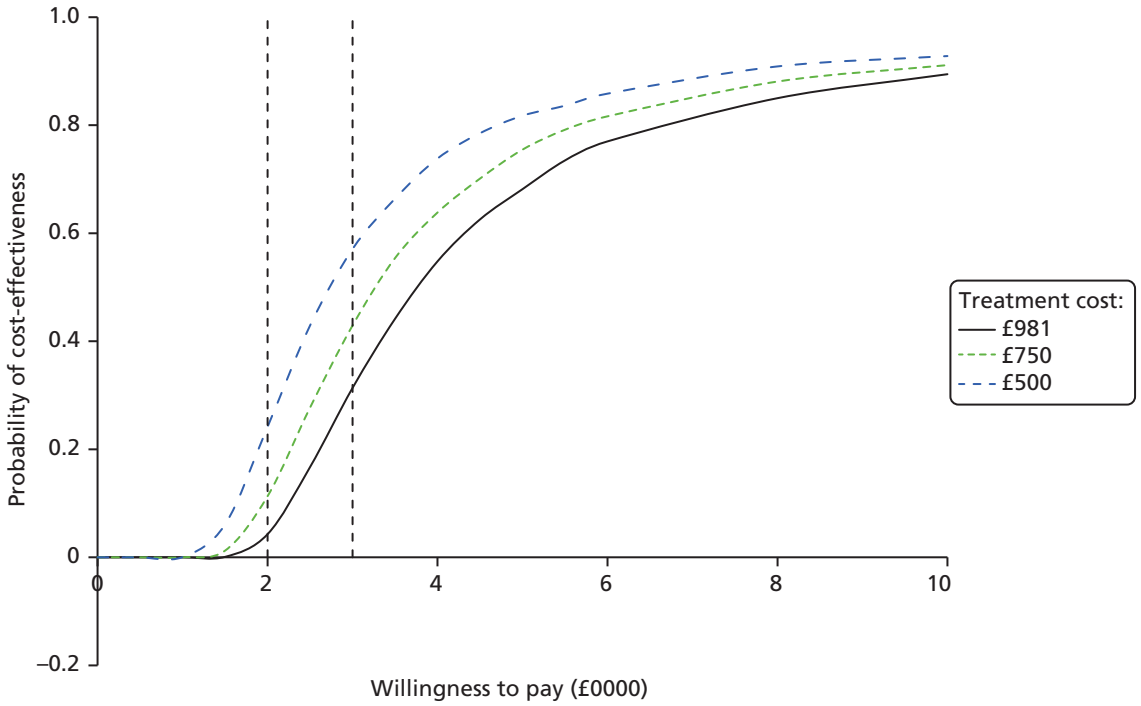

FIGURE 16 Cost-effectiveness acceptability curves showing the probability of IT being more cost-effective than RC based on net benefit values from bootstrap samples using three different costs of delivering IT. The two dotted lines show the cost-effectiveness acceptability thresholds of £20,000 and £30,000 per QALY. Source: reproduced from Tao *et al.*,[99] under the Creative Commons Attribution 4.0 International licence (CC BY 4.0).

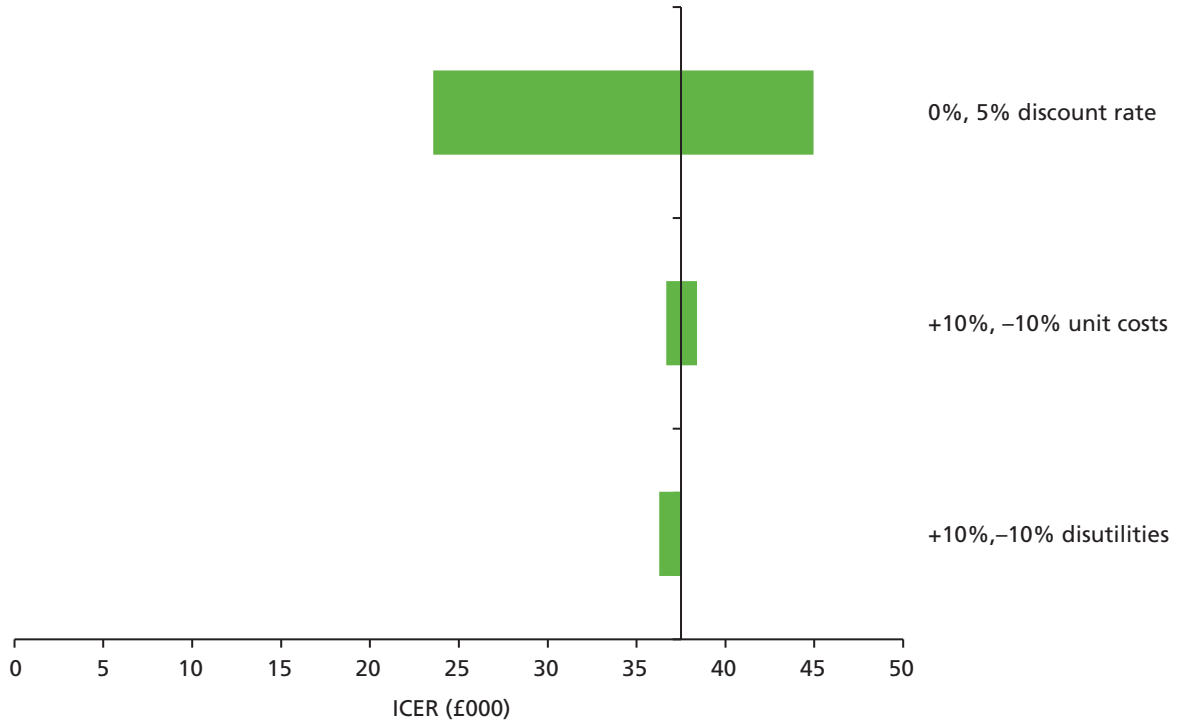

FIGURE 17 Tornado diagram showing the influence of changing different parameters that contribute to the ICER in the long-term cost-effectiveness modelling analysis. The choice of discount rate has the greatest impact on the ICER (lower discount rate, unit costs and utility decrements all associated with a higher point estimate ICER). Source: reproduced from Tao *et al.*,[99] under the Creative Commons Attribution 4.0 International licence (CC BY 4.0).

Chapter 5 Discussion and conclusions

Change in treatment and risk factors

Results from the ADDITION-Europe trial show that screening for type 2 diabetes and early intensive multifactorial treatment of individuals found to have screen-detected diabetes is feasible in primary care. Screening identifies people with high levels of modifiable cardiovascular risk factors. The proportion of participants prescribed one or more blood pressure-, lipid- and glucose-lowering drugs and aspirin increased significantly from baseline to 5 years' follow-up in both study groups. There were small differences in treatment between groups at 5 years favouring the IT group.

In both the IT group and the RC group, intermediate outcomes such as blood pressure and cholesterol improved considerably in the 5 years following diagnosis by screening; weight and glycaemia levels did not increase. In terms of change from baseline, and absolute levels of risk factors at 5 years, our results compare well with those of other trials in which patients were recruited at diabetes diagnosis and followed for 6 years.[110,111] However, the between-group differences observed at 1 year,[49] which were clinically significant, were not maintained at 5 years and differences were smaller than those achieved in similar studies.[29,110] It is possible that adherence to treatment targets were suboptimal in this pragmatic trial. In three of the centres, the screening algorithm included the use of risk scores encompassing treatment for high blood pressure as one of the variables to predict diabetes risk. This limited the achievable differences in blood pressure levels between groups. Indeed, at baseline in the UKPDS, which began recruitment 20 years before the ADDITION-Europe study, 12% of patients were prescribed antihypertensive medication and 0.3% were prescribed lipid-lowering medication. In the ADDITION-Europe study, at baseline, 45% of patients were prescribed antihypertensive medication and 16% were prescribed lipid-lowering medication. Our trial was undertaken during a time of improvements in the delivery of diabetes care in general practice. This included the introduction of evidence-based guidelines in Denmark[112] and the Netherlands[113] and the Quality and Outcomes Framework for primary care in the UK.[114] Again, these guidelines and frameworks are likely to have reduced the achievable differences in treatment and risk factors between groups.

Despite increasing age and duration of diabetes there was a significant decline in 10-year modelled CVD risk in the 5 years following diagnosis in both the RC group [–5.0% (SD 12.2%)] and the IT group [–6.9% (SD 9.0%)]. Within all four centres the modelled CVD risk was lower in the IT group than in the RC group at 5 years. Comparable improvements in the CVD risk factors that drive modelled CVD risk have been reported among newly diagnosed patients enrolled in lifestyle interventions over 12 months.[54,115] Such changes were also observed among clinically diagnosed diabetes patients in the UKPDS trial at 6 years of follow-up.[110]

Cardiovascular outcomes and all-cause mortality

The intervention to promote intensive target-driven management of individuals with screen-detected diabetes was associated with a non-statistically significant 17% relative reduction in the incidence of a composite cardiovascular event end point over 5 years. For all components of the primary end point, differences favoured the IT group. Differences were smallest for stroke and largest for MI. Cardiovascular event rates began to diverge after 4 years of follow-up. We found no evidence of an increased risk of adverse events including self-reported hypoglycaemia or mortality. The incidence of cardiovascular events in the ADDITION-Europe study (8.5% in the RC group) was lower than expected and less than event rates among newly diagnosed patients in the UKPDS (12.1%).[110]

The combined mortality hazard ratio for the IT group compared with the RC group was 0.91 (95% CI 0.69 to 1.21). The heterogeneity in results between countries was not statistically significant. In the UK there were significantly fewer deaths in the IT group. In Denmark there was a non-significant reduction in cumulative risk in the RC group. The mortality rate (6.7% in the RC group) was also lower than expected. In the Hoorn study[116] the mortality rate was 25% over 10 years in screen-detected patients and in newly diagnosed patients in Denmark[111] the mortality rate was 33% over 7.4 years. The mortality rate in the ADDITION-Europe trial was similar to that seen in the Danish general population (without diabetes) of the same age between 1995 and 2006.[117] As before, this is most likely because of the high quality of care that was delivered to patients early in the course of the diabetes disease trajectory in both the RC group and the IT group.

Microvascular outcomes

Trial results for microvascular outcomes were similar to those for the cardiovascular outcomes. At 5 years, increases in prescribed treatment and improvements in cardiovascular risk factors were not associated with significant reductions in microvascular events. Differences between study groups favoured the IT group, with differences smallest for neuropathy and greatest for retinopathy. As for the CVD outcomes, the frequency of microvascular complications at 5 years' follow-up was lower than expected. It was also lower than the reported frequencies among individuals with diabetes for a similar length of time.[32] We concluded that this was most likely because of the early detection of diabetes and the high-quality treatment that we observed in both study groups.

In terms of the nephropathy outcomes, 18.5% of ADDITION-Europe participants had any albuminuria at diagnosis.[50] This figure is not directly comparable to the estimate of 7.2% of patients with microalbuminuria at baseline in the UKPDS as a higher level of urinary albumin excretion was used to define microalbuminuria in the UKPDS.[32] The rate of progression of albuminuria in the ADDITION-Europe study, from 18.5% at baseline to 23.5% (1% per year), was half that observed in the UKPDS, despite ADDITION-Europe participants being older (mean age 60 years vs. 52 years in the UKPDS) and more likely to have high blood pressure at diagnosis.[32] Similarly, higher progression rates were reported in the VADT (Veterans Affairs Diabetes Trial),[118] ACCORD[119] and ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation)[120] trials. However, these studies recruited older people who had long-standing diabetes.

We observed a beneficial increase in eGFR in both the IT group and the RC group. This is probably linked to the treatment of multiple cardiovascular risk factors, including lipid-lowering treatment, glucose-lowering treatment and ACE or ARB treatment.

As with the nephropathy outcomes, retinopathy frequency was lower than expected. Just 12% of ADDITION-Europe RC patients developed retinopathy after 5 years of follow-up. In the UKPDS, 37% of patients had retinopathy at diagnosis and a further 22% developed the condition during the next 6 years.[31] Again, this is likely to reflect early treatment in the lead time between screen detection and clinical diagnosis.

A similar trend was observed for neuropathy, with 5% of the population reporting peripheral neuropathy at 5 years, with no difference between groups. This is markedly lower than the 11% reported in a population with an average diabetes duration of 16 years.[67] However, caution should be exercised in the interpretation of this result. We used the Michigan neuropathy questionnaire, which may not be sufficiently sensitive[121] or reliable to detect early progress of neuropathy and/or differences between the IT group and the RC group.[122] There was heterogeneity in the effect size estimates for peripheral neuropathy across all centres, which supports this view.

Patient-reported outcomes

Compared with RC, IT was not associated with differences in any PROMs (health status, well-being, quality of life and treatment satisfaction) after 5 years of follow-up. Health status, as measured by the EQ-5D, did not change between diagnosis and follow-up. Again, we conclude that the time period within which our trial was undertaken, for example when targets for cholesterol and blood pressure became stricter for diabetes patients, resulted in smaller than expected differences between study groups.

Baseline health-related quality of life was high in our cohort (median EQ-5D score of 0.85). EQ-5D estimates remained stable over follow-up in spite of participants' age increasing by 5 years. This is an important finding, particularly as the burden of treatment increased over this time. In a study among 1136 Dutch people with type 2 diabetes (mean age 64.9 years), the average EQ-5D score was 0.74 (SD 0.27).[123] Older patients, women and those with a longer duration of diabetes reported lower levels of health-related quality of life. In a cluster-randomised trial in 55 Dutch general practices, there was no change in diabetes-related health over 1 year between standard and intensive multifactorial therapy, although a negative effect on the SF-36 social functioning score could not be ruled out.[124] In the UKPDS, intensively treating blood pressure and blood glucose in newly diagnosed diabetes patients did not adversely affect health status.[39] In an ACCORD substudy, there was a difference in change in the SF-36 physical component score and the DTSQ scale over 4 years between the standard group and the intensive glucose-lowering group.[40] However, the absolute difference in the SF-36 score was only 0.5 units, considerably less than the general threshold of 3–5 points recognised as an important difference. ACCORD participants differed from ADDITION-Europe patients in that they were older, they had had clinically diagnosed diabetes for an average duration of 9–10 years, 35% were on insulin treatment and they had a different ethnic background. Overall, the findings from other studies are largely in line with the results from the ADDITION-Europe trial, that is, no significant differences in PROMs between treatment groups.

It is worth noting that, although pooled analyses from all centres showed no differences between the treatment groups, for some PROMs the results in Leicester clearly favoured the IT group. This might be linked to the nature of the intervention. This was delivered by an intermediate care team at a community-based diabetes specialist care facility. Patients also received weight management advice, a glucometer at diagnosis and the DESMOND structured education programme.[53] Other ADDITION-Europe centres relied on existing primary care teams to achieve the IT targets.

Validation of the UK Prospective Diabetes Study outcomes model

The UKPDS-OM had moderate discriminatory ability to predict non-fatal MI and stroke among ADDITION-Europe participants. However, the model overestimated absolute risk. As diabetes patients begin to be diagnosed earlier in the disease trajectory, and their CVD risk is therefore lower, the UKPDS-OM may need updating for CVD risk prediction in contemporary diabetes populations.

The accuracy of the UKPDS-OM (version 1.3) in estimating the risk of non-fatal MI and stroke varied between countries. It performed particularly poorly in the Netherlands compared with the UK and Denmark. This could be because of a difference in baseline characteristics between the ADDITION-Europe cohorts and the UKPDS cohort. The UKPDS population had some baseline characteristics associated with a lower risk of CVD, including lower mean age, mean body mass index and mean systolic blood pressure, and some characteristics associated with a higher risk, for example a higher percentage of men, a lower mean HDL cholesterol level and a slightly higher mean HbA_{1c} level. The UKPDS also excluded people with previous CVD. However, the purpose of the UKPDS-OM is to provide coefficients for the inputted risk factors. As such, the accuracy of the predicted risk should be relatively insensitive to the baseline characteristics. We could reject a model on the basis of baseline characteristics only if the two populations

were very different, for example predicting the risk of CVD based on a cohort of individuals aged 80 years and applying these risks to a cohort of individuals aged 20 years.

The most likely reason for the overestimation of risk is because of improvements in treatment between the time that the UKPDS data were collected (1977–97) and the time of ADDITION-Europe data collection (2002–6). The ADDITION-Europe intervention also included a much more comprehensive set of preventative treatments offered from an earlier stage in the disease. Our results are consistent with those of other studies examining the predictive ability of the UKPDS and Framingham models in populations with lower disease rates.[88,125]

As AF and PVD data were not collected at baseline, these variables were set to zero in the UKPDS-OM. PVD was a risk factor only for amputation in the UKPDS-OM and so the omission of these data should not affect our results. AF is a risk factor for stroke in the UKPDS-OM;[85] missing data for this variable are likely to underestimate stroke risk. However, in one study the prevalence of AF ranged from 1.2% to 2.8% among people aged 60 years[126] and so missing data for this variable are unlikely to have a large effect on our results.

The UKPDS-OM performed differently in predicting the differences in CVD risk factors between the intervention groups. It underestimated the incremental risk of MI between groups and slightly overestimated differences for stroke. Assessment of the cost-effectiveness of health-care interventions necessitates knowledge of the increment between the comparator groups, rather than the difference in absolute levels of each group. It is ultimately a subjective decision whether or not these differences are sufficient to render the UKPDS-OM unsuitable for extrapolating the ADDITION-Europe data. The insight from our work shows that, if the UKPDS-OM is unadjusted, it will underestimate any reductions in MI risk attributable to IT and consequently potentially underestimate the cost-effectiveness of the intensive intervention (i.e. overestimate the ICER). The small disparity in the predicted compared with observed risk of stroke may be of limited consequence because of the effects of discounting.

As stated above, the UKPDS-OM had moderate discriminatory ability for predicting non-fatal MI and stroke. The aROC curve ranged from 0.65 to 0.79 and goodness of fit was acceptable. The UKPDS-OM is based on a set of Weibull survival regression equations. For the model to perform successfully, it is important to choose a suitable baseline distribution and relevant covariates. The best-fit model for the ADDITION-Europe data was an exponential distribution. Our analyses showed that age, sex and HbA_{1c} level were important covariates and should be included in the UKPDS-OM.

Cost-effectiveness results

Cumulative costs and QALYs over a time horizon of 1–5 years indicated that IT was not cost-effective over the short term. This result may be linked to the improvements in cardiovascular risk factors that were observed in both trial groups between baseline and follow-up.[55] In the long-term modelling analysis, the 30-year simulated ICER was greater than the recommended UK National Institute for Health and Care Excellence threshold (£20,000–30,000 per QALY),[105] suggesting that interventions to promote delivery of intensive multifactorial treatment in the ADDITION-UK study were not cost-effective compared with RC in the long term.

The intervention becomes cost-effective only if it can be delivered at a cost of < £631 per participant. The cost of delivering IT in our analysis (£981 per participant) was calculated based on the study protocol,[47] which covered all aspects of the intervention. This figure may overestimate the cost of reproducing the intervention as trial materials would not require complete redevelopment (although some adaptation to local needs would be likely). Alternative approaches to influencing practitioner behaviour, such as point-of-care reminders and decision aids, might be cheaper than practice visits by specialists. Furthermore, treatment costs were based on payments made to GP practices according to predicted costs based on the

study protocol rather than actual costs. These costs may have been overestimated as GPs prescribed less medication than expected.[55] Finally, as per our validation analysis, the UKPDS tends to overestimate the risks of cardiovascular events, which could have led to overestimation of the ICER.

Our finding of a general improvement in cost-effectiveness over the long term is exemplary of the nature of preventative treatments. As most of the costs of such interventions are borne 'up front', and chronic disease complications take a long time to develop, health and cost benefits are usually seen only over the longer term. We used a 30-year modelling horizon in our analyses as the average age of participants at baseline was 60 years. We therefore assumed that a 30-year time horizon would equate to a lifetime horizon for the majority of individuals. A key question for policy-makers is whether or not they are prepared to consider a lifetime horizon in their decision-making. The optimal time horizon for any economic evaluation is one that is sufficient to capture all impacts on incremental costs and outcomes.[127] In our case, this suggests a lifetime horizon. However, investing in an intervention now means spending the money from this year's budget without seeing any benefit for many years. During this time personnel, governments and government policy may change. Introducing such polices is therefore a challenge given pressures (political or otherwise) to show the benefits from investment decisions over the short to medium term.

The DESMOND study examined the benefits of a structured education and self-management programme for people with newly diagnosed diabetes in the UK from 2004 to 2006.[53,128] The authors found that the intervention was likely to be cost-effective compared with usual care over a lifetime horizon (ICER £5387). One reason for the difference between our results and the results of the DESMOND study and other studies might be the early disease stage of participants in our study. Early detection might help prevent complications in the future by attenuating disease progression. However, intervening 'too early' might be less cost-effective. For example, intervening when an individual presents with diabetes-related symptoms may reduce the risk of an event that would otherwise have occurred in 5 years' time. Intervening at an earlier stage, after detection of IGT, for example, may prevent an event that would not otherwise occur for 20 years. In general, individuals and society have a preference for benefits now rather than in the future. As such, they would value preventing an event in the next 5 years more highly than preventing the same event in 20 years' time.

Strengths and limitations

The ADDITION-Europe study participants were drawn from representative population-based samples in three different European countries. Practices were recruited from a large geographical area in each country. Randomised practices (26% of those invited) were nationally representative in terms of key clinical and sociodemographic characteristics.[43,48,49] However, recruitment was non-random and the generalisability of our findings to other settings should be considered with caution. Furthermore, participants were predominantly white (93%), which might limit the extrapolation of our data to more ethnically diverse regions. Individuals were identified using a range of different screening programmes and were diagnosed according to 1999 WHO criteria.[56]

The study intervention included algorithms and targets based on well-established trial data and we used a range of methods associated with changes in practitioner and patient behaviour. We randomised general practices rather than individuals (as the intervention was delivered mainly by practitioners) to minimise the risk of contamination. We achieved high levels of participant retention and independently adjudicated end-point ascertainment in both trial groups (99.9%). Trained staff were unaware of study group allocation. We assessed clinically important outcomes using standardised equipment and protocols. For the modelled CVD risk analysis, we used the latest version of the UKPDS risk score (version 3). This was derived from > 40,000 patient-years of data and 1115 CVD events.[75] For PROMs we used both generic and diabetes-specific measures.

There was variation between centres in the approaches to population-based screening for diabetes. However, all participants were diagnosed according to WHO guidelines.[56] Furthermore, the differences in screening programmes do not affect the internal validity of the study as they apply equally to both study groups in each centre. Rather, they increase the external validity or generalisability of the trial by including patients detected using a range of different screening programmes. There was also variation in the methods used to encourage the general practice teams to follow the treatment algorithms. However, there was one common set of treatment targets and algorithms for the IT group in all centres and, as stated above, this heterogeneity should increase generalisability without diminishing internal validity. We pooled centre-specific estimates using fixed-effects meta-analysis and formally tested for heterogeneity between centres using the I^2-statistic. Although we acknowledge that this test has limited power, the primary outcome and all of its components did not exhibit significant between-centre heterogeneity and so we have not formally explored in this report explanations for any observed heterogeneity. Furthermore, there are a number of other centre-level covariates other than those previously mentioned relating to the different health systems in each country that may have contributed to variation in participant characteristics and response to the intervention. The different approaches taken in each centre to promote IT of multiple risk factors represent complex interventions. As the study was pragmatic, it is not possible to determine which aspects of the interventions might have been effective and which aspects might have been less so.

Cluster randomisation occurred before screening and patient recruitment. This design feature can introduce a difference between groups in participant characteristics. Although individuals in the IT and RC groups were well matched overall, in Denmark the intervention may have influenced the number and type of patients recruited to the IT group. Staff undertaking opportunistic screening may have conducted more tests in individuals at high CVD risk as they were aware of the potential benefits of early detection and treatment. This may have attenuated the effects of the intervention and might explain some of the differences in results between centres. Differences appeared to be present but might not have been statistically significant because of the limited power of the test of heterogeneity. Our intracluster correlation coefficients were small[55] and did not adversely affect study power. Methods of screening, laboratory testing and outcome assessment were standardised across study groups in each centre in this pragmatic trial but did differ between centres. This may also have contributed to some of the observed heterogeneity. Measurement of biochemical outcomes differed slightly between baseline and follow-up in two centres but not between groups. Reassuringly, interlaboratory validation suggested that methods were consistent between centres. Primary end points were adjudicated using a standardised manual and case report form in each centre. Other potential sources of heterogeneity in our trial arise from variation between centres in participant characteristics. This might be because of differences in the screening programmes and underlying populations, different modes of delivering the intervention and other unmeasured factors.

For the CVD outcomes analyses there were few differences between those with and those without follow-up data. For the modelled CVD risk analysis, 27% of data were missing. Sensitivity analyses suggested that the primary analysis was likely to represent an accurate ITT analysis. We accounted for missing data at baseline using the missing indicator method and assumed that those lost to follow-up had a 10% higher risk than those with available data at 5 years. There was qualitatively no change to the final results and the difference in modelled CVD risk between groups remained significant. It is likely that we overestimated the level of modelled CVD risk in our contemporary trial cohort as the UKPDS model is based on a historical cohort diagnosed 20 years before the ADDITION-Europe study participants. However, this would not have affected the effect size estimate differentially by group. There was no difference between self-reported AF at 5 years between the RC group (13.3%) and the IT group (14.0%), suggesting that the exclusion of this variable from the UKPDS model was unlikely to affect our findings.

For the microvascular outcomes analysis there were differences in the proportions of individuals with data for different outcomes at 5 years. For example, 77% had retinopathy data and 95% had eGFR data. There was some evidence of healthy volunteer bias when examining the characteristics of participants with and

without microvascular outcome data; however, absolute differences were small [e.g. 0.19% (2 mmol/mol) for HbA_{1c}]. There were no differences between the IT group and the RC group in terms of the proportion with missing microvascular data. However, the prevalence of retinopathy and neuropathy might have been underestimated considering the adverse risk profile of individuals with missing data for these outcomes. Microvascular outcome assessment and laboratory testing were standardised across participants from the IT and RC groups in each centre but did differ between centres; for example, there was no standardised procedure for retinal photography. Some centres used routine secondary data sources, whereas others collected retinal data during remeasurement of participants at the 5-year follow-up examination. This variation might have led to differences in the precision of outcome assessment between centres but not between study groups. Furthermore, we assessed only gradable photos and they were coded using a standard scale (ETDRS[65]) by three experienced ophthalmologists who were unaware of study group allocation.

For the PROMs, patients who completed the questionnaires differed from those who did not. However, we believe that these differences are unlikely to have had an important effect on the outcomes as the differences were small, were not in one direction and were similar for both the IT group and the RC group. Our multiple imputation analysis confirmed the results of the main analysis, which supports our conjecture that selective dropout of patients did not introduce significant bias. As most of the PROMs were not measured at baseline, we were not able to examine changes in PROMs over time, nor adjust for baseline measurement of each PROM. This would not have been possible for diabetes-specific outcome measures such as the DTSQ and ADDQoL. We adjusted for a number of possible confounding variables, which were similar between the IT group and the RC group at baseline. We also adjusted all models for the baseline EQ-5D score as a proxy for baseline health status.

For the UKPDS-OM validation work we used multiple imputation, which allows the best use of the available data and takes into account the uncertainty in missing values. Both the imputed data set and the complete-case data set produced similar results, confirming the robustness of our results. Our validation work was limited by a lack of annual CVD risk factor measurement. In the UKPDS cohort, biochemical data were collected every year. We had to average baseline and follow-up values for the year of event in regression analyses as they were not available for every year. We did not have information on baseline AF, PVD, years since pre-existing CVD, blindness and renal failure. This might have introduced some bias in model prediction and influenced the efficiency of the model, most likely contributing to an underestimation of risk of CVD. We validated the UKPDS-OM using 5-year data and extrapolated the model to a longer time horizon in our cost-effectiveness work to estimate the 30-year incremental cost-effectiveness of the IT intervention. As follow-up continues more events will occur. We will revise our estimate of the cost-effectiveness of the intervention once longer-term data are available.

For the cost-effectiveness work we examined outcomes over both the short term and the long term and performed sensitivity analyses to test the robustness of our findings. We used data from the UKPDS, a UK study of individuals with diabetes and long-term CVD outcomes to calculate unit costs, utility decrements and modelled CVD risk. We adjusted for centre (Cambridge/Leicester) rather than practice as the intervention differed slightly between the centres; however, within the same centre practices shared standardised practitioner guidelines. Intraclass correlation coefficient values for GP practice for the primary outcome were very small in the main ADDITION-Europe trial, supporting our decision to adjust for centre rather than practice.

There were some limitations. First, we focused on only macrovascular outcomes (CVD and associated acute events). Microvascular outcomes such as retinopathy and nephropathy are also important in assessing the impact of type 2 diabetes on both quality of life and costs. Exclusion of these is likely to underestimate the benefit from any preventative intervention and thus underestimate cost-effectiveness (i.e. overestimate the ICER), particularly in the longer term as patients avoid CVD and live with diabetes long enough to develop microvascular complications.

Second, although the treatment protocol was identical, the lifestyle intervention was different in Leicester and Cambridge. To represent the cost of implementing an 'ADDITION-like' intervention that reflected a degree of diversity across the country we simply averaged the costs of the two interventions. We did, however, include centre in the adjusted analyses estimating incremental costs and QALYs. Results were similar when we adjusted for cluster (GP practice) and when running analyses separately by centre.

Third, we used an additive method to calculate treatment costs and utility decrements for individuals with multiple events. This is a commonly used method and was applied in the UKPDS-OM,[100,129] but it is unclear if the cost and utility decrements of subsequent complications should be additive or multiplicative. A review of health state utilities in patients with type 2 diabetes published after completion of our analysis[130] recommends the use of the Clarke data set for most comorbid events, or health state utilities very close to those used in our analysis, with one notable exception: we assigned a disutility of 0.263 for renal failure, whereas Beaudet *et al.*[130] recommend values between 0.204 and 0.164. Using a higher disutility will overestimate the health gain from averting renal failure. However, we estimated the difference in risk of renal failure over 30 years between the IT group and the RC group to be –0.05% (SE 0.06%). The impact of this on the incremental QALY gain per patient in each arm is therefore likely to be negligible.

Fourth, most of the equations in the UKPDS-OM predict future risk factors and events based on baseline values, time since diagnosis and the value of biometrics such as HbA_{1c} level in the previous time period (year). It is an individual-level model in which patient data are calculated individually (rather than as mean values of a cohort). Thus, the model assumes that any trends present at 5 years will continue into the future, effectively assuming a continuation of the effect of the small differences in treatment generated by the intervention at 5 years. The 10-year follow-up of the UKPDS cohort found that, although between-group differences in HbA_{1c} level and blood pressure were both lost within 12 months of the end of the active phase of the study, those who had previously achieved tighter control over HbA_{1c} still had a lower event rate at 10 years than those who had not, while any benefit from lower blood pressure was not maintained.[131,132] Current guidelines and practice have changed since the initiation of the ADDITION-Europe trial, with patients recommended to receive at least as IT as the 'intensive' arm. Trial patients in the RC arm received a higher level of treatment than observed in 'standard practice', which may have diluted the observed incremental health gain. However, after 5 years of treatment, there was room for improvement in the prescription of cardioprotective treatment in both groups. Current evidence suggests that delays in treatment intensification in people with type 2 diabetes (clinical inertia) are still very common.

On the cost side, the official duration of the IT intervention was 3 years, for which practices were reimbursed for additional activity and prescriptions. We projected additional prescribed drug costs in the IT arm over the full 30 years under the assumption that patients in the RC arm would not increase their medication and patients in the IT arm would not decrease their medication over time. We may, therefore, have overestimated the cost of the IT arm. Whether this is true or not will be assessed once the 10-year follow-up data from the ADDITION-Europe cohort are available for analysis.

Finally, although we used the most appropriate CVD risk model available, as outlined earlier, the UKPDS-OM was derived using data from a historical cohort of people with clinically diagnosed diabetes. The ADDITION cohort included people with screen-detected diabetes. Other research[125,133] has shown that the UKPDS-OM tends to overestimate absolute CVD risk, a finding replicated in our own investigation of the suitability of the UKPDS-OM to extrapolate ADDITION study data.[96] Furthermore, the utility decrements for MI and stroke derived from the ADDITION study were smaller than those in the UKPDS, a finding that is consistent with contemporary patients receiving better care and hence reporting higher quality of life. This underlines the importance of our sensitivity analyses, which showed that changes to these parameters did not substantially affect the ICER. Of the discount rate, intervention unit cost and utility decrement, variations in the discount rate had the biggest impact on the ICER.

Conclusion

Improvements in the quality of diabetes care in general practice during the duration of the ADDITION-Europe trial meant that treatment in the RC group was better than expected and not very different from the care provided in the IT group.[55] Cardiovascular risk factors (weight, blood pressure, cholesterol and modelled CVD risk[82]), including health-related behaviours (smoking), improved substantially following detection of diabetes by screening, even among those receiving RC. The small differences between groups in the intensity of treatment during the 5 years following diagnosis were associated with a non-significant 17% reduction in the primary composite cardiovascular end point in favour of the IT group.[55] There was no difference between the groups at 5 years in the prevalence of microvascular outcomes[83] or in health status, well-being, quality of life or treatment satisfaction.[84] Recent trials of IT of glycaemia among patients with long-standing diabetes suggest that adverse effects occur early[35,134] and that any benefit in terms of a reduction in cardiovascular risk takes longer than 5 years to be realised.[131] Whether or not the small difference in the intensity of treatment of multiple CVD risk factors early in the course of the disease in the ADDITION-Europe study will translate into a significant reduction in cardiovascular events and mortality over the longer term is uncertain.

We demonstrated that it was feasible to use the UKPDS-OM model to extrapolate the ADDITION-Europe data.[96] We took account of the possible underestimation of any reductions in MI and used the model in our cost-effectiveness analysis. Cost-effectiveness work showed that promotion of IT compared with RC was not cost-effective over a short- to medium-term time horizon for people with screen-detected diabetes in the UK. However, the intervention has the potential to be cost-effective if it can be delivered for approximately £630 per patient rather than £981. Such savings may be plausible through adaptation of predeveloped materials and economies of scale in delivery. Although there were few differences between screened and unscreened populations, the small proportion (2.9%) of individuals whose diabetes was detected by screening did appear to benefit.[23]

Implications for clinical practice

The ADDITION-Europe randomised trial did not deliver conclusive evidence to justify implementation of a systematic screening and early treatment programme. Uncertainties remain, particularly concerning the overall cost-effectiveness of screening and early treatment for undiagnosed diabetes. However, the overall results of the ADDITION-Europe study suggest that earlier detection and treatment of diabetes is associated with net benefits. Although it remains uncertain whether or not IT is associated with a reduction in CVD or microvascular end points over the long term, there was no evidence that IT adversely affects PROMs early in the course of the disease. Furthermore, despite increases in age and diabetes duration, modelled CVD risk estimates decreased in the whole trial cohort from baseline to follow-up. Our research suggests that practitioners can safely treat multiple cardiovascular risk factors early and intensively in the diabetes disease trajectory when the rate of CVD risk progression may be slowed.

The observed absolute and relative risks of cardiovascular events and mortality among participants with an average HbA_{1c} level of around 6.5% 5 years after diagnosis should reassure practitioners concerned about IT for hyperglycaemia. There was no interaction between IT and age or previous history of cardiovascular events, although there was a suggestion that benefits associated with IT were greatest among participants aged ≥ 60 years 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.

In summary, primary care teams might consider the benefits of earlier detection (albeit not necessarily through population-based screening), lifestyle advice and IT for risk factors among those at high risk of diabetes and high risk of CVD. This might include opportunistic screening among those known to be at highest risk, based either on routinely available information such as age, body mass index and the presence of related conditions such as hypertension or on risk questionnaires/scores. Individuals identified in this way might be offered lifestyle interventions and preventative drug treatment appropriate to their level of risk.

Future research recommendations

Future research might focus on ways to increase the yield of programmes for the earlier detection of diabetes and assessment of cardiovascular risk. There is also a need to examine and implement effective and cost-effective care pathways for individuals who screen negative but who are at high risk of diabetes and CVD. The ADDITION-Europe study focused on the treatment of people with screen-detected diabetes, but the screening programme in each centre identified many more individuals without diabetes but who were at high risk of developing diabetes and CVD. In Denmark, for each person found with screen-detected diabetes, two people at high risk of developing diabetes and a further six people without diabetes but fulfilling guideline indications for preventative treatment of high risk factors for CVD were identified. Most of these people were not treated optimally according to current guidelines.[50,135] There is clearly an efficiency to combining strategies to identify individuals at high risk of both diabetes and CVD. Future research should also examine ways to intensify treatment and adherence. There was evidence of suboptimal treatment in this pragmatic trial.[55]

Finally, future research should focus on whether or not the slowing of CVD risk progression observed in ADDITION-Europe trial participants in the first 5 years following diagnosis[82] leads to a sustained reduction in CVD events over the long term. Outcomes tended to favour the IT group among ADDITION-Europe participants; however, the low frequency of events means that the 5-year duration of follow-up may have been insufficient to detect potentially clinically important differences between the RC group and the IT group. The apparent divergence of event rates from 4 years also suggests that further follow-up of the ADDITION-Europe trial is justified to examine whether early intensive multifactorial treatment reduces cardiovascular risk in the long term as seen in the UKPDS.[131] Longer-term follow-up of the ADDITION-Europe trial cohort alongside examination of microvascular, quality of life and cost data is therefore needed to establish the cost-effectiveness of IT among screen-detected patients.

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For *Chapters 3* and *4*, the following authors contributed to the design of the work; the acquisition, analysis and interpretation of data; drafting the work and revising it critically for important intellectual content; and preparing the results for publication: **Knut Borch-Johnsen**, **Melanie J Davies**, **Simon J Griffin**, **Kamlesh Khunti**, **Torsten Lauritzen**, **Guy EHM Rutten**, **Annelli Sandbæk**, **Stephen J Sharp** (Senior Statistician), **Rebecca K Simmons** (Senior Investigator Scientist, Diabetes Epidemiology), **Maureen van den Donk** (Scientific Staff Member, Epidemiology) and **Nicholas J Wareham**.

For the modelled CVD risk section of *Chapter 3*, **James A Black** (PhD student, Epidemiology) completed the data analysis, drafted the work and revised it critically for important intellectual content and prepared the results for publication.

For *Chapter 4*, the following authors contributed to the design of the work; conducted the economic analysis and interpretation of data, drafted the work and revised it critically for important intellectual content; and prepared the results for publication: **Libo Tao** (Research Fellow, Health Economics) and **Edward CF Wilson** (Senior Research Associate, Health Economics).

All authors gave final approval for this version of the work to be published. **Professor Simon J Griffin** agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data sharing statement

The ADDITION-Europe data are available to share via http://epi-meta.medschl.cam.ac.uk/ (accessed 28 January 2016).

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Appendix 1 Further details of the intervention in each study centre

The intervention in ADDITION

Description of the centre specific intervention in the intensive arm

June - Sept 2006

Updated Sept 2007 and May 2010

In overall

The aim of the intervention is to optimise the management of blood glucose, blood pressure, blood cholesterol, microalbuminuria and cardiovascular risk among people with screendetected type 2 diabetes recruited to the ADDITION study.

The ADDITION study, will quantify the effect of intensive treatment in people with screen detected diabetes on cardiovascular events and mortality. Patients detected with diabetes by screening receive either routine care (RC) or intensive treatment (IT) according to their practice group randomisation. In the RC group care is delivered by the GP according to national and local recommendations. Intensive treatment follows an overall model with centre specific modifications. The aim of the intensive treatment intervention is to use treatment targets, management algorithms and a range of additional approaches to optimise the management of blood glucose, blood pressure, blood cholesterol, microalbuminuria and cardiovascular risk among the people with screen-detected type 2 diabetes.

A detailed description of the specific activities undertaken to promote intensive treatment in each centre is provided in the subsequent text.

The ADDITION 'intensive treatment' intervention in Denmark.

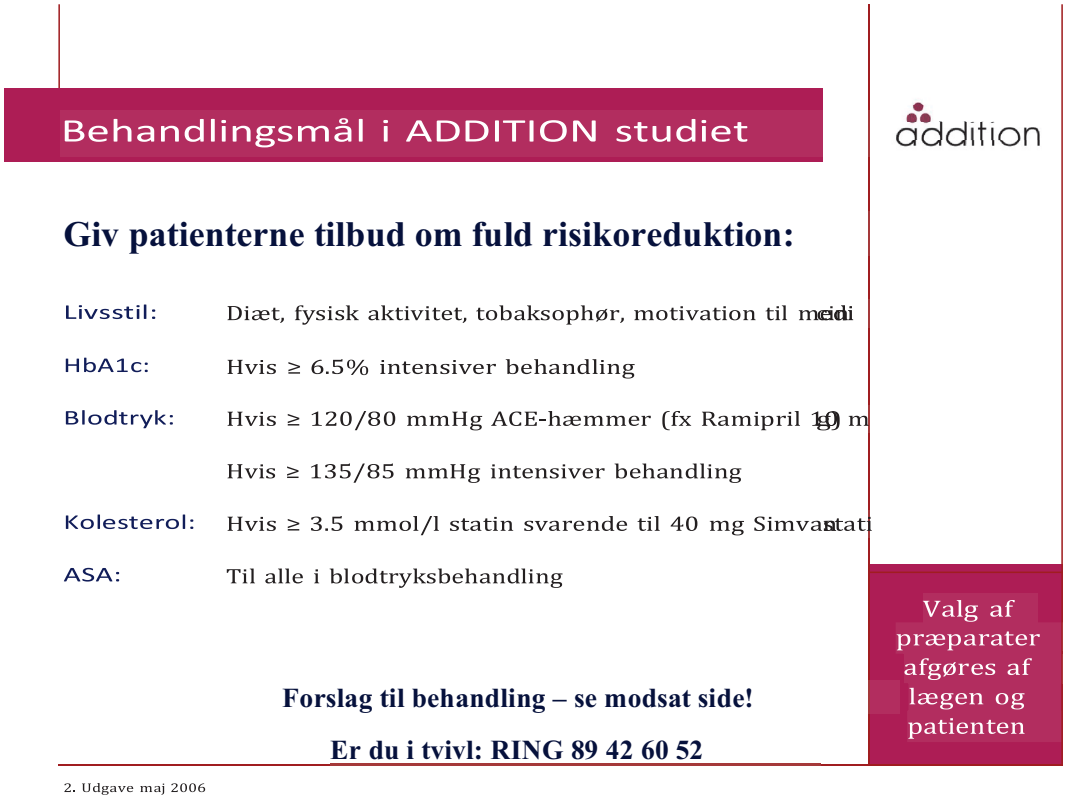
Practitioner level

Model of

care:

- The GPs in the intervention arm is responsible for the care of patients with type 2 diabetes. In some of the included practices the 3-monthly visits are undertaken by nurses. The GPs are nevertheless always responsible for the care. Initiation and all changes of pharmacological treatment are done by the GP. GPs are encouraged to use patient-centred consultations. All GPs are able to refer patients to an outpatient clinic for a second opinion if necessary.

Treatment guidelines:



Educational content:

- Meetings at the end of the normal working day's (2 hours) ○ Every ½ year during the first 2½ years, and thereafter yearly ○ All intervention practice staff are invited (arranged in each county) ○ Topics: treatment targets, treatment strategies, diet, insulin treatment, eye complications, discussion of cases

Educational materials:

- Slides made for the meetings are distributed to all practices together with a summary of the meeting topics.
- Reports describing the status of each of the patients are sent to practices a total of four times during the study period.
- Newsletters are sent to intervention practices, these include a description of study status and new published recommendations about diabetes from the general practice organisations and other scientific associations.

Financial incentives:

- Consultations for screening, and care for diabetes are reimbursed by the NHS as normal consultations. In the first year after diagnosis GPs in the IT group are encouraged to carry out three "long" consultations with the aim of discussing lifestyle changes, disease development and principles of pharmacological treatment. This "long" consultation is supported by funds equivalent to three times a normal consultation fee (approximately 45 Euros). In addition, the

Intervention practices in the intervention arm are reimbursed to report on Case Record Forms (CRFs) at months: 0, 3, 6, 9, 12, 18, years 2, 3, 4, 5 and 6.

Reminders/recall/prompts:

- Twice per year intervention GPs are prompted by mail if CRFs are not returned within three months.

Audit and feedback:

- GPs are sent reports summarising current treatment and levels of blood pressure, HbA_{1c}, cholesterol and BMI, for each of their patients and providing advice concerning how to optimise treatment.

Academic detailing:

- Offices of all participating intervention GPs are visited by the PIs: Torsten Lauritzen or Annelli Sandbaek.
- Subsequently practices whose patients are not meeting the treatment targets are visited or contacted by telephone on further occasions.
- The material for the academic detailing includes patient specific reports describing treatment targets and advice concerning how to optimise treatment.

Opinion leaders:

- The PIs in the study: KB-J, TL and AS act as opinion leaders. Moreover experts in the field of diabetes are invited to attend the meetings to give a second opinion concerning recently published research or to discuss optimal treatment strategies.

Target setting:

- The GPs were informed that in the process of reaching the overall trial targets more steps with individualized target setting for each patient is appropriate.

Patient level

Recommendation for frequency of contacts:

- 3 Monthly
- When a new pharmacological treatment is initiated more frequent contacts are recommended

Educational content and Educational materials::

- All GPs in the intervention arm are provided with a list of topics and educational material suitable for consultations with patients. The topics are:
    - ○ Information about diabetes and its complications ○ Smoking cessation ○ Diet ○ Physical activity ○ Foot care

Reminder/recall/prompts

- Patients are reminded to visit their GP if there is no record of an HbA1c test result in the preceding 6 months or a total cholesterol test result in the preceding 12 months. This procedure is repeated every 3 months from mid 2006. GPs are sent a copy of the patient reminder.

The ADDITION 'intensive treatment' intervention in Leicester

Practitioner level

Model of care (who is seeing patients and where, who is prescribing medication):

The intensive treatment follows an intermediate care model, which involves more frequent contact between patients and healthcare professionals (including a diabetes specialist doctor and diabetes specialist nurse) compared to normal current practice. Our Specialist Care Team (specialist registrar and diabetes specialist nurse) is responsible for the care of the IT patients. Prescribing of pharmacological treatment is undertaken by the specialist doctor.

Treatment guidelines:

The guidelines are shown in the attached document.

Educational content:

The Specialist Care Team which is responsible for the treatment of the IT patients follows the protocol, SOP's and treatment algorithms set out for the study.

Financial incentives:

All ADDITION study practices are reimbursed, quarterly, in arrears for the prescribing costs and the additional costs of care associated with earlier treatment of screen-detected cases. Practices in the RC treatment arm receive a higher level of reimbursement to cover the increased consultation frequency (see attached practice reimbursement document). These payments are funded through Support for Science funding in an agreement with the Department of Health, University Hospitals of Leicester and the Primary Care Research Alliance.

Reminders/recall/prompts:

All IT patients are cared for by our Specialist Care Team which follows study SOP's to prompt them with regards to patient contact.

Audit and feedback:

Patient results (RC and IT) from the one year annual review are sent to all GPs in ADDITION. Our Specialist Care Team updates GPs of the IT patients in writing, following every visit, concerning patient progress and any medication changes.

Academic detailing:

Recent evidence concerning intensive treatment (with associated citations) are presented to practices at the initial recruitment visit in handout form.

Opinion leaders:

Our Specialist Care Team undertakes all practice, home and hospital visits for the IT patients, in consultation with Professor Melanie Davies and Dr Kamlesh Khunti, Principal Investigators for the ADDITION – Leicester study.

Target setting:

IT patient treatment targets for control of blood glucose, blood pressure and blood cholesterol levels are included in the treatment guidelines

Treatment targets

HbA1c < 7%*
Blood pressure ≤ 130/80 mmHg
Cholesterol ≤ 3.5 mmol/l

(* requires action at 6.5%)

Patient level

Recommendation for frequency of contacts:

To retain patients the Specialist Care Team sees them at the most logistically convenient place. This may be at the patients' home, their GP surgery or the local hospital.

After every contact with a patient, the relevant GP is sent a formal follow-up letter to apprise them of their patient's progress, changes to treatment or management and any issues raised during the consultation.

The recommended consultation schedule is given below.

Annual consultation schedule

1 hr Specialist Care Team appointments – diagnosis and 2 months (including retinal screen and complications check)
30 minute Specialist Care Team appointments – 4, 6, 8 and 10 months
15 minute Diabetes specialist nurse appointments – 2 weeks and 4 weeks

1hr annual review (including complications check) with Specialist Care Team –

12 months

Plus any further interim contact required or requested by the patients

Educational content and Educational materials:

All IT patients are provided with a standard Diabetes UK brochure at their initial visit and given the option to be educated on how to do home blood glucose monitoring. The IT group are also invited to attend a DESMOND education session within 2 months of diagnosis. The DESMOND program fulfils the recent DOH/DUK criteria on Education Programs for newly diagnosed diabetic patients and is recommended as 'best practice'. Those who cannot attend these sessions have an individual diabetes education session with a Diabetes Advanced practitioner for approximately 1hr.

Desmond
Diabetes Education and Self Management for Ongoing and Newly Diagnosed

The course has a set number of learning objectives which are designed:

- To provide individuals with information regarding the causes, effects and management of type 2 diabetes.
- To enable newly diagnosed individuals to discuss and explore their experiences and successes of living with diabetes.
- To ensure that those living with type 2 diabetes are aware of their specific health risks for developing the complications of diabetes.
- To provide an expert forum for participants to discuss methods of reducing their identified risk factors.
- To support individuals in developing their own diabetes management plan.

The DESMOND Philosophy is:

- Each individual is responsible for the day to day management of their diabetes.
- People make the best possible decisions for themselves to achieve their best quality of life.
- All the barriers to self management lie in the individual's personal world.
- The consequences of self management decisions impact solely on them, their family and carers
- Acquiring new information is not easy.
- Many factors influence self management and we must create the environment to address these.

Reminder/recall/prompts

No reminders are issued to the RC patients from the study team to see their GP, although all patients (RC and IT) are recalled by letter by the Specialist Care Team for measurement at one of our testing centres around one year after diagnosis for their annual review.

The Specialist Care Team organise appointments in line with the protocol for the IT patients through regular telephone contact

The ADDITION 'intensive treatment' intervention in Cambridge

The aim of the intervention is to optimise the management of blood glucose, blood pressure, blood cholesterol, microalbuminuria and cardiovascular risk among the people with screendetected type 2 diabetes recruited to ADDITION. This is achieved through a combination of regular practice-based educational meetings targeting the general practitioner and nurse incorporating guidelines, academic detailing, opinion leaders, target setting and audit and feedback, alongside theory-based educational materials for patients.

Practitioner level

Model of care (who is seeing patients and where, who is prescribing medication):

- The GP and practice nurse are responsible for care. A small proportion of patients are referred to outpatients, for example for consideration for transfer to treatment with insulin as per routine practice. Prescribing of pharmacological treatment is undertaken by the GP.

Educational content:

- Following recruitment and set-up visits for all participating practices, at least three 11.5 hour lunchtime, practice-based meetings have been undertaken with practices in the intensive treatment arm of the study.
- The initial visit focuses on a presentation of the evidence underpinning intensive treatment and a presentation of the treatment targets, treatment guidelines and patient educational materials
- Subsequent visits at around 8 and 16 months after the practice commences screening reiterate the treatment targets and provide an audit and feedback of the practice performance against the treatment targets, and discussions about the management of individual study participants

Educational materials:

- Slide presentation and associated handouts.
- Treatment guidelines.

Financial incentives:

- All ADDITION study practices receive reimbursement for the costs of screening and the additional costs of care associated with earlier treatment of screen-detected cases. Practices in the intensive treatment arm receive a higher level of reimbursement to cover the increased consultation frequency and increased prescribing costs associated with delivering intensive treatment

Reminders/recall/prompts:

- During individual case discussions GPs and nurses are prompted to recall patients if no blood tests have been undertaken since baseline assessment.
- Patient results from one year measurement are faxed to all GPs in ADDITION.

Audit and feedback:

- Interactive practice-based audit and feedback sessions (median 3, range 1 to 4) are organised around 6 and 14 months after the initial education session and annually thereafter. They consist of an interactive discussion of overall achievement against treatment targets and optimisation of the management of individual patients. Standardised data for each study participant are requested from intensive treatment practices prior to follow up visits. The care of each patient is discussed unless the practice has very high numbers of patients, in which case we select patients to illustrate the main issues for each practice.

Academic detailing:

- Recent evidence concerning intensive treatment (with associated citations) is presented to practices at the initial meeting, in handout and algorithm form in the treatment guidelines and during case discussion at follow up visits.

Opinion leaders:

- All practice-based meetings are undertaken by SG and a local diabetes consultant. Both sit on the local Diabetes Managed Care Network (with responsibility for local delivery of the National Service Framework for diabetes) and have been involved with production of the local diabetes guidelines.

Target setting:

- Patient treatment targets for control of blood glucose, blood pressure and blood cholesterol levels are included in the guidelines, initial practice presentations and audit/feedback sessions (see below).

Treatment targets

HbA_{1c} < 7.0% (requires action at 6.5%)
Blood pressure ≤ 135/85 mmHg
Cholesterol <4.5 mmol/l (IHD +ve)
<5.0mmol/l (IHD -ve)

Provision of glucometers for patients:

Capillary blood glucometers and training in their use are provided to the primary care team. However, the decision to offer a glucometer to an individual patient is left to practitioners.

Patient level

Recommendation for frequency of contacts:

- The recommended schedule for consultations, on which financial remuneration is based, is given below.

Annual consultation schedule

5 x 10 minute GP appointments – diagnosis, 2, 4, 6, 9 months
1 x 30 minute GP annual review – 12 months
7 x 15 minute practice nurse appointments – diagnosis, 2 weeks, 4 weeks, 2, 4, 6, 9 months

Educational content and Educational materials:

- Practice nurses were provided with theory-based education materials to give to patients shortly after diagnosis in order to provide a shared framework for discussion of the causes, consequences and treatment of diabetes (Getting Started with Diabetes). The materials were developed by a multidisciplinary team and drew on Leventhal's selfregulation model applied to chronic disease. They cross-referred to 'Diabetes for Beginners-Type 2' a Diabetes UK publication that was included in the patient information pack. The materials stressed the importance of a healthy lifestyle for the control of diabetes and associated health problems. Specifically, participants with a BMI>28kg/m^2 were encouraged to lose 5-10% of their body weight, to increase their physical activity gradually (recommendations to reach the equivalent of 35 minutes of brisk walking per day for 7 days per week), to avoid excessive alcohol intake, to take their medication regularly, to self-monitor their blood glucose level (if applicable) and to attend annual health checks. Participants who smoked were encouraged to stop.

Reminder/recall/prompts

No reminders are issued from the study team, although all patients are recalled for measurement at one of our testing centres around one year after diagnosis.

The ADDITION 'intensive treatment' intervention in the Netherlands

General Practitioner (GP) level

Model of care (who is seeing the patients and where; who prescribes the medication).

Specially trained diabetes study nurses see the patients at three-monthly intervals. At the fourth appointment (the annual check-up) the patient consults the GP. The diabetes nurses are allowed to change the dosage of the prescribed medicine. Also start of new medication may be suggested by the nurse, but new medication is prescribed by the GP. After the diabetes nurse has seen the patient she discusses with the GP possible changes in medication according to the guideline

ADDITION: intensieve multi-farmacologische therapie

	Basis behandeling	**Aanvullende behandeling**			
	Dosering medicatie ophogen met 2 weken interval. Ga naar de volgende stap in de behandeling bij maximale dagdosis. Zie de patient elke 2 weken tot het doel bereikt is; vaker wanneer insuline gestart wordt.				
	Behandel Drempel:	***Indien boven de behandel drempel voeg toe:***	***Indien nog steeds erboven voeg toe:***	**Indien nog steeds erboven**	
HbA_{1c}	≤ 6.5% dieet	> 6.5% • Metformine of • Meglitinide (bijv repaglinide) of • SU (bijv. gliclazide) *Eerste keuze metformine, tenzij..*	> 6.5% • meglitinide (bijv. repaglinide) of • SU (bijv. gliclazide) of • TZD (bijv. rosiglitazone)	> 6.5% Start insuline therapie met of zonder tabletten	
Bloeddruk	≤ 120/80 mmHg geen	> 120/80 mmHg • ACE-remmer (bijv. ramipril) of indien bijwerking: • A2 (bijv valsartan)	> 135/85 mmHg • Ca-antagonist of • diureticum(lage dosis thiazide)	> 135/85 mmHg • diureticum of • Ca-antagonist	> 135/85 mmHg β-blokker (bijv. metroprolol)

DOI: 10.3310/hta20640

Cholesterol	≤ 3.5 mmol/l dieet	> 3.5 mmol/l statine (bijv. simvastatine 40 mg of ander statine in vergelijkbare dosering)	> 5.0 mmol/l statine tot maximum dosering
Acetylsalicyl zuur	80 mg voor alle patiënten die behandeld worden met antihypertensieve medicatie		

Education of the GPs in the intervention group

- At the start of the study all GPs are informed, in small groups of 2-4, about the study aim, the treatment targets and the strategies in the ADDITION study.
- In the first year most of our effort went to educating the diabetes nurses. Dr Paul Janssen, a GP and a researcher in the ADDITION study team, met them twice per year. As a spin-off the GPs were reinforced to adhere to the treatment algorithm since the GPs had regular consultations with the diabetes nurses in their own practices. The latter procedure is continued up till now.
- After 12 months the GPs in the IT group are invited for a meeting (9-12 persons) at which the ADDITION treatment guidelines are reinforced.
- From 2005, a postdoc GP, Mrs Meggy van Kruijsdijk, has been trained to encourage the GPs to follow the ADDITION treatment guidelines during practice visits at least annually. In most cases the diabetes nurse is also present during these meetings, during which all ADDITION patients are discussed in detail, depending upon the degree to which treatment targets are met for each patient.
- During the consultations between GPs and diabetes nurses, and between GPs and GP-trainer, the records of all patients are discussed including difficulties in following the treatment guidelines.

Educational materials

No additional educational materials are used.

Financial incentives

The GPs from the intervention group received 55 Euro/year for 5 years handing over relevant data and for attending training and consultations sessions.

Reminders

The diabetes nurse monitors the completeness of the CRFs.

Audit and feedback

This takes place during the consultation between the GP-trainer and the GPs each year. No benchmark is provided. The biomedical values of the patients are compared with the targets from the common ADDITION treatment guidelines

All the GPs in the IT group are visited at least once a year by a GP-trainer (see above)

The purpose of this visit is:

- To monitor the quality of care
- To emphasise the targets of the intervention
- To maintain the interest of the GPs
- To discuss difficulties related to ADDITION, such as:
- Collaboration between GP and diabetes nurse
- Difficulties in following the treatment guidelines

- How to encourage patients to reach target values • If necessary advice is given to improve the treatment.
- If the targets of HbA_{1c}, blood pressure or cholesterol are not reached advice is given such as: extra measurement (including home measurements in the case of blood pressure); increasing dose of medication, adding another cholesterol lowering drug or no action since maximal blood pressure medication (4 drugs) is already prescribed

Patient level

Frequency of contact:

- After screening patients are seen frequently (1x every 3-4 weeks) until they reach most of the target levels
- After reaching targets patients are seen 3 monthly.

Educational content and educational materials

- The diabetes study nurses and the GP's are trained to educate the patient, and educational materials are made available as hand-outs.
- Education was not 'extra-ordinary'. The difference between the IT group and the RC group was more concerned with the treatment guidelines than the life-style advice.
- The nurses are responsible for most of this education. The topics they discuss with the patients are:
- Information about diabetes and complications
- Diet
- Physical activity
- Smoking cessation
- Foot care

Reminder/recall/prompts

Patients are reminded to visit the GP or the diabetes nurse when no laboratory results are available within the scheduled time, e.g. HbA_{1c} 6 months; cholesterol 12 months,

January 2007 Outline of treatment recommendation in the intensive-therapy arm. The protocol allows for advantage to be taken of new drug development and the final decision will depend on the individual doctor and patient.; PGR, prandial glucose regulator; SU, sulphonylureas; BG, biguanide; TZD, glitazone; TD, thiazide diuretic; LD, loop diuretic; IHD, ishaemic heart disease; fbg, fasting blood glucose.

	Basic treatment		**Supplementary treatment**		
	Increase dose over 2-4 weeks intervals; go to next treatment step when maximum daily dose is reached or if side-effects appear. See patient every 2nd week until target is reached, more frequently with the onset of insulin treatment.				
	Treatment threshold:	***If above add***	***If still above add***	***If still above***	
HbA_{1c}	**≤ 6.5%*:** **diet**	**> 6.5%:** **BG (eg Metformin) or** **PGR (eg Repaglinid)** **or SU (eg Gliclazin) or** **TZD (Glitazone)** **Optional first choice**	**> 6.5%:** **PGR (eg Repaglinid)** **or SU (eg Gliclazin)** **or BG (eg Metformin)** **or TZD (Glitazone)**	**>6.5%:** **Continue oral hypoglycaemic medication, add Insulatard 12IU at bed time, increasing with 4-6IU every week until fbg < 7 mmol/l.** **If more than 40 units then divide dose ~~and quit oral drugs~~.**	
BP	**< 120/80 mmHg:** **none**	**≥ 120/80 mmHg:** **ACE-inhibitor (eg Ramipril) low to maximum dose**	**≥ 135/85 mmHg:** **Ca antag (eg amlodipine) or TD (eg bendroflumethiazide)**	**≥ 135/85 mmHg:** **TD (eg bendroflumethiazide) or LD (furosemide) or Ca antag (eg amlodipine)**	**≥ 135/85 mmHg:** **B-blocker (eg metroprolol)**

Cholesterol	**< 3,5 mmol/l:** **none**	**≥ 3.5 mmol/l:** **lipid lowering treatment (eg simvastatin 40 mg)**	**- IHD: ≥ 5.0 mmol/l: diet + statin dose up to maximum + IHD: ≥ 4.5 mmol/l: diet + statin dose up to maximum**	
Acetylsalicylic acid	**75 - 80 mg to all patients treated with antihypertensive agents.**			

* In order to achieve the overall goal of the ADDITION Study, ie to keep the HbA1c under 7%, alterations or additions to therapy should seriously be considered when the HbA1c is > 6.5%.

EME
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HTA
PGfAR
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