Webb David (Orcid ID: 0000-0002-3932-3339)

Intensive versus standard multifactorial cardiovascular risk factor control in screen-detected type 2 diabetes: 5 year and longer-term modelled outcomes of the ADDITION-Leicester study

Running title:

ADDITION-Leicester CV-risk intervention

David Webb[1*], Jolyon Dales[1], Francesco Zaccardi[1], Sian Hill[1], Corran Moore[1], Azhar Farooqi[2], Simon Griffin[3], Melanie Davies[1], Kamlesh Khunti[1]

1. Leicester Diabetes Centre, University of Leicester, Leicester, UK

2. NHS Leicester CCG , St John's House , 30 East Street, Leicester, UK

3. Primary Care Unit, Cambridge Institute of Public Health, Cambridge, UK

***Corresponding Author**

Dr David Webb, Senior Lecturer in Diabetes Medicine, Diabetes Research Centre, Leicester General Hospital, Leicester, UK. Phone: +44 0116 258 8554 – Fax: +44 0116 258 4499 Email: david.webb@uhl-tr.nhs.uk

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Abstract

Aims: Diabetes treatment algorithms recommend intensive intervention in those with a shorter duration of disease. Screening provides opportunities for earlier multifactorial cardiovascular risk factor control. Using data from the ADDITION-Leicester study (NCT00318032), we estimated the effects of this approach on modelled risk of diabetes related complications in screen-detected patients.

Methods: 345(41% South Asian) people with screen-detected type 2 diabetes were cluster randomised to receive 5-years of 1)intensive multifactorial risk factor intervention or 2)standard treatment according to national guidance. Estimated 10-20 year risk of ischaemic heart disease, stroke, congestive cardiac failure and death were calculated using UK-PDS risk equations.

Results: Compared to standard care, mean treatment differences for intensive management at 5 years were; -11.7(95%CI:-15.0,-8.4) and -6.6(-8.8,-4.4) mmHg for systolic and diastolic blood pressure, respectively; -0.27 (-0.66, -0.26) % for HbA1c; and -0.46(-0.66; -0.26), -0.34 (-0.51; -0.18), and -0.19 (-0.28; -0.10) mmol/l for total cholesterol, LDL-cholesterol, and triglycerides, respectively. There was no significant weight gain in the intensive group despite additional medication use. Modelled risks were consistently lower for intensively managed patients. Absolute risk reduction associated with intensive treatment at 10 and 20

years were 3.5% and 6.2% for ischaemic heart disease and 6.3% and 8.8% for stroke. Risk reduction for congestive heart failure plateaued after 15 years at 5.3%. No differences were observed for blindness and all-cause death.

Conclusion: Intensive multifactorial intervention in a multi-ethnic population with screen-detected type 2 diabetes results in sustained improvements in modelled ischaemic heart disease, stroke and congestive cardiac failure.

Introduction

Multifactorial cardiovascular risk factor intervention combining behaviour change, lifestyle modification and often poly-pharmacotherapy is highly effective in selected high-risk patients with type 2 diabetes and is now considered standard practice in many countries [1-4]. Theoretically, screening for type 2 diabetes provides a window of opportunity to deliver treatment earlier, before the onset of potentially less reversible cardiovascular pathology but when absolute risk is lower[5]. There is good evidence that this approach is effective at improving outcomes and screen-detected populations are known to have worse cardiovascular risk factor control than comparable populations with conventionally diagnosed diabetes, an observation possibly reflecting limited opportunities for prior intervention in screened cases[6-8].

The Anglo-Danish-Dutch study of Intensive Treatment In peOple with Newly diagnosed screen detected Diabetes in primary care (ADDITION-Europe) demonstrated that screening for type 2 diabetes is feasible and subsequent modelling studies have suggested modest improvements in coronary heart disease risk maybe sustained up to 10 years after identification through screening[7,9]. To date, however, screening has not been shown to improve mortality in the short-term and longer follow-up of screened cohorts such as ADDITION-Europe are required[10]. Furthermore, predicted longer term trajectory of ischaemic heart disease, stroke and congestive cardiac failure risk and its response to risk factor intensification amongst those initially identified through screening has not been described. This is important in light of recent evidence about the effectiveness of intensive multifactorial therapy in established type 2 diabetes[11]

The ADDITION-Leicester study (NCT00318032), which contributed to ADDITION-Europe, focused screening in a particularly high risk multi-ethnic population and randomised newly diagnosed cases of type 2 diabetes to either intensive multifactorial intervention or standard treatment[12]. It has been suggested that screening programmes targeting specific populations known to be at higher risk of metabolic disease may be particularly effective[13]. In this analysis, we report five year outcomes of ADDITION-Leicester and use them to estimate differences in modelled risk for all-cause death, cardiovascular diseases (ischaemic heart disease, stroke and congestive heart failure), and blindness using United Kingdom Prospective Diabetes Study outcomes risk prediction models[14].

Methods

ADDITION-Leicester recruited patients from 20 General Practices situated within an ethnically diverse conurbation of approximately 1.1 million people covering around 2000 square kilometres[15] of the United Kingdom. Over half of the inhabitants of Leicester city are a first or second generation Indo-Asian diaspora (hereafter referred to as South Asians). Random samples of people aged 40-75 years (or 25 – 75 if South Asian) were invited for universal screening with a 75g Oral Glucose Tolerance Test (OGTT). Following a diagnosis of type 2 diabetes mellitus (WHO 1999 criteria) participants were asked if they wished to enter a cluster randomised trial comparing intensive or standard multifactorial diabetes care. Three hundred and forty-five people with newly-diagnosed type 2 diabetes were enrolled between August 2004 and July 2009 (**Figure 1**).

Intervention

Multifactorial cardiovascular risk management of cases randomised to the intensive arm of the ADDITION-Leicester study protocol included; an evidence based and now nationally adopted structured education programme (DESMOND)[16] , 3-6 monthly specialist multidisciplinary peripatetic clinics, support in the use of capillary glucose monitoring and direct access to a nurse led advisory service. Treatment targets in the intensive group were based on those with proven efficacy at the time, notably an HbA1c at or below 7% or 53 mmol/mol (with treatment started at 6.5% or 48 mmol/mol), blood pressure below 130/80

mmHg and total cholesterol below 3.5 mmol/l. The standard care group received nationally accepted care at the time for type 2 diabetes, defined as an HbA1c at or below 7.5 % (58 mmol/mol), blood pressure below 140/85 mmHg and total cholesterol below 4.0 mmol/l. Patients were prescribed aspirin, lipid lowering, anti-hypertensive and glucose lowering medications according to specific algorithms and licensed indications[12].

Measurements

Anthropometric measurements including height, weight, hip and waist circumference were recorded at baseline and five years by trained staff following standard operating procedures. Blood pressure was measured using a portable digital sphygmomanometer (Omron M4, Omron Healthcare-UK) and a standard 12-lead electrocardiogram (ECG) was performed with cases of atrial fibrillation and left ventricular hypertrophy recorded by the study clinician according to validated criteria[17]. HbA_{1c} was quantified using the Bio-Rad Variant II HPLC system which is DCCT aligned. Analyses for total and HDL-cholesterol and triglycerides were carried out on the Abbott Aeroset clinical chemistry analyser; calculated LDL-cholesterol was determined using the Friedewald equation. Serum creatinine concentration was determined by the modified kinetic Jaffe method. Urine albumin creatinine ratio was measured on spot urine specimens (preferably first void sample) using the Olympus OSR6167 Microalbumin Analyser (sensitivity of 0.46mg/l). Neuropathy was assessed using the Michigan Neuropathy Screening Instrument (MNSI) which is a validated measure of distal symmetrical sensorimotor polyneuropathy. In addition to MNSI, a clinical

diagnosis of neuropathy was assumed when a prescription for lower limb neuropathic pain was issued during the trial (amitriptyline, gabapentin, pregabalin, duloxetine accepted)[18]. Retinopathy was assessed by accessing clinical reports for the digital retinal eye screening undertaken on the date closest to the 5 year visit. Background retinopathy was only included if there was a second confirmatory digital retinal assessment within the preceding 18 months. Nephropathy was assessed using repeated early morning urine samples for estimation of albumin creatinine ratio. A new albumin creatinine ratio greater than 2.5 mg/mmol in men and 3.5mg/mmol in women was defined as microalbuminuria as per international consensus guidance[19].

Outcomes

Primary outcome of ADDITION-Leicester was modelled UKPDS coronary heart disease risk 5 years after diagnosis of type 2 diabetes. Secondary measures were composites of macrovascular (acute myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, angioplasty for peripheral vascular disease, carotid endarterectomy, ischaemic or haemorrhagic stroke) or microvascular (nephropathy, neuropathy, retinopathy) disease, hospital admission for heart failure, atrial fibrillation and all-cause mortality. Additional information pertaining to individual cardiovascular risk factors, body mass index and medication use were also collected. For each possible macrovascular outcome relevant clinical information was adjudicated by an independent expert committee blinded to treatment allocation.

Statistical analysis

We firstly summarised baseline and 5-year continuous variables as mean (SD) or median (IQR), according to their distribution, and categorical variables as count and percentage. Treatment differences for continuous variables were estimated with complete-case linear regression using 5-year values as outcome and corresponding baseline values and treatment as independent variables (analysis of covariance, ANCOVA). For the binary variables, differences were estimated with logistic regressions adjusted, when available, for baseline distributions.

Using previously published United Kingdom Prospective Diabetes Study (UKPDS) risk equations (**Supplementary Table S1**), we estimated the absolute predicted risk for five outcomes: all-cause death, ischaemic heart disease, congestive heart failure, stroke and blindness. We first calculated arm-specific predicted risk of event using baseline and 5-year data for a period of observation up to 20 years. Subsequently, for each year, we quantified between-arm difference (i.e., treatment effect comparing intensive vs standard) with ANCOVA.

All analyses were performed with Stata 15 and results are reported with 95% confidence interval (CI). We considered $p<0.05$ statistically significant.

Results

Of 20 practices included in the study, 9 were randomised to intensive management and 11 to standard care; after 5 years, information was available for 144 out of 146 (99%) and 192 out of 199 (97%) participants, respectively (**Figure 1**). Five-year risk factors are summarised in **Table 1**: age at baseline was 59.3 years in the intensive and 59.6 years in the standard treatment arm; 41% of participants were South Asian and 58% were men. There were reductions in systolic and diastolic blood pressure, HBA1c, BMI and lipid indices in both standard and intensive care arms 5 years after diagnosis. Between-arm comparisons revealed mean treatment differences in blood pressure (systolic -11.7 [95% CI: -15.0, -8.4] and diastolic -6.6 [-8.8, -4.4] mmHg), serum total cholesterol and LDL cholesterol concentration (-0.46 [-0.66, -0.26]; -0.34 [-0.51, -0.18] respectively), triglyceride (-0.19 [-0.28, -0.10] mmol/l), and HBA1c (-0.27 [-0.5, -0.1] %) while the difference in body mass index was minimal (-0.04 [-0.09; 0.00] kg/m^2). There were no statistically significant between-arm differences in macrovascular, microvascular disease or mortality at 5 years (**Table 2**); in total, 8 deaths (2.3%) occurred during the follow-up. Blood pressure, lipid and oral glucose lowering medications (metformin and dipeptidyl-peptidase 4 inhibitor) were initiated more frequently in the intensive arm (**Supplementary Table S2 and Figure S1**).

Arm-specific risk for each outcome up to 20 years of follow-up is depicted in **Figure 2**. For both arms, the predicted risk comparing 5-year vs baseline was higher at any time points for the outcomes all-cause death, congestive heart failure, and blindness. Conversely, for stroke the risk was lower in intensive and higher in standard care; while for ischaemic heart disease both intensive and standard arms showed a reduced risk (**Figure 2**). Such findings translated

in significant between-arm mean differences for ischaemic heart disease, congestive heart failure, and stroke and no treatment effect for all-cause death and blindness (**Figure 3**). In particular, the modelled benefit of intensive versus standard care was progressively higher over-time for ischaemic heart disease (3.5% and 6.2% reduction at 10 and 20 years, respectively) and stroke (6.3% and 8.8% reduction), while the risk reduction for congestive heart failure plateaued at around 15 years (5.3% reduction).

Discussion

Consensus guidance recommends pursuing patient-centred glucose, blood pressure and cholesterol goals in the prevention of diabetes-related complications. This approach is based upon evidence from trials in which individual or combined intensive cardiovascular risk factor management has resulted in significant macro- and micro-vascular disease benefits within selected patient groups[1,2,20-22]. Adopting intensive multifactorial strategies for all patients with type 2 diabetes may be ineffective or even counterproductive and in this context targets are commonly relaxed in patients judged to be at significant risk of adverse effects. Conversely, more individualised approaches to care are likely to result in greater variation and inconsistency in the intensity and duration of interventions. It is therefore important that robust data relating to complications risk is available to aid decision makers across a range of populations over time. This is particularly pertinent in people with type 2 diabetes identified through screening and within perceived high risk

ethnic minority populations, where a significant number of cardiovascular risk factor treatments are indicated and many years of diabetes exposure potentially accrued[23]. Screening activity has dramatically increased over the last twenty years and is now recommended in many countries, yet the long term effects of earlier identification remain unknown.

Here we show in a screen-detected population that macrovascular and microvascular outcomes together with predicted UKPDS derived estimates of ischaemic heart disease, stroke and importantly congestive cardiac failure risk are reduced in cases of type 2 diabetes identified via screening and then managed intensively for five years. Reduced risk in this group compared favourably with a less intensively managed control population, an effect that extended potentially to 20 years after diagnosis in our predictive modelling and would support the use of combined approaches to intervention in "early" type 2 diabetes.

As a result of insulin resistance and slow beta-cell decline, symptom-free hyperglycaemia and other obesity-related co-morbidities often precede diagnosis of type 2 diabetes by many years, exposing the vasculature to unchecked and potentially irreversible damage. This so-called "metabolic memory" hypothesis has been advanced to explain why successive major trials have failed to convincingly demonstrate that glucose-lowering in isolation has a significant impact on mortality in people with established or advanced type 2 diabetes[24]. Screening theoretically shortens this untreated and presumed deleterious phase of type 2 diabetes by offering opportunities for earlier detection and intervention. The ADDITION-

Europe study did not demonstrate any advantage of intensive management in this regard five years after identification of type 2 diabetes through screening[10]. As it could only compare treated newly identified cohorts (intensive and standard), it is argued that this study is unable to establish whether screening is truly beneficial in terms of reducing the risks of future cardiovascular morbidity and mortality. Subsequent complex simulation modelling of the ADDITION-Europe dataset suggests that earlier identification and intervention is likely to be beneficial in terms of cardiovascular morbidity and mortality[6,7]. In the absence of long-term observational outcomes, we are reliant upon validated extrapolation models designed to assess the burden of disease over time. Black et al. performed modelling of this nature on the ADDITION-Europe population and concluded that the risk of cardiovascular disease but not death was reduced by intensive multifactorial intervention in screen-detected patients[9]. This study was restricted to 10 year predictions and did not use recently updated UKPDS equations incorporating stroke and congestive cardiac failure risks. The latter condition is becoming a particularly important outcome as more chronic forms of cardiac disease become manifest in older populations who are surviving longer. We have opted to examine ADDITION-Leicester data in isolation for two reasons. Firstly, the unique ethnic make-up of this population makes it a particularly important cohort to study early intervention effects; and secondly, cardiovascular risk factor management in this group was particularly intensive compared with other ADDITION-Europe centres. Mean differences in risk factors a year after diagnosis were the largest in this group and unlike other intervention protocols, ADDITION-Leicester featured a diabetes

specialist peripatetic clinic, supported glucose monitoring and a now nationally adopted structured education programme[16,25].

The majority of multivariable risk prediction models are developed for the general population and are not specific to type 2 diabetes. Clinical guidelines continue to recommend using UKPDS risk equations for cardiovascular disease prediction despite recent claims that they overestimate contemporary CHD risk[26]. We believe that the main message of sustained differences between standard and intensive multifactorial management approaches in screen-detected cases remains valid, even if the impact of the factors determining baseline risk may have changed since the UKPDS study.

One strength of the ADDITION-Leicester study is the large multi-ethnic population (41% South Asians) diagnosed with WHO defined type 2 diabetes following a population-level screening programme. Other strengths of the study include the practice level randomisation process which limited contamination, the intensive nature of the intervention compared with other ADDITION-Europe centres and participant retention of over 99% at five years. Our standard operating procedures enabled us to collect information for variables included in all the most recent UKPDS equations, including atrial fibrillation. We searched primary and secondary care resources to obtain events and reduce missing data.

It is plausible that a number of limitations may have influenced the results obtained. Firstly, the data used in this analysis is derived from one centre with a specific ethnic makeup and method of diagnosis, so may not be directly applicable to other populations or settings.

Secondly, inevitably there was some missing data for variables included in the UKPDS models, but attrition was relatively limited.

Thirdly, whilst this analysis demonstrates the potential benefits of aggressive cardiovascular risk factor modification in screen-detected patients, before judging overall impact, it is important to consider plausible adverse effects not accounted for by the simulation model. For example aggressive cardiovascular risk management may be associated with higher rates of iatrogenic hypoglycaemia and hypotension, both of which have been linked to worse outcomes and patient distress. Whilst in this study intensive treatment at one year was not associated with an increase in self-reported hypoglycaemia or hospital admission for hypotension, careful consideration of these important adverse consequences would be required in clinical practice. It is should also be appreciated that risk factor modification will inevitably inform equations modelled on this risk, and do not reflect true outcomes or treatment effects. Future research should explore whether this modification of cardiovascular risk progression leads to a long-term reduction in actual events in this population.

Conclusion

We have shown that intensive multifactorial intervention in screen-detected cases of type 2 diabetes results in sustained improvements in modelled ischaemic heart disease and stroke

outcomes. This effect is seen in a multi-ethnic population typical of those being invited for screening in the United Kingdom.

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List of Abbreviations

ADDITION Study: The Anglo-Danish-Dutch study of Intensive Treatment In peOple with Newly diagnosed screen detected Diabetes in primary care. UKPDS: United Kingdom Prospective Diabetes Study. DCCT: Diabetes Control and Complications Trial

Declarations and Consent

Ethical approval was obtained from the University Hospitals of Leicester (UHL09320) and Leicestershire Primary Care Research Alliance (64/2004) local research ethics committees. The study was conducted in accordance with the principles of the 1996 Helsinki Declaration. Written informed consent was obtained for all participants involved in both phases of ADDITION-Leicester study at the time of diabetes screening.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Competing interests

The authors declare that they have no competing interests" in this section.

Authorship

DW is a co-investigator of the study and contributed to the design; data acquisition, analysis, and interpretation; drafting of the manuscript; and critical revision of the manuscript for intellectual content. FZ performed data analyses and contributed to the production of all draft manuscripts. KK, SG, AF, and MJD are principal investigators of ADDITION-Leicester and contributed to the study design; data acquisition, analysis, and interpretation; and critical revision of the manuscript for intellectual content. JD and CM contributed to data collection and co-wrote draft manuscripts. DW and KK are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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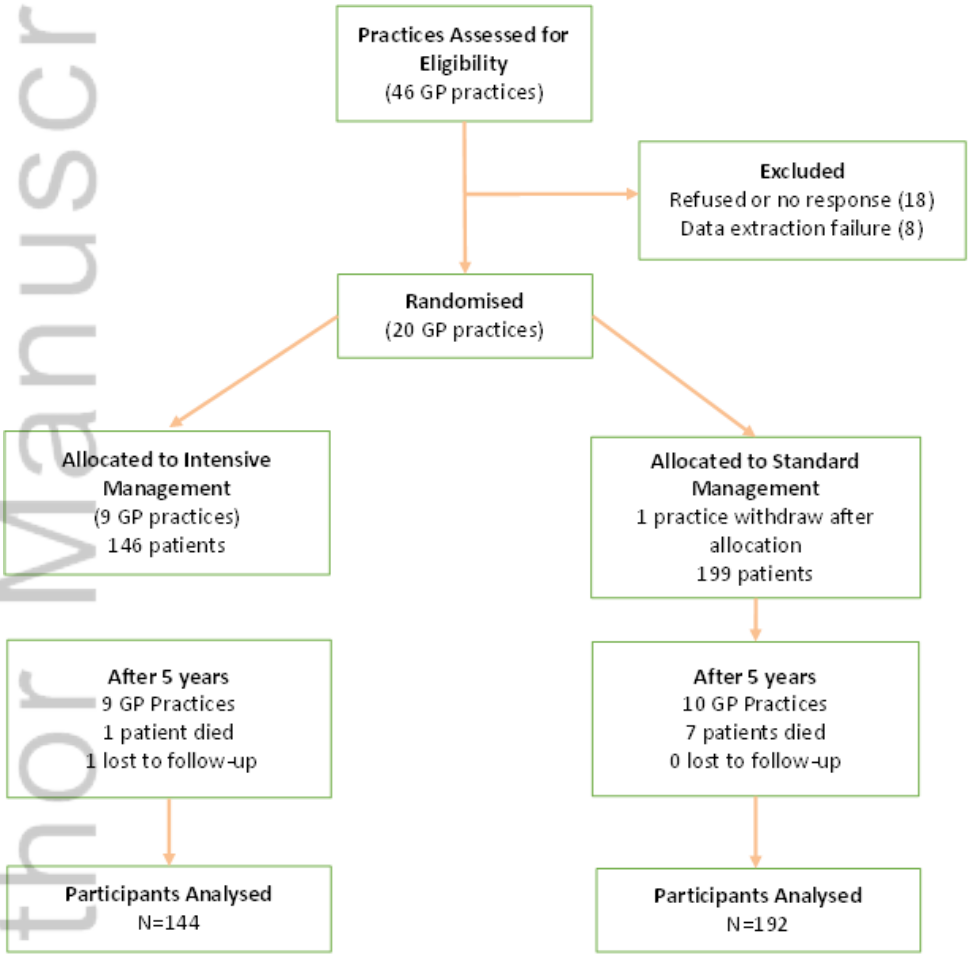

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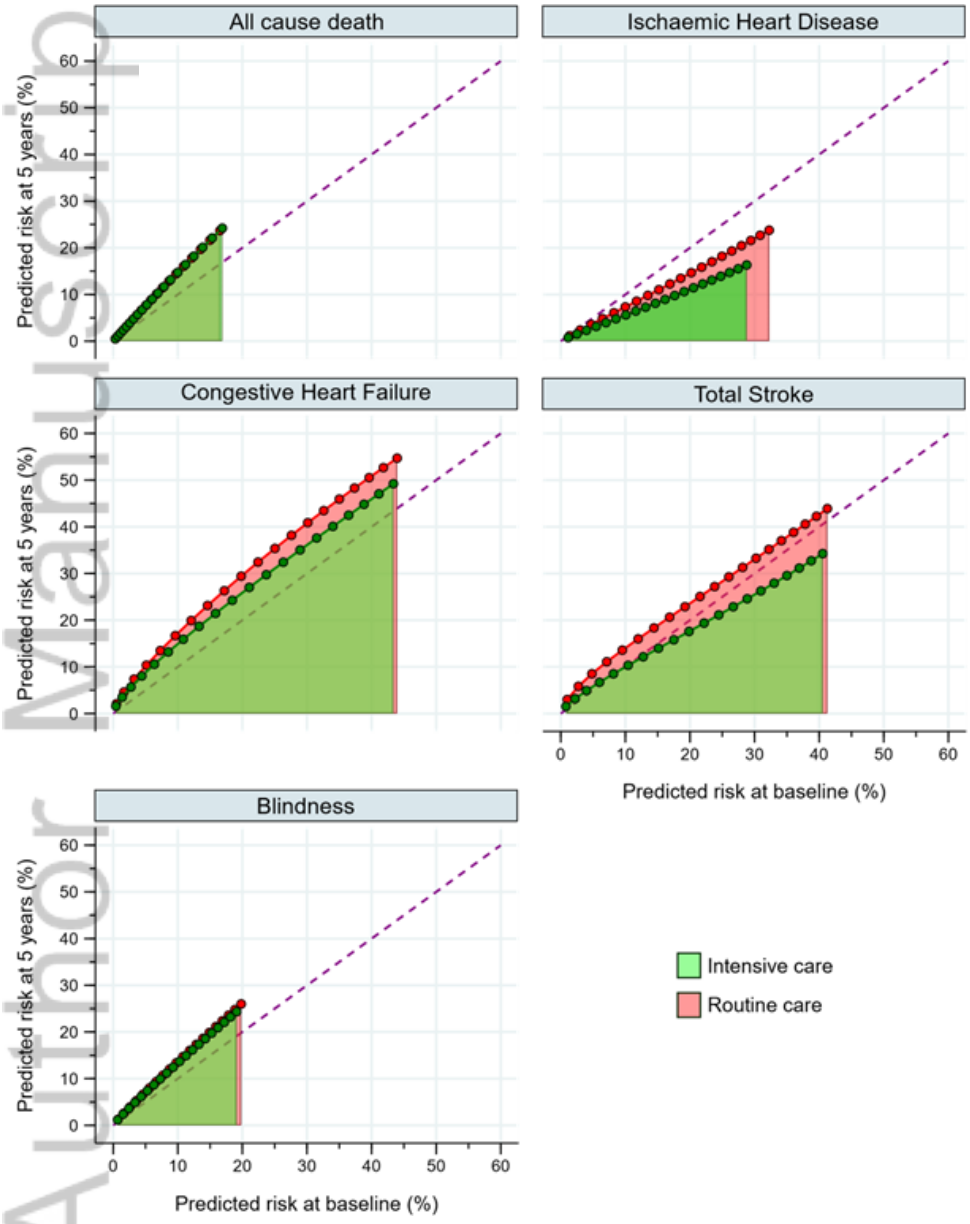

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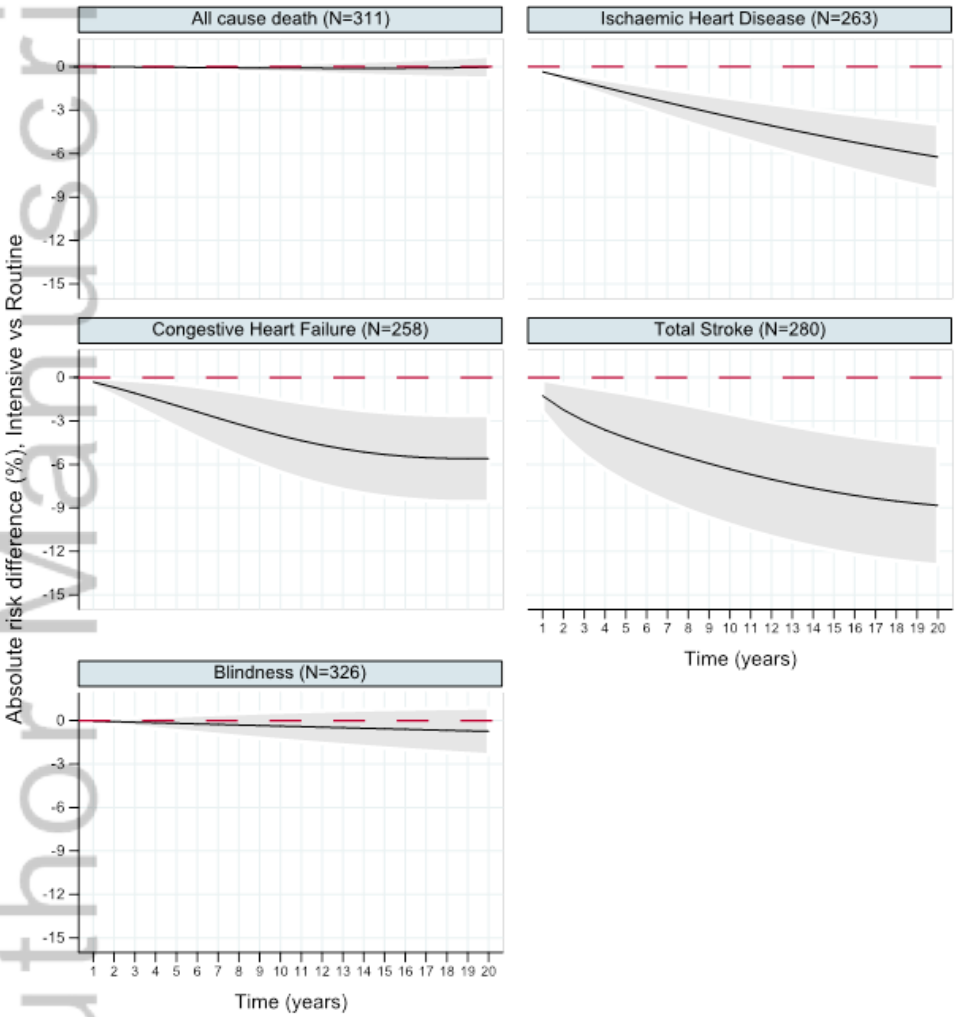

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Table 1: Differences in characteristics of the ADDITION-Leicester population

		Intensive Treatment Arm		Standard Treatment Arm			
Variable	**Time (years)**	**n**	**Mean (SD) or median (IQR)**	**n**	**Mean (SD) or median (IQR)**	**N**	**Mean treatment difference (95% CI)***
Age (years)	0	144	59.3 (9.9)	192	59.6 (10.0)	336	-
	5	144	64.2 (9.9)	192	64.4 (10.0)		
Body mass index (kg/m^2)*	0	142	30.8 (26.0-35.0)	189	30.4 (27.5-35.0)	295	-0.04 (-0.09; 0.00)
	5	136	28.8 (24.9-33.8)	162	29.7 (26.7-34.3)		
HbA1c (%)	0	142	7.2 (1.5)	191	7.3 (1.8)	326	-0.27 (-0.48; -0.06)
	5	144	6.8 (1.0)	185	7.1 (1.0)		
Systolic BP (mmHg)	0	142	145.8 (18.6)	190	148.3 (20.3)	293	-11.71 (-14.98; -8.44)
	5	136	126.9 (13.3)	159	139.2 (16.8)		
Diastolic BP (mmHg)	0	142	88.0 (10.4)	190	89.7 (10.1)	293	-6.61 (-8.82; -4.41)
	5	136	73.7 (10.1)	159	80.9 (10.3)		
Total cholesterol (mmol/l)	0	144	5.3 (1.2)	192	5.7 (1.3)	329	-0.46 (-0.66; -0.26)
	5	143	3.8 (0.9)	186	4.3 (1.0)		
LDL cholesterol (mmol/l)	0	141	3.2 (1.0)	190	3.5 (1.0)	321	-0.34 (-0.51; -0.18)
	5	143	1.9 (0.7)	183	2.3 (0.8)		
HDL cholesterol (mmol/l)*	0	141	1.2 (1.0-1.3)	190	1.2 (1.0-1.4)	321	0.01 (-0.05; 0.06)
	5	143	1.2 (1.0-1.4)	183	1.2 (1.0-1.4)		
Triglycerides (mmol/l)*	0	144	1.7 (1.2-2.3)	192	1.8 (1.3-2.4)	329	-0.19 (-0.28; -0.10)
	5	143	1.3 (0.9-1.7)	186	1.6 (1.1-2.2)		
Albumin/Creatinine (iu/l)*	0	137	1.0 (0.6-2.0)	187	1.0 (0.6-2.3)	300	-1.15 (-3.37; 1.08)
	5	128	0.8 (0.4-1.5)	182	0.8 (0.5-2.3)		
Creatinine (µmol/l)	0	141	83.4 (16.7)	192	86.4 (15.2)	323	1.96 (-0.95; 4.87)
	5	144	77.2 (18.6)	182	78.2 (19.7)		
		n	**Cases (%)**	**n**	**Cases (%)**	**N**	**Odds Ratio I vs R**
Ethnicity, white	0	139	75 (54%)	191	120 (62.8%)	330	-
Sex, men	0	144	81 (56.3%)	192	113 (58.9%)	336	-
Current smoking, yes	0	143	21 (14.7%)	192	18 (9.4%)	333	1.62 (0.63; 4.21)
	5	144	14 (9.7%)	190	10 (5.3%)		

* Ln transformed values for variables reporting median and IQR

Table 2: Comparison of Diabetes Related complications at 5 years between Intensive (I) and Standard (S) treatment arms

	Intensive Treatment Arm		Standard Treatment Arm			
Variable	**n**	**Cases (%)**	**n**	**Cases (%)**	**N**	**Odds Ratio I vs S**
Neuropathy, yes	132	6 (4.5%)	135	7 (5.2%)	267	0.87 (0.28; 2.66)
Retinopathy, yes	143	14 (9.8%)	189	32 (16.9%)	332	0.53 (0.27; 1.04)
Nephropathy, yes*	128	21 (16.4%)	182	38 (20.9%)	310	0.74 (0.41; 1.34)
Atrial fibrillation, yes	144	5 (3.5%)	192	11 (5.7%)	336	0.59 (0.20; 1.74)
Congestive Heart Failure, yes	144	4 (2.8%)	192	5 (2.6%)	336	1.07 (0.28; 4.05)
Microvascular disease, yes	118	32 (27.1%)	127	41 (32.3%)	245	0.78 (0.45; 1.35)
Macrovascular disease, yes^	144	10 (6.9%)	190	12 (6.3%)	334	1.11 (0.46; 2.64)
All cause death	144	1 (0.7%)	199	7 (3.5%)	345	0.19 (0.02, 1.58)

* Defined as ACR≥2.5 in men and ACR≥3.5 in women

^ Macrovascular Disease – composite outcome of acute myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, angioplasty for peripheral vascular disease, carotid endarterectomy, ischaemic or haemorrhagic stroke

Author/s:
Webb, D; Dales, J; Zaccardi, F; Hill, S; Moore, C; Farooqi, A; Griffin, S; Davies, M; Khunti, K

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