

Stepwise screening for diabetes identifies people with high but modifiable coronary heart disease risk. The ADDITION study

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Abstract

Aims/hypothesis The Anglo–Danish–Dutch study of intensive treatment in people with screen-detected diabetes in primary care (ADDITION) is a pragmatic randomised controlled trial of the effectiveness of intensified multifactorial treatment on 5 year cardiovascular morbidity and mortality rates in people with screen-detected type 2 diabetes in the Netherlands, UK and Denmark. This paper describes the baseline characteristics of the study population, their estimated risk of coronary heart disease and the extent to which that risk is potentially modifiable.

Methods Stepwise screening strategies were performed using risk questionnaires and routine general practice data plus random blood glucose, HbA_{1c} and fasting blood glucose measurement. Diabetes was diagnosed using the 1999 World Health Organization criteria and estimated 10 year coronary heart disease risk was calculated using the UK Prospective Diabetes Study risk engine.

Results Between April 2001 and December 2006, 3,057 people with screen-detected diabetes were recruited to

the study (mean age 59.7 years, 58% men) after a stepwise screening programme involving 76,308 people screened in 334 general practices in three countries. Their median estimated 10 year risk of coronary heart disease was 11% in women (interquartile range 7–16%) and 21% (15–30%) in men. There were differences in the distribution of risk factors by country, linked to differences in approaches to screening and the extent to which risk factors had already been detected and treated. The mean HbA_{1c} at recruitment was 7.0% (SD 1.6%). Of the people recruited, 73% had a blood pressure $\geq 140/90$ and of these 58% were not on antihypertensive medication. Cholesterol levels were above 5.0 mmol/l in 70% of participants, 91% of whom were not being treated with lipid-lowering drugs.

Conclusions/interpretation People with type 2 diabetes detected by screening and included in the ADDITION study have a raised and potentially modifiable risk of CHD.

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Abbreviations

ADDITION Anglo–Danish–Dutch study of intensive treatment in people with screen-detected diabetes in primary care
UKPDS UK Prospective Diabetes Study

Introduction

People with type 2 diabetes mellitus are at increased risk of developing micro- and macrovascular complications and a substantial reduction in life expectancy [1]. The onset of this increased risk predates the point of clinical recognition by several years [2] such that at diagnosis approximately 50% of people have evidence of diabetes-related complications [3–8]. Given the high prevalence of undiagnosed diabetes [9–11] and the evidence that in people with clinically diagnosed diabetes the risk of complications can be effectively reduced by intensive treatment of hyperglycaemia [5–8] hypertension [12–14] and dyslipidaemia [15, 16], screening and earlier initiation of such treatment has been the subject of considerable debate [17–19]. However, critical uncertainties exist about the cost-effectiveness and potential adverse consequences of screening, and given this uncertainty, many international and national bodies have concluded that population-based screening should not be recommended without further evidence. A key uncertainty factor in assessing the balance between the costs and benefits of implementing policies for early detection of diabetes is the magnitude of cardiovascular risk reduction following early detection and intensive therapy [11]. Quantification of this risk reduction is the goal of the Anglo–Danish–Dutch study of intensive treatment in people with screen-detected diabetes in primary care (ADDITION), a randomised controlled trial of intensive multifactorial therapy in people with screen-detected diabetes in primary care. The aim of the analysis reported in this paper is to describe the baseline characteristics of the participants in the ADDITION study and in particular to quantify their estimated risk of CHD using the risk prediction equations developed in the UK Prospective Diabetes Study (UKPDS). We also describe the extent to which the estimated CHD risk in ADDITION study participants is potentially modifiable.

Methods

Study design The ADDITION study is a pragmatic randomised controlled trial of intensive multi-factorial treatment

compared with standard care in people with screen-detected diabetes. The rationale and design of the study have been reported previously [20]. Recruitment to the study commenced in April 2001 and was completed in December 2006 by which time 3,057 people with screen-detected diabetes were recruited from four centres: one in Denmark, two in UK (Cambridge and Leicester) and one in the Netherlands. The primary endpoint for the 5 year follow-up in December 2009 will be a composite cardiovascular outcome comprised of cardiovascular mortality and morbidity (myocardial infarction, non-fatal stroke) revascularisations and amputations.

Screening procedures In order to identify potential recruits to this study, ADDITION undertook a programme of population-based stepwise screening among people aged 40 to 69 years who were not known to have diabetes. Individuals at high risk of diabetes were initially identified using self-administered questionnaires in Denmark [21] and the Netherlands [22, 23] or by automated search of computerised general practice records in the UK [24]. Those at high risk were asked to contact their physician (Denmark), attend a community-based screening clinic (the Netherlands) or were invited by letter to attend their local general practice (Cambridge) or a screening clinic (Leicester). A sequential process of screening using random glucose measurements and HbA_{1c}, followed by fasting glucose and OGTT as diagnostic tests was undertaken. In the Leicester centre, all people at high risk were invited directly for OGTT without the intermediate testing steps. Participants were diagnosed with diabetes according to the WHO criteria [25] using the requirement for confirmatory tests on separate occasions.

Biochemical assessment Whole-blood glucose was analysed by near-patient testing using a glucose analyser (HemoCue, Angelholm, Sweden). Calibration stability was checked on a daily basis using control cuvettes. All machines were registered with the HemoCue quality assurance scheme and were externally calibrated at the start of screening and subsequently recalibrated at regular intervals. HbA_{1c} was analysed in venous samples in five local laboratories. The laboratories in Denmark (at Steno Diabetes Centre, Gentofte, and Aarhus University Hospital, Tage Hansensgade, Aarhus) and Cambridge (Department of Clinical Biochemistry at Addenbrookes Hospital, Cambridge) used ion-exchange high-performance liquid chromatography on Tosoh machines (Tosoh Bioscience, Redditch, UK). The laboratory in the Leicester centre (Leicester Royal Infirmary) used the Biorad Variant II system (Bio-Rad Laboratories, Hemel Hempstead, UK) and that in the Netherlands (SHL Center for Diagnostic Support in Primary Care, Etten-Leur, the Netherlands) used a Menarini 8140 machine (Menarini,

Florence, Italy). A validation study comparing the different laboratories demonstrated no noticeable systematic differences (<0.2%) in the HbA_{1c} range of 3 to 11%. The repeatability and reproducibility were within the range 0.1 to 0.5% in all laboratories. Fasting serum samples were analysed in the same local laboratories for cholesterol, HDL-cholesterol and triacylglycerol using standard enzymatic methods. LDL-cholesterol was calculated using the Friedewald formula [26]. Plasma creatinine concentration was analysed with kinetic colorimetric methods. Urinary albumin was measured on spot urine by the immunoturbidimetric method and urinary creatinine by the colorimetric method. The urinary albumin: creatinine ratio was used to define microalbuminuria as ≥ 2.5 mg/mmol in women and ≥ 3.5 mg/mmol in men.

Clinical measures Anthropometric measurements were undertaken at baseline by trained staff following standard operating procedures with height being measured to the nearest 0.1 cm using a fixed rigid stadiometer and weight in light indoor clothing measured to the nearest 0.1 kg with a Seca scale. Body mass index (kg/m²) was defined as weight in kilograms divided by height in metres squared. Waist circumference was measured at the mid-point between the lower costal margin and the level of the anterior superior iliac crest to the nearest 0.1 cm. Blood pressure was measured using an Omron M4 blood pressure recorder (Omron Healthcare, Milton Keynes, UK) with the participant in a sitting position.

Questionnaires Self-completed questionnaires were used to assess baseline smoking status, alcohol consumption, occupational status, ethnicity and self-reported medication. Where needed, instruments were translated and back-translated and the accuracy of translation verified using established methods [27].

UKPDS risk engine The estimated absolute 10 year risk of CHD was calculated using the previously published UKPDS risk engine [28]. The risk was only estimated for those participants with complete data on all the composite risk factors required for the calculation, i.e. age, sex, ethnicity, smoking status, HbA_{1c}, systolic blood pressure, total cholesterol and HDL-cholesterol, and duration of diabetes, which for this population was by definition 0 years since all the participants had screen-detected diabetes.

Ethics The study was approved by the local scientific ethics committees in the specific countries and counties and was conducted in accordance with the principles of the 1996 Helsinki Declaration. All participants provided informed consent.

Data-handling and statistics The comparison of the baseline characteristics of the study participants by group was undertaken using Student's *t* tests for continuously distributed data and χ^2 tests for categorical variables. The Kruskal–Wallis test was used where data were not normally distributed or unequal variances were present. We used an imputation method to estimate the impact of missing data for the UKPDS risk score on our results. Missing continuous data such as HbA_{1c}, systolic blood pressure, total cholesterol and HDL-cholesterol were imputed using the best-subset regressions procedure [29]. Missing data for the categorical variables (ethnicity and smoking status) were imputed using logistic regression imputation. Where the predicted value was <0.5 it was coded as 0 and where it was ≥ 0.5 it was coded as 1. No sensitivity analyses of the imputation procedure were done. All analyses were undertaken using Intercooled STATA 9.0 (StataCorp LP, College Station, TX, USA).

Results

Recruitment By the end of the screening phase of the ADDITION study, 334 general practices (182 in Denmark, 49 in Cambridge, 24 in Leicester and 79 in the Netherlands) had screened 76,308 people (28,031 in Denmark, 24,654 in Cambridge, 5,740 in Leicester and 17,883 in the Netherlands). In total, 3,233 individuals with screen-detected diabetes were identified and a total of 3,057 individuals (1,533 in Denmark, 867 in Cambridge, 159 in Leicester and 498 in the Netherlands) were recruited to the ADDITION study. There were no significant differences in the characteristics of the 3,057 participants recruited to the trial compared with the 176 patients with screen-detected diabetes who were eligible but chose not to participate.

Baseline characteristics The baseline characteristics of the participants recruited to the trial including the risk factors for CHD are shown in Table 1. Across the centres significant differences were seen in the demographic characteristics of the participants, largely by virtue of differences in the underlying populations and the approach to screening. The Leicester population differed from the other three centres by having the youngest population (mean age=57.2 years compared with 59.9 years in the other three groups, $p<0.001$), the highest proportion of participants who were non-white (41.3 compared with 3.9% in the other groups, $p<0.001$) and the highest proportion of people who were not employed (7.7 compared with 2.2% in the other centres, $p<0.01$). The Danish population had the highest proportion of smokers (35% compared with 26% in the Netherlands, 18% in Cambridge and 16% in Leicester, $p<0.001$) and also had the highest intake of alcohol units per week. The mean

Table 1 Baseline characteristics of the 3,057 participants (1,771 men, 1,286 women) with screen-detected diabetes recruited to the ADDITION study (2001–2006)

| | <i>n</i> with complete information | Total | Men | Women |
|---|------------------------------------|-----------|-----------|------------|
| Age at diagnosis (years) | 3,057 | 59.7±6.8 | 59.2±7.0 | 60.4±6.6** |
| Non-white (%) | 2,941 | 5.3 | 5.0 | 5.8 |
| Alcohol consumption (units/week) | 2,675 | 4 (0–162) | 8 (0–162) | 2 (0–115) |
| Current smokers (%) | 2,996 | 27 | 29 | 25** |
| Unemployed (%) | 2,955 | 2.5 | 2.8 | 2.1 |
| Already on antihypertensive treatment (%) | 2,803 | 41 | 37 | 47** |
| Already on lipid-lowering treatment (%) | 2,803 | 14 | 15 | 13* |
| HbA _{1c} (%) | 2,888 | 7.0±1.6 | 7.1±1.7 | 6.9±1.4* |
| Systolic BP (mmHg) | 2,961 | 151±23 | 152±22 | 151±23 |
| Diastolic BP (mmHg) | 2,962 | 87±12 | 88±12 | 86±11** |
| BMI (kg/m ²) | 2,960 | 31.6±5.6 | 31.0±5.0 | 32.3±6.2** |
| Waist (cm) | 2,959 | 107±13 | 109±13 | 103±14** |
| Total cholesterol (mmol/l) | 2,892 | 5.6±1.1 | 5.4±1.1 | 5.7±1.1** |
| Total triacylglycerol (mmol/l) | 2,873 | 2.0±1.5 | 2.1±1.7 | 1.9±1.1** |
| HDL-cholesterol (mmol/l) | 2,856 | 1.3±0.4 | 1.2±0.4 | 1.4±0.4** |
| LDL-cholesterol (mmol/l) | 2,762 | 3.4±1.0 | 3.3±1.0 | 3.5±1.0** |
| Plasma creatinine (μmol/l) | 2,830 | 84±18 | 90±17 | 75±15** |
| With microalbuminuria (%) ^a | 2,757 | 18.4 | 17.6 | 19.5 |

Data shown are mean±SD, median (range) or percentages

^aUrinary albumin:creatinine ratio >2.5 (women), >3.5 (men)

**p*<0.05 vs men

***p*<0.001 vs men

HbA_{1c} was lower in the Danish population (6.8%) than in the other three centres (overall mean 7.3%, *p*<0.001).

Anti-hypertensive, lipid-lowering and antiplatelet therapy

In the total study population 73% of the participants had a blood pressure greater than 140/90 mmHg and of these 58% had not been prescribed antihypertensive medication. Therefore, overall 42% of the cohort was hypertensive but not being treated. Even in the subpopulation of people already receiving antihypertensive therapy (Table 2) there was evident room for enhancement of blood pressure lowering, since the mean blood pressure level in this

Table 2 Baseline characteristics of participants with screen-detected diabetes recruited to the ADDITION study (2001–2006), stratified by antihypertensive therapy status

| | Already on antihypertensive therapy | No antihypertensive therapy |
|--------------------------|-------------------------------------|-----------------------------|
| <i>n</i> (%) | 1,159 (41) | 1,644 (59) |
| Age (years) | 60.9±6.5 | 59.0±7.0** |
| BMI (kg/m ²) | 32.4±5.7 | 31.0±5.4** |
| Systolic BP (mmHg) | 151±22 | 152±23 |
| Diastolic BP (mmHg) | 86±12 | 88±12* |

Data shown are mean±SD, unless otherwise indicated

**p*<0.05 vs participants on antihypertensive therapy

***p*<0.001 vs participants on antihypertensive therapy

supposedly treated group was 151/86 mmHg. Indeed the blood pressure levels in the population receiving therapy were only marginally lower than those in the untreated group. In this group, 67% of people did not meet the treatment goal of a blood pressure of 140/90 showing the potential for intensified therapy or for behavioural modifications to enhance treatment adherence. Similarly, 70% of the cohort had a cholesterol level above 5.0 mmol/l. More women (75%) than men (65%, *p*<0.001) were hypercholesterolaemic. Nearly all of these people with high cholesterol levels (91%) were not being treated with lipid-lowering pharmaceuticals. Overall 64% of the participants in the ADDITION trial had a total cholesterol level above 5 mmol/l at baseline but were not being treated. Among the people who were receiving lipid-lowering therapy (Table 3), there was evidence, as with blood pressure, that scope for intensifying therapy or enhancing adherence existed, since the mean cholesterol level in those receiving treatment was 4.9 mmol/l with a mean LDL-cholesterol of 2.8 mmol/l. Of these individuals, 41% were not meeting the treatment goal of a cholesterol level lower than 5 mmol/l. Of the total population 15% had aspirin treatment at inclusion.

The two UK centres had the highest proportion of people already on antihypertensive and lipid-lowering treatment at baseline. In Cambridge and Leicester 49 and 58% of the participants respectively were already on antihypertensive therapy compared with 32% in Denmark and 37% in the Netherlands (*p*<0.001). The mean systolic BP was lower in

Table 3 Baseline characteristics of participants with screen-detected diabetes recruited to the ADDITION study (2001–2006), stratified by lipid-lowering therapy status

| | Already on lipid-lowering therapy | No lipid-lowering therapy |
|--------------------------------|-----------------------------------|---------------------------|
| <i>n</i> (%) | 405 (14) | 2,398 (86) |
| Age (years) | 61.4±6.0 | 59.5±6.9** |
| BMI (kg/m ²) | 31.3±5.2 | 31.7±5.2 |
| Total cholesterol (mmol/l) | 4.9±1.0 | 5.6±1.1** |
| Total triacylglycerol (mmol/l) | 2.2±2.0 | 2.0±1.4* |
| HDL-cholesterol (mmol/l) | 1.2±0.4 | 1.3±0.4** |
| LDL-cholesterol (mmol/l) | 2.8±0.9 | 3.5±1.0** |

Data shown are mean±SD, unless otherwise indicated

* $p<0.05$ vs participants on lipid lowering therapy

** $p<0.001$ vs participants on lipid lowering therapy

the UK populations (145 mmHg) and in Denmark (151 mmHg) than among the Dutch (165 mmHg, $p<0.001$). The mean diastolic blood pressure was significantly lower in the Cambridge population than in the other populations (83 mmHg compared with 89 mmHg in all other centres, $p<0.001$). A similar pattern was seen for lipid-lowering therapy, which was being prescribed to 26 and 21% of the participants in Cambridge and Leicester respectively, compared with 9% in Denmark and 15% in the Netherlands ($p<0.001$). The mean total cholesterol concentration was lowest in the Cambridge population compared with the other centres (5.3 mmol/l vs 5.6 mmol/l in all other centres, $p<0.001$).

CHD risk Table 4 shows the estimated absolute 10 year CHD risk by age-group and sex. In the whole group, the median 10 year risk was 16% (interquartile range 10–25%). The estimated risk for CHD was higher for men (median value=21%; interquartile range: 15–30) than for women (11%; 7–16; $p<0.001$), and the oldest age group had a

significant higher risk than the younger groups ($p<0.001$). We also observed minor differences in estimated risk between countries, with the Dutch population having the highest risk of developing CHD in the older age groups ($p<0.001$). These high levels of estimated risk, together with the high mean level of baseline HbA_{1c} plus the untreated hyperlipidaemia and hypertension, provide clear justification for examining the impact of intensified multifactorial therapy on this potentially modifiable risk.

Missing data As the UKPDS CHD risk score uses multiple factors, it is susceptible to missing data since all variables must be present for each individual for risk to be calculated. A full dataset was available for 83% of the total population. However, we investigated the effect of missing data on the overall median CHD risk by imputing missing variables in the remaining 17% of the population. As the results in Table 4 demonstrate, the median CHD risk estimates were unchanged when we included the values calculated using imputation. This suggests that the results are not biased by any specific characteristics of the individuals for whom some data were missing.

Discussion

This analysis of the baseline data from the recruited participants in the multi-national ADDITION trial demonstrates that stepwise screening for diabetes in general practice identifies people with type 2 diabetes whose estimated 10 year CHD risk is high. In addition to their untreated hyperglycaemia, the majority of the people with demonstrable hypertension or hypercholesterolaemia were not receiving treatment or were not being treated sufficiently at baseline, suggesting that the elevated risk may be modifiable through intensified lifestyle and pharmacological therapy. In this trial, participants were randomised at the general practice level to standard care or an intensified approach geared to reducing cardiovascular risk. The 5 year follow-up of the trial participants in 2009 will show

Table 4 Median estimated 10 year absolute CHD risk calculated from the UKPDS risk engine at baseline in the ADDITION study participants (2001–2006), stratified by age and sex

| Age group | <i>n</i> | Men | Women | Total | Total including imputed values ^a |
|------------------|----------|------------|------------|------------|---|
| 40–49 years | 216 | 12 (8–15) | 5 (3–7) | 9 (5–14) | 9 (6–13) |
| 50–59 years | 930 | 18 (13–24) | 8 (6–11) | 14 (9–20) | 14 (9–20) |
| 60–69 years | 1,398 | 26 (19–34) | 13 (10–18) | 19 (13–28) | 19 (13–28) |
| Total population | 2,544 | 21 (15–30) | 11 (7–16) | 16 (10–25) | 16 (10–24) |

Data are % (interquartile range), unless otherwise indicated. UKPDS risk can only be estimated in cases with complete data for all included variables

^a Imputed values used when data were missing

whether this approach to intervention will realise the potential for benefit on cardiovascular outcomes that the present analysis demonstrates.

Strengths and weaknesses of the study This study is large, involving the screening of 76,308 people in 334 general practices in order to find the 3,057 people with screen-detected diabetes who were randomised to different approaches to care. A key element of the ADDITION trial design is that the intervention is delivered in primary care. The trial is a pragmatic evaluation of the magnitude of the costs and benefits of screening and intensified treatment in this real-world setting. This design has the advantage that one can generalise from the results of the trial to the expected outcome if and when the approach is more widely adopted. The disadvantage is that it is much more difficult from a practical perspective to undertake a trial embedded within everyday primary care practice than it is in a specialist research organisation. In the trial, a total of 334 general practices participated and although reminder systems were established to ensure that datasets were as complete as possible, there is a higher degree of missing data than would be present if the trial had been conducted in a more controlled environment.

Comparison with other studies The level of CHD risk estimated by the UKPDS risk engine in ADDITION trial participants who had been detected by a stepwise process of diabetes screening is comparable with that of diabetic patients of a similar age who have been diagnosed conventionally in routine clinical practice. In the analysis by Song and Brown of CHD risk estimation in 700 British patients with prevalent type 2 diabetes (mean age 59.8 years), the mean (SD) 10 year CHD risk in men was 24.9% (SD 13.2), whereas it was 16.5% (SD 9.4) in women [30]. Although the risk estimator ranks risk well, it may result in an underestimation of true risk. In a comparison of risk estimated by the UKPDS risk engine or the Framingham risk score compared with true risk, Guzder and colleagues demonstrated that the Framingham risk score underestimated coronary events in a population of people with type 2 diabetes by 32%. At 13%, the degree of underestimation by the UKPDS risk engine was lower [31]. As with all other risk calculators, the computation of risk for CHD by the UKPDS risk engine is heavily influenced by age and sex, since these are dominant factors that determine absolute risk levels. Thus in our study, by definition, estimated risk is higher in men and in the older age groups. Compared with the cohort of patients in the UKPDS study [4], the participants recruited to the ADDITION study were older, more obese, more hypertensive and had higher levels of serum cholesterol.

Similar differences also exist between the ADDITION study cohort and previous populations of people with screen-detected type 2 diabetes. Overall, ADDITION study participants are older, more obese and more hypertensive than people with prevalent but undiagnosed diabetes in the Ely [10] and Inter99 [9] studies. These differences between our participants and previous studies of prevalent and previously undiagnosed diabetes may be connected (1) with our requirement for confirmation of the biochemical diagnosis of diabetes on a different day, which was not a characteristic of some previous epidemiological studies, or (2) with the screening strategy employed by us, which used risk scores that predict prevalent but undiagnosed diabetes. Factors including age, BMI and presence of known hypertension are part of these risk scores. Thus, through their use as part of a process of stepwise screening, we may have combined screening for diabetes with the selection of individuals who are at higher cardiovascular risk. The only subpopulation in the ADDITION study in whom universal screening rather than a stepwise approach was used was that of the Leicester centre. As 40% of the recruited people with diabetes in Leicester were non-white, this approach is still likely to lead to the selection of a population at higher CHD risk [32]. We demonstrated between-country differences in the distribution of metabolic risk factors, which were due in part to variations in approaches to screening, variations in the prevalence of lifestyle behaviours (e.g. cigarette smoking), and differences in the extent to which risk factors such as blood pressure and lipids had already been detected and adequately treated.

Interpretation of our findings A key criterion that determines whether a screening programme for any particular condition should be considered is the availability of evidence showing that earlier detection and treatment is associated with improved outcomes. In the context of diabetes, if people whose disease was detected by screening were already receiving intensive treatment for CHD risk factors apart from hyperglycaemia, diagnosis of their diabetes should be unlikely to have a major impact on CHD risk. Thus the observation made in this study that people with screen-detected diabetes are at high CHD risk and that this risk is potentially modifiable by intensification of treatment could have a potentially critical impact. The scope for intervention is considerable, since in addition to untreated or insufficiently treated hyperglycaemia, hypertension and hypercholesterolaemia, nearly one third of the cohort were current smokers and almost all were overweight, high-lighting the potential for lifestyle intervention in addition to intensified pharmacological therapy. The task of determining whether such intensification of treatment is possible in primary care and whether it will have the

expected impact on reducing cardiovascular events is a key goal of the 5 year follow-up of the ADDITION trial, which will be complete in 2009.

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Duality of interest The authors declare that, apart from the funding described above, there is no duality of interest associated with this manuscript.

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