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

Running title:

Sandbaek A et al: CHD risk of people with screen-detected diabetes

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Abstract

Aim:

The ADDITION study is a pragmatic randomised controlled trial of the effectiveness of intensified multi-factorial treatment on 5 year cardiovascular morbidity and mortality in people with screen-detected type 2 diabetes in the Netherlands, the United Kingdom 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.

Material and methods:

Stepwise screening strategies were performed utilising 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 10 year coronary heart disease risk was calculated using the United Kingdom Prospective Diabetes Study risk engine.

Results:

Between April 2001 to December 2006, 3057 people with screen-detected diabetes were recruited to the study (mean age 59.7 years, 58% men). Their median estimated 10-year risk of coronary heart disease was 11% in women (interquartile range 7 – 16%) and 21% (15 - 30%) in men. The mean HbA_{1c} at recruitment was 7.0% (SD 1.6%). Seventy three percentage of these people had a blood pressure ≥ 140/90 and 58% of those were not on antihypertensive medication. Seventy percent had a cholesterol level above 5.0 mmol/l and 91% of those people were not being treated with lipid lowering drugs.

Conclusion

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

The RCT trial registration number of the ADDITION study is NCT 00237549.

Key words:

Type 2 diabetes mellitus, screening, general practice, diagnosis, coronary heart disease.

Abbreviations:

ADDITION, Anglo-Danish-Dutch study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care; CHD, coronary heart disease; T2DM, type 2 diabetes mellitus; DK, Denmark; NL, The Netherlands; UK, United Kingdom; WHO, World Health Organization; fBG, fasting blood glucose; 2hBG, 2 hour blood glucose; OGTT, oral glucose tolerance test; UKPDS, United Kingdom Prospective Diabetes Study; BMI, body mass index; sys BP, systolic blood pressure; dia BP, diastolic blood pressure. ASA: Acetylsalicylic Acid

Introduction:

People with type 2 diabetes mellitus (T2DM) 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 of effectiveness in people with clinically diagnosed diabetes of reducing risk of complications 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 could not be recommended without further evidence. A key uncertain factor in assessing the balance between the costs and benefits of implementing policies for early detection of T2DM is the magnitude of cardiovascular risk reduction following early detection and intensive therapy (11). Quantifying this risk reduction is the goal of the ADDITION study, 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 coronary heart disease (CHD) using the risk prediction equations developed in the United Kingdom Prospective Diabetes Study (UKPDS). We also describe the extent to which the estimated CHD risk in the participants in the ADDITION study is potentially modifiable.

Material and methods:

The ADDITION study is a pragmatic randomised controlled trial of intensive multi-factorial treatment compared to standard care in people with screen-detected T2DM. 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 when 3057 people with screen detected diabetes were recruited from four centres; one in Denmark (DK), two in United Kingdom (UK) centres (Cambridge and Leicester) and one in the Netherlands (NL). The primary endpoint for the five 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 for diabetes were initially identified using self-administered questionnaires in Denmark (21) and NL (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 (DK), attend a community-based screening clinic (NL) 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 (rBG) and glycosylated haemoglobin (HbA_{1c}), followed by fasting glucose (fBG) and oral glucose tolerance test (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 T2DM according to the World Health Organization (WHO) criteria (25) using the requirement for confirmatory tests on separate occasions.

Biochemical assessment

Whole blood glucose was analysed by near-patient testing using the HemoCue® Glucose Analyzer (HemoCue AB, 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 regularly subsequently. HbA_{1c} was analysed in venous samples in five local laboratories. The laboratories in Denmark (Steno Diabetes Centre, Gentofte and at 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. The laboratory in the Leicester centre (Leicester Royal Infirmary) used the Biorad Variant II system and that in the Netherlands (SHL Center for Diagnostic Support in Primary Care, Etten-Leur) used a Menarini 8140 machine (Menarini Florence, Italy). A validation study comparing the different laboratories demonstrated no noticeable systematic differences (< 0.2%) in the HbA1c range from 3 – 11%. The repeatability and reproducibility were within the range 0.1 – 0.5% in all laboratories. Fasting serum samples were analysed in the same local laboratories for cholesterol (Chol), HDL-cholesterol (HDL) and triglycerides (TRG) using standard enzymatic methods. LDL-cholesterol was calculated using the Friedewald formula. Plasma creatinine concentration (Crea) was analysed with kinetic colorimetric methods. Urinary albumin was measured on spot urine by immunotubidumetric method and urinary creatinine by colorimetric method. The urinary albumin-creatinine (UAC) ratio was used to define microalbuminuria when it was ≥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 (BMI) (kg/m^2) 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 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 (26).

UKPDS risk engine

The estimated absolute ten year risk of coronary heart disease (CHD) was calculated using the previously published UKPDS risk engine (27). 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 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 chi-squared 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 HbA1c, systolic blood pressure, total cholesterol and HDL cholesterol were imputed using the best-subset regressions procedure (28). Missing data for the categorical variables (ethnicity and smoking status) was 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.

Results:

Recruitment

By the end of the screening phase of the ADDITION study, 334 general practices (182 in DK, 49 in UK-C, 24 in UK-L and 79 in NL) had screened 76,308 people (28,031 in DK, 24,654 in Cambridge, 5,740 in Leicester and 17,883 in NL). In total 3233 individuals with screen-detected diabetes were identified and a total of 3057 individuals (1533 in DK, 867 in Cambridge, 159 in Leicester and 498 in NL) were recruited to the ADDITION study. There were no significant differences in the characteristics of the 3057 participants recruited to the trial compared to the 176 patients with screen-detected diabetes who were eligible but did not choose 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 compared with 59.9 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 the Danish people also had the highest intake of alcohol units per week. The mean HbA1c 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 mm Hg and 58% of these people had not been prescribed antihypertensive medication. Therefore, overall 42% of the cohort was hypertensive but not being treated. Even in the population of people who were already receiving antihypertensive therapy (table 2) there was evident room for enhancement of blood pressure lowering since the mean blood pressure level in this supposedly treated group was 151/86 mm Hg. Indeed the blood pressure levels in the population receiving therapy were only marginally lower than those in the untreated group. Among 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 5mmol/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, to suggest that there was scope for intensifying therapy or enhancing adherence since the mean cholesterol level in those receiving treatment was 4.9 mmol/l with a mean LDL cholesterol of 2.8 mmol/l. 41% of these individuals were not meeting the treatment goal of a cholesterol 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 in already were on antihypertensive therapy compared to 32% in Denmark and 37% in the

Netherlands ($p < 0.001$). The mean systolic BP was lower in the UK populations (145mm Hg) and in Denmark (151mm Hg) than among the Dutch (165mm Hg, $p < 0.001$). 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 compared to 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 compared with 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 to 25%). The estimated risk for CHD was higher for men (median value = 21%) (interquartile range: 15 – 30) compared to 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 for 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 with missing data.

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 coronary heart disease 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 treated sufficiently at baseline suggesting that the elevated risk may be modifiable through intensified lifestyle and pharmacological therapy. In this trial participants have been randomised at the general practice level to standard care or an intensified approach to reducing cardiovascular risk. The 5 year follow up of the trial participants in 2009 will show 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

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 the more controlled environment.

Comparison to other studies

The level of coronary heart disease risk estimated by the UKPDS risk engine in the participants in the ADDITION trial detected by the stepwise process of diabetes screening is comparable with that

of patients with diabetes of a similar age who have been diagnosed conventionally in routine clinical practice (29). 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 (29). 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 to 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%. The degree of underestimation by the UKPDS risk engine was less at 13% (30). As with all other risk calculators, the computation of risk for coronary heart disease 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 the men and in the older age groups. Compared with the cohort of patients in the UKPDS study (4), the participants recruited to ADDITION 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 the participants in ADDITION are older, more obese and hypertensive than those people with prevalent but undiagnosed diabetes in the Ely (10), Inter99 (9) and Hoorn studies (3). These differences between the participants in ADDITION and previous studies both of prevalent and previously undiagnosed may relate to 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 to the screening strategy that we employed which utilised 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 sub-population in ADDITION in which universal screening was used rather than a stepwise approach

was in 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 coronary heart disease risk (31).

Interpretation of our findings:

One of the key criteria that determines whether a screening programme for any particular condition should be considered is the availability of evidence demonstrating 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, then it would be unlikely that the attribution of the diagnostic label of diabetes would have a major impact on CHD risk. Thus the observation that we make 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 is a critical finding. The scope for intervention is considerable since in addition to the untreated or insufficiently treated hyperglycaemia, hypertension and hypercholesterolaemia, nearly one third of the cohort were current smokers and almost all were overweight, highlighting the potential for lifestyle intervention in addition to intensified pharmacological therapy. Determining whether such intensification of treatment is possible in primary care and whether it will have the expected impact on reducing cardiovascular events, is the goal of the 5-year follow-up of the ADDITION trial which will be complete in 2009.

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Table 1 Baseline characteristics of the participants with screen detected diabetes recruited to the ADDITION study (2001-2006).

	n	Total 3057	Men N = 1771	Women N = 1286
Age at diagnosis	3057	59.7 (6.8)	59.2 (7.0)	60.4 (6.6)*
% Non-white	2941	5.3	5.0	5.8
Alcohol consumption (units/week) +	2675	4 (0-162)	8 (0-162)	2 (0-115)
% current smokers	2996	27	29	25 *
% unemployed	2955	2.5	2.8	2.1
% already on antihypertensive treatment	2803	41	37	47 *
% already on lipid lowering treatment	2803	14	15	13 ¤
HbA1c (%),	2888	7.0 (1.6)	7.1 (1.7)	6.9 (1.4) ¤
Systolic BP (mmHg)	2961	151 (23)	152 (22)	151 (23)
Diastolic BP (mmHg)	2962	87 (12)	88 (12)	86 (11)*
BMI (kg/m^2)	2960	31.6 (5.6)	31.0 (5.0)	32.3 (6.2)*
Waist (cm)	2959	107 (13)	109 (13)	103 (14)*
Total cholesterol (mmol/l)	2892	5.6 (1.1)	5.4 (1.1)	5.7 (1.1)*
Total triglyceride (mmol/l)	2873	2.0 (1.5)	2.1 (1.7)	1.9 (1.1)*
HDL cholesterol (mmol/l)	2856	1.3 (0.4)	1.2 (0.4)	1.4 (0.4)*
LDL choleseterol (mmol/l)	2762	3.4 (1.0)	3.3 (1.0)	3.5 (1.0)*
Plasma creatinine (µmol/l)	2830	84 (18)	90 (17)	75 (15)*
% with microalbuminuria (urinary albumin:creatinine ratio >= 2.5 (women) / 3.5 (men))	2757	18.4	17.6	19.5

Data shown are mean (SD) or percentage except where indicated.
+ : median (range)
¤ : $p < 0.05$ in gender groups
* : $p < 0.001$ in gender groups

Table 2 Baseline characteristics of the participants with screen detected diabetes recruited to the ADDITION study (2001-2006) stratified by whether or not they are already on antihypertensive therapy

	Patients already receiving antihypertensive therapy	Patients not receiving antihypertensive therapy
N = 2803	1159 (41%)	1644 (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) ¤

* $p < 0.001$
¤ $p < 0.05$

Table 3 Baseline characteristics of the participants with screen detected diabetes recruited to the ADDITION study (2001-2006) stratified by whether or not they are already on lipid lowering therapy

	Patients already receiving lipid lowering therapy	Patients not receiving lipid lowering therapy
N = 2803	405 (14%)	2398 (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 triglyceride (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)*

* $p < 0.001$
¤ $p < 0.05$

Table 4. Median estimated 10 year absolute CHD risk (% with interquartile range) calculated from the UKPDS risk engine at baseline in the participants in the ADDITION study (2001-06) by age and sex.

Age-group	Men	Women	Total	Total *including imputed values when missing data*
40 – 49 years (n = 216)	12 (8 -15)	5 (3 – 7)	9 (5 – 14)	9 (6 – 13)
50 – 59 years (n = 930)	18 (13 - 24)	8 (6 – 11)	14 (9 – 20)	14 (9 – 20)
60 – 69 years (n = 1398)	26 (19 – 34)	13 (10 – 18)	19 (13 – 28)	19 (13 – 28)
Total population (n = 2544)	21 (15 – 30)	11 (7 – 16)	16 (10 – 25)	16 (10 – 24)

* UKPDS risk can only be estimated in cases with complete data for all included variables.