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The ADDITION† study: proposed trial of the cost-effectiveness of an intensive multifactorial intervention on morbidity and mortality among people with Type 2 diabetes detected by screening

T Lauritzen[1]*, S Griffin[2], K Borch-Johnsen[3], NJ Wareham[2], BHR Wolffenbuttel[4] and G Rutten[5] for the ADDITION Study Group

[1]*Department of General Practice, University of Aarhus, Denmark;* [2]*Department of Public Health and Primary Care, University of Cambridge, UK;* [3]*Steno Diabetes Centre, Denmark;* [4]*Department of Endocrinology and Diabetes, University Hospital of Maastricht, The Netherlands; and* [5]*Department of General Practice, University of Utrecht, The Netherlands*

OBJECTIVE: The overall aims of the ADDITION study are to evaluate whether screening for prevalent undiagnosed Type 2 diabetes is feasible, and whether subsequent optimised intensive treatment of diabetes, and associated risk factors, is feasible and beneficial.
DESIGN: Population-based screening in three European countries followed by an open, randomised controlled trial.
SUBJECTS AND METHODS: People aged 40–69 y in the community, without known diabetes, will be offered a random capillary blood glucose screening test by their primary care physicians, followed, if equal to or greater than 5.5 mmol/l, by fasting and 2-h post-glucose-challenge blood glucose measurements. Three thousand newly diagnosed patients will subsequently receive conventional treatment (according to current national guidelines) or intensive multifactorial treatment (lifestyle advice, prescription of aspirin and ACE-inhibitors, in addition to protocol-driven tight control of blood glucose, blood pressure and cholesterol). Patients allocated to intensive treatment will be further randomised to centre-specific interventions to motivate adherence to lifestyle changes and medication. Duration of follow-up is planned for 5 y. Endpoints will include mortality, macrovascular and microvascular complications, patient health status and satisfaction, process-of-care indicators and costs.
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Keywords: Type 2 diabetes; screening; multifactorial intervention; intensive; randomised controlled trial; family practice

Introduction

The aim of this paper is to describe the underlying rationale and proposed methods of the ADDITION study.

Type 2 diabetes meets many of the criteria for suitability for screening.[1–3] It is increasingly common[4,5] and is associated with a substantial burden of premature mortality, morbidity, suffering and financial cost, both through its macrovascular and microvascular complications.[6] When people first develop diabetes, either they have no symptoms, or if they do, they are frequently unable to recognise them.[7] Half of those meeting the diagnostic criteria for diabetes are undiagnosed[8] and extrapolation of the association between prevalence of retinopathy and duration of disease implies that diagnostic criteria might be met up to 12 y before clinical recognition.[9–11] When patients are diagnosed 25% already have established retinopathy,[12] half have clinical evidence of diabetic tissue damage,[13] and many exhibit additional adverse cardiovascular risk factors.[12,14] Furthermore, the options for treatment of hyperglycaemia in people with diabetes diagnosed clinically, and the effectiveness of these options are limited.[15]

A growing body of evidence suggests that earlier detection and treatment of hyperglycaemia and related metabolic abnormalities may be beneficial. The degree and duration of hyperglycaemia are associated with the development of microvascular complications.[16] Hyperglycaemia is also associated with the development of macrovascular disease.[17] The risk of complications can be reduced by intensive treatment of hyperglycaemia[15,18] and more substantially through reduction of associated cardiovascular risk factors among people with clinically diagnosed disease.[19–22] Screening for hyperglycaemia can identify patients at an early stage of the disease[23] who are likely to benefit

*Correspondence: T Lauritzen, Department of General Practice, University of Aarhus, Aarhus, Denmark.
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†**ADDITION**: **A**nglo-**D**anish-**D**utch Study of **I**ntensive **T**reatment **I**n Pe**o**ple with Scree**n** Detected Diabetes in Primary Care. Principal investigators: T Lauritzen and K Borch-Johnsen.

from intensive treatment of cardiovascular risk factors.[14,20,24] Indeed, the results of recent trials suggest that much of the potential benefit of detection of undiagnosed diabetes is likely to accrue from intensive management of several cardiovascular risk factors as well as hyperglycaemia.[21,22] It also seems that patients who are given the label of diabetes may benefit from becoming involved in a more organised and effective system of risk factor management.[25,26] However, the benefits of initiation of intensive treatment, with newer therapies and stricter management targets, among people with diabetes detected by screening, have not been quantified.

There are also few data on the costs, both economic and psychological, of screening. Cost-effectiveness has been modelled using data from existing trials of treatment effectiveness and observational studies.[9,27,28] The conclusions of these studies are highly dependent upon certain crucial assumptions, and reach different conclusions about whether screening should be undertaken and which sub-groups could potentially benefit. None of the studies include more recent trial evidence. Nevertheless, screening is now recommended by the American Diabetes Association.[29]

Intensive management of diabetes and cardiovascular risk includes changes in behaviours such as smoking, physical activity, food choice and taking medication. Previous health promoting interventions in primary care, aimed at reducing cardiovascular risk, have produced modest benefits.[30] Patients also find taking regular medication difficult, particularly for multiple drugs in asymptomatic conditions.[31] It is unclear whether additional interventions, based on theory and evidence from psychology,[32–34] and studies of consultation skills,[35–37] designed to facilitate and maintain changes in behaviour (including medication adherence) could be cost-effective among screen-detected cases.

Type 2 diabetes is increasingly diagnosed and managed in primary care,[38] and there is growing evidence that family practitioners are able to provide standards of care as good as that achieved in hospital outpatient departments.[39,40]

The overall aims of ADDITION (**A**nglo-**D**anish-**D**utch Study of **I**ntensive **T**reatment **I**n Pe**o**ple with Scree**n** Detected Diabetes in Primary Care) are to evaluate whether screening for prevalent undiagnosed Type 2 diabetes is feasible, and whether subsequent optimised intensive treatment of the disease, and associated risk factors, is feasible and beneficial.

Design and methods

The ADDITION study in Type 2 diabetes will consist of two phases: a screening study and a subsequent treatment study. In the screening study, we will evaluate the feasibility and results of three similar approaches to identifying people with undiagnosed Type 2 diabetes. Following completion of the screening study, the treatment study will compare the effects of standard treatment according to national guidelines, with intensive multifactorial therapy on mortality, macrovascular and microvascular disease. We will also assess the impact of treatment on patients' health status, quality of life, treatment satisfaction and health service use.

Screening study

In Denmark, primary care physicians participating in the study will send diabetes-related information to all individuals aged 40–69 y enrolled in their practice. The information will deal with risk factors for Type 2 diabetes, and an accompanying letter and questionnaire will encourage individuals at high risk of diabetes to contact their physician for a blood glucose screening test. The questionnaire includes items on risk factors; symptoms of hyperglycaemia; family history of Type 2 diabetes; obesity; and previous cardiovascular disease, hypertension or dyslipidaemia. Criteria for contacting the physician will be chosen to encompass at least 75% of previously undiagnosed people with diabetes through examination of no more than 20% of the population receiving information.

In England, a simple previously validated risk score, based on routine general practice data (age, gender, prescribed medication and body mass index),[41] will be used to identify people at high risk of having prevalent undiagnosed diabetes from their computerised medical records. The score should enable identification of 80% of those with undiagnosed diabetes through blood glucose testing of approximately 30%.[41] In The Netherlands all patients aged 40–69 y, without known diabetes, in participating practices will be offered a screening test.

In all three countries random capillary blood glucose will be measured in general practice using a HemoCue.[42] If the random capillary blood glucose is less than 5.5 mmol/l the person is told that diabetes is highly unlikely. If the random blood glucose is equal to or greater than 5.5 mmol/l, the person will be invited to attend for a fasting capillary blood glucose, and if needed, a 2-h post-glucose-challenge measurement (OGTT), as determined by the algorithm in Figure 1. The cut-off value of 5.5 mmol/l will be reviewed after testing the first 500 people and assessing the number requiring a second visit for a fasting sample. Individuals diagnosed with Type 2 diabetes will be asked to complete baseline measures including quality of life, health utility and self-perceived health.

Diagnostic criteria for Type 2 diabetes will follow current World Health Organization guidelines[43] (Figure 1). The algorithm differentiates individuals with Type 2 diabetes from those with impaired glucose tolerance and impaired fasting glycaemia, who will not be included in the treatment study.

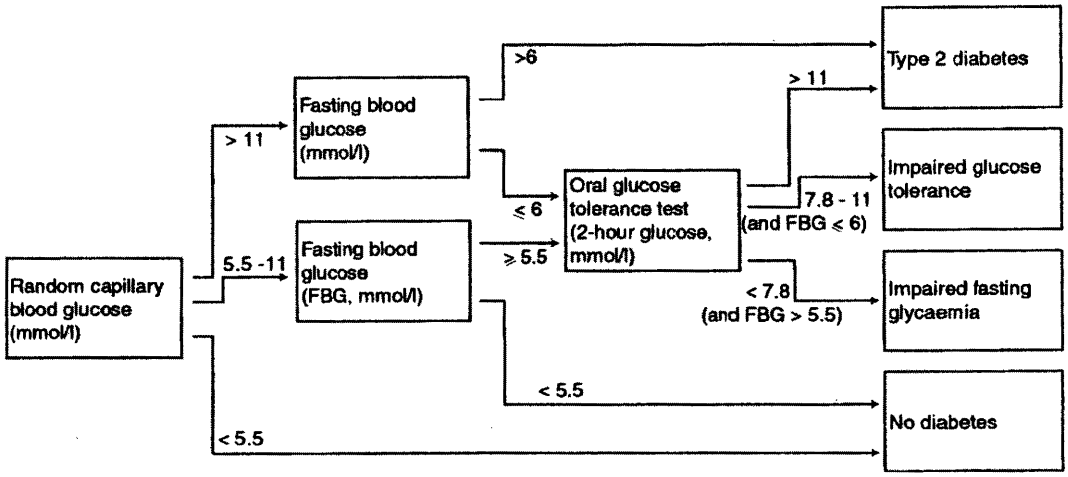

Figure 1 Outline of algorithm for diagnosis for Type 2 diabetes using HemoCue for immediate measurement of capillary whole blood glucose.

Patients previously diagnosed with diabetes, or treated with blood glucose lowering agents will be excluded. Outcome measures for the screening study are listed in Table 1. These include measures of epidemiology and the performance of the screening campaign, the objective health status of patients newly identified by the campaign, its feasibility as reported by the primary care physician, and the costs of such a programme.

We will also assess the broader impact of the information campaign by interviewing and sending questionnaires to a number of people who: (a) received the information but did not respond (for any reason); (b) contacted their physician and were not diagnosed with Type 2 diabetes; and (c) contacted their physician and were newly identified with Type 2 diabetes. The interviews and subsequent analysis will explore the psychosocial aspects of identifying an at risk population and conducting a screening campaign for Type 2 diabetes.

Treatment study

Patients newly identified with Type 2 diabetes will be invited to enter the ADDITION treatment study. This will compare the long-term effects of standard treatment with that of intensive multifactorial treatment, on key endpoints of mortality and morbidity. The study will be a pragmatic open, multicentre, randomised controlled trial with a duration of follow-up of 5 y.

Table 1 Outcome measures for the ADDITION screening study

Number of (high-risk) individuals presenting for examination
Number of people with newly diagnosed Type 2 diabetes
Psychological status of people invited for screening
Metabolic status of people with newly diagnosed Type 2 diabetes
Cardiovascular risk profile in people with newly-diagnosed Type 2 diabetes and all those with random capillary blood glucose > 5.5 mmol/l
Self-perceived health in people with newly-diagnosed Type 2 diabetes
Practitioner assessment of feasibility and workload
Health service costs
Patient costs

All patients newly diagnosed with Type 2 diabetes in the screening study will be eligible to participate, unless they are found to have: contraindications or intolerance to study medication; a history of alcoholism, drug abuse, psychosis or other emotional problems that are likely to invalidate informed consent or adherence to treatment; malignant disease with a poor prognosis; or are pregnant or lactating. Informed consent will be sought and obtained from all patients and the study will be performed in accordance with the Declaration of Helsinki.

General practices will be randomised into two groups: the conventional therapy group will give standard care according to broadly similar national recommendations[44–47] for the management of Type 2 diabetes and prevention of cardiovascular disease. The other group will receive education and training in the provision of intensive multifactorial treatment. The intensive therapy will include prescription of aspirin, lifestyle advice (concerning diet, physical activity and tobacco consumption) and stepwise increases in drug treatment of blood glucose, blood pressure and lipids according to strict targets as shown in Figure 2. Within the intensive group, a further randomisation will allocate some patients to country-specific interventions concerned with motivating adherence to lifestyle changes and medication. This intervention, delivered either by a trained facilitator (England and The Netherlands) or through training of practitioners (Denmark), will be based on a client-centred, non-directive counselling style to help patients explore and resolve ambivalence and stimulate lifestyle changes, appropriate diabetes self-care and adherence to medical treatment.[35,36]

	Basic treatment		Supplemetary treatment		
	Increase dose with 2 to 4 weeks interval, go to next treatment step when max. daily dose is reached or if side-effects appears. See patient every 2nd week until target is reached, more frequent with start of insulin treatment.				
	TARGET:	*if above target add*	*if still above add*	*if still above*	
HbA_{1c}	≤ 7.0%:	> 7.0%:	> 7.0%:	> 7.0%:	
BMI ≤27	diet	PGR (eg repaglinide) or SU (eg gliclazide)	BG (eg metformin)	continue PGR or SU, add Insulatard 12IU at bed time, increasing with 4-6IU every week until fbg < 7 mmol/l. If more than 30 unit then divide dose and quit oral drugs.	
BMI>27	diet	BG (eg metformin) or PGR (eg repaglinide) or SU (eg Gliclazide)	PGR (eg repaglinide), or SU (eg Gliclazide) or BG (eg metformin)	continue BG, add Insulatard 12IU at bed time, increasing with 4-6IU every week until fbg < 7 mmol/l. If more than 30 unit then divide dose and quit oral drugs.	
BP	≤ 120/80 mmHg:	> 120/80 mmHg:	> 135/85 mmHg:	> 135/85 mmHg:	> 135/85 mmHg:
	none	ACE-inhibitor low to max dose	B-blocker (eg metoprolol) or TZD (eg bendrofluazide)	TZD (eg bendrofluazide) or LD (eg frusemide) or B-blocker (eg metoprolol)	Ca antag (eg amlodipine)
Cholesterol					
-CVD*	≤ 5.0 mmol/l: diet	> 5.0 mmol/l: diet + statin small dose	> 5.0 mmol/l: statin dose up to maximum		
+CVD*	≤ 4.5 mmol/l: diet	> 4.5 mmol/l: diet + statin small dose	> 4.5 mmol/l: statin dose up to maximum		
Acetylsalicylic acid	75 mg to all patients treated with antihypertensive agents				

Figure 2 Outline of treatment recommendation in the intensive-therapy arm. The protocol allows for advantage to be taken of new drug developments and the final decision will depend on the individual doctor and patient. BMI, body mass index (kg/m^2); NPH, neutral protamine Hagedorn; PGR, prandial glucose regulator; SU, sulphonylureas; BG, biguanide; TZD, thiazide diuretic; LD, loop diuretic; CVD, cardiovascular disease; fbg, fasting blood glucose.

Table 2 Endpoints of the ADDITION treatment study

Primary endpoints
- All-cause mortality
- Cardiovascular mortality/morbidity
- Nonfatal myocardial infarction
- Nonfatal stroke
- Amputations
- Hospitalisation for angina
- Hospitalisation for congestive heart failure
- Coronary revascularisation
- Peripheral revascularisation

Secondary endpoints
- Development of renal impairment
- Diabetic ulcers
- Blindness
- Reduced visual acuity
- Macular oedema
- Retinopathy
- Health status
- Health utility
- Quality of life
- Patient satisfaction
- Health service costs
- Patient costs

Intermediate endpoints
- Smoking status
- Diet
- Physical activity
- Medication adherence
- Haemoglobin A_{1c}
- Total cholesterol
- LDL-cholesterol
- HDL-cholesterol
- Triglycerides
- Blood pressure
- Hypoglycaemic episodes
- Microalbuminuria
- Body mass index

Process-of-care endpoints
- Visits to outpatient clinics
- Hospital admissions

Recommendations on drug choices in Figure 2 are based on balancing treatment effect, side-effects and cost—the main priority being achievement of treatment targets with a flexible lifestyle and low rates of side-effects such as hypoglycaemia and weight gain. The final decision on choice of medication will be determined by the individual doctor and patient.

Initial therapies will be adjusted at 2 to 4-weekly intervals until targets are reached (thereafter every 3 months). When the maximum daily dose of an agent is reached the next treatment step will be made. Blood pressure, blood glucose, haemoglobin A_{1c} and body weight will be measured by practitioners at least quarterly throughout the study. In addition, urinary albumin and creatinine, cholesterol (total, LDL and HDL) and triglycerides will be measured annually, at which time an electrocardiogram, foot examination and eye examination will also be performed. Questionnaires will be used to assess patient health status and treatment satisfaction.

Endpoints of the treatment study are given in Table 2. These include measures of mortality and morbidity; macrovascular and microvascular complications of diabetes; measures of metabolic and hypertensive control; and endpoints related to the process of care.

Sample size and statistical power

The expected event rate in the treatment study, based on levels of risk in the conservative-treatment arm of the UKPDS, is 3% annually for the combined endpoint of all-cause mortality, nonfatal myocardial infarction, stroke or amputation.[15] We calculate that a sample size of 1350 patients in the treatment study will allow the detection of a 30% relative risk

reduction in the intervention group at a significance level of 5%. To allow for the effects of clustering, approximately 3000 patients will be included in total.

Timescale

The screening study will begin in late 2000. Patients will be enrolled into the treatment study following diagnosis in the screening study: thus the treatment study will proceed concurrently with the evaluation phase of the screening study, extending until the end of 2001. A duration of follow-up of 5 y means that the final study visit will occur during 2006.

Concluding remarks

Ideally, our goal is to prevent Type 2 diabetes, but for those who do develop the condition, we must ensure that they receive the best available treatment as soon as possible. Many people have undetected Type 2 diabetes, who we often see when they present with late diabetic complications. As with all screening programmes there is a balance between the potential benefits and psychological, physical and economic costs. This balance is particularly precarious when treatments are intensive, lifelong and expensive. The ADDITION study will inform judgements about these issues.

The results of the study will be of immediate relevance to policy decisions about screening for diabetes, and subsequent treatment internationally. The results of the sub-study will inform approaches to health promotion, to the management of chronic disease and risk, and to strategies to support adherence.

The ADDITION Study Group

A Adeler, T Bek, ML Bartelink, J Bensing, JS Christiansen, T Jørgensen, H Juel, S Kajsa, AL Kinmonth, M Kjølbye, A Larsen, CE Mabeck, OB Pedersen, A Sandbaek, J Søgaard, R Stolk, B Christensen, L Ovesen, S Arnold, K Mai, H Lund-Andersen, L Heikendorff.

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