

Screening for diabetes: what do the results of the ADDITION trial mean for clinical practice?



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Practice Points

- In Denmark, only 20% of those with undiagnosed diabetes were identified by screening.
- For each person with diabetes identified, another two at high risk of diabetes and six at high risk of cardiovascular disease were identified.
- Screening for diabetes had limited short- and long-term adverse psychological impact on participants.
- Cardiovascular risk factors (weight, blood pressure and cholesterol), including health-related behaviors (smoking), improved substantially following detection of diabetes by screening.
- Small increases in treatment intensity of screen-detected patients were associated with a nonsignificant 17% reduction in risk of a first cardiovascular event.
- Among people with screen-detected diabetes, all-cause mortality over 7 years was twice as high for those with HbA1c <6.0% compared with those with HbA1c ≥6.5% at screening. Those with HbA1c <6.0% were less intensively treated than those with HbA1c ≥6.5%. The latter group had an all-cause mortality that was not significantly different from people with normal glucose tolerance and HbA1c <6.0% at screening, presumably due to more intensive treatment.
- At the population level, invitation of high-risk individuals to screening was not associated with a reduction in all-cause or diabetes-related mortality over 10 years.
- The ADDITION study provides further evidence of the net benefit associated with earlier detection and treatment of Type 2 diabetes. Rather than screening the population for diabetes, primary care teams should focus efforts on earlier detection and treatment of risk factors among those with diabetes, at high risk of diabetes and high risk of cardiovascular disease.

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SUMMARY The main ADDITION study was planned as a screening study followed by a randomized, intervention study comparing routine treatment with more intensive treatment in people with screen-detected diabetes. The stepwise screening programs had low yield, but for each person with diabetes identified, another two at high risk of diabetes and six at high risk of cardiovascular disease were identified. Screening for diabetes had limited short- and long-term adverse psychological impacts on participants. The intervention study showed substantial improvements in cardiovascular risk factors following detection of diabetes, even among those receiving routine general practice care. The randomized trial did not deliver conclusive evidence to justify implementation of a systematic screening program. Uncertainties remain concerning the overall cost-effectiveness. However, the overall results of the ADDITION study, including cohort analyses, suggest that earlier detection and treatment of diabetes is associated with net benefits. Thus, primary care teams are encouraged to develop systems to enable earlier detection. This might include opportunistic screening. Individuals identified should be offered lifestyle interventions and preventive drug treatments appropriate to their level of risk.

Type 2 diabetes fulfils many of the criteria for screening. It is a common chronic disease affecting 350 million people worldwide in 2011 and is predicted to reach 550 million by 2030 [1]. A significant proportion of people with diabetes, (up to 50% in many studies), remain undiagnosed and, therefore, untreated. Expenditure related to diabetes in 2010 was estimated to be approximately 10% of total healthcare budgets, and is projected to rise to 17% in 2035 [2]. People with diabetes have raised cardiovascular risk and up to 50% exhibit evidence of micro- or macro-vascular complications at diagnosis. Complications of diabetes are associated with reduced life expectancy and quality of life. Intensive treatment of single and multiple risk factors (elevated glucose, lipids and blood pressure) has been shown to reduce the risk of developing micro- and macro-vascular complications in people with clinically diagnosed Type 2 diabetes [3–6]. Based on these observations, screening for diabetes has been recommended in several countries (e.g., the USA [7] and UK [8]) in line with conclusions from a modeling study [9]. This is in spite of the lack of direct evidence from randomized controlled trials [10,11] and the remaining uncertainty concerning the magnitude of the benefit of treatment early in the disease trajectory and the direct and indirect harms associated with screening. In addition, data on overall cost-effectiveness of screening programs [12,13] are not available.

The ADDITION study was planned in 1999 to evaluate whether population-based screening for undiagnosed Type 2 diabetes was feasible in a primary care setting, whether subsequent optimized intensive treatment of diabetes, and associated risk factors, among screen-detected patients was feasible in primary care and

benefited patients, and to quantify the harms associated with screening. Previous screening studies have focused on people with prediabetes and how to prevent progression from prediabetes to diabetes.

The aim of this article is to summarize the findings of the ADDITION study and to speculate on what the results mean for clinical practice.

Design of the ADDITION trial

In brief, the ADDITION trial consists of two phases: a screening phase, followed by a subsequent treatment phase designed as a pragmatic, cluster-randomized trial in four centers (Aarhus and Copenhagen [Denmark], Utrecht [The Netherlands], and Cambridge and Leicester [UK]). Of the 1312 general practices invited to participate, 29% agreed and were randomized to screening and subsequent routine care of diabetes or intensive multifactorial treatment. Patients were unaware of their general practice's group assignment throughout the study. The rationale and detailed design have been described elsewhere [14–16].

■ Screening programs

Seven different population-based screening programs targeted 395,000 people without known diabetes, aged 40–69 years (50–69 years in The Netherlands). Screening was conducted between April 2001 and December 2006, as previously described [14–18]. With the exception of the Leicester center, where all middle-aged participants were invited to attend for oral glucose tolerance tests without prior risk assessment, screening programs targeted a subset of the population at an increased risk of prevalent undiagnosed diabetes. The first screening step in Cambridge

involved calculation of a risk score based on data from electronic records. In Denmark and The Netherlands, risk was assessed by diabetes risk questionnaires. The second screening step included random capillary glucose testing and, in Cambridge and Denmark, HbA1c measurements. In Denmark, a small subgroup of practices conducted two different opportunistic screening programs.

Diabetes was diagnosed according to WHO criteria [19], including a confirmatory glucose test on a separate day. Exclusion criteria were: an illness with a life expectancy of less than 12 months, homebound, pregnancy or lactation, or psychological or psychiatric problems that were likely to invalidate informed consent.

Overall 3057 eligible participants with screen-detected diabetes agreed to take part in the intervention study (Denmark: 1533, Cambridge: 867, The Netherlands: 498 and Leicester: 159).

■ **Intervention: training of general practitioners & staff to deliver intensive treatment**

In Cambridge, Denmark and The Netherlands, general practitioners and practice nurses in the intensive treatment group were educated in target-driven management. This included the promotion of a healthy lifestyle and medication for hyperglycemia, blood pressure and cholesterol, based on the stepwise regimen used in the Steno-2 study [6]. In Leicester, an intermediate care model was used involving a specialist team [20]. Treatment targets and algorithms used in all centers are shown in [Table 1](#). Prescribing decisions, including choice of individual drugs, were shared between the individual patient and the general practitioner/nurse or the specialist team (Leicester).

Except in Leicester, intensive treatment was promoted through small group- or practice-based educational meetings arranged for general

practitioners and nurses to discuss treatment targets, lifestyle advice and drug treatment algorithms. Audit and feedback was included in follow-up meetings up to twice per year and in mailed quality control data. In The Netherlands, patients were seen in the general practice by diabetes nurses who were authorized to prescribe medication and adjust doses. In Denmark and Cambridge, practice staff were provided with educational materials for patients. In Denmark and The Netherlands patients were sent reminders if annual measures were overdue. In all centers, practices received a small amount of additional funding to support the delivery of care. In Leicester, patients received the DESMOND structured education self-management program [20]. Further details of the intensive treatment program are described on our website [101] and in separate papers [14–17].

■ **Control arm: routine care**

In the routine care group, general practitioners were asked to follow respective current national treatment guidelines [17].

■ **Outcomes**

Outcome measures for the screening study included, among others, the yield in terms of the percentage of people diagnosed with Type 2 diabetes, the cardiovascular risk of identified people, self-evaluated health and psychological measures.

Outcome measures for the treatment study were as follows: the primary end point was a composite of first cardiovascular event, including cardiovascular mortality, cardiovascular morbidity (nonfatal myocardial infarction and nonfatal stroke), revascularization and nontraumatic amputation. Secondary end points were all-cause mortality, microvascular disease, health status, health utility, quality of life, patient satisfaction and cost. Intermediate end points were lifestyle and biochemical measures.

Table 1. Treatment algorithm in the intensive arm of the ADDITION study.

Topic	Recommendation
Lifestyle	Diet, physical activity and smoking cessation
HbA1c	If $\geq 6.5\%$ treatment should be intensified
Blood pressure	If $\geq 120/80$ mmHg prescribe ACEI If $\geq 135/85$ mmHg treatment should be intensified
Total cholesterol	If ≥ 5.0 mmol/l and no CVD or ≥ 4.5 mmol/l and CVD, recommend diet and statin Since 2002: if ≥ 3.5 mmol/l, recommend diet and statin
Low-dose aspirin	To everyone on blood pressure treatment
ACEI: ACE inhibitor; CVD: Cardiovascular disease. Data taken from [17].	

Results

■ Low yield from screening for diabetes

The yield of screen-detected patients was low compared with the target population of 40–69 years (The Netherlands: 50–69 years) [18,21]. The yield was very similar and much lower than expected in all of the seven screening programs [18,21]. The lowest yield was 0.34% of those invited directly to an oral glucose tolerance test, without prior risk stratification. In the other centers using high-risk screening strategies, between 0.64 and 1.09% of the target population was identified with screen-detected diabetes. The highest yield (1.09%) was found using opportunistic screening with a risk assessment by questionnaires before the consultation and immediate blood tests after the consultation. If blood samples were taken at a later date, fewer people were identified with screen-detected diabetes (0.6%). The opportunistic screening program was associated with a lower cost [22].

When comparing the yield with those attending screening due to high risk, the yield was 2.6–6.0% in the ADDITION trial [18]. In Denmark where the target population was very similar to the general population of 40–69-year-old people, the yield was 5.2–6.0%. This yield seems similar to that of the Finnish National Diabetes Prevention program [23].

From a Danish substudy, we could estimate that we identified only 20% of those with undiagnosed diabetes corresponding to an estimated prevalence of people with undiagnosed diabetes of approximately 4% in Denmark. The main reasons for the low yield were that only 50% of those at high risk responded to the risk questionnaires and, as with most screening programs, nonresponders are likely to be those at highest risk. Furthermore, each test in the stepwise screening program had less than 100% sensitivity, for example, the risk questionnaire had a sensitivity of only 75%.

■ Factors associated with screening uptake

Knowledge about factors associated with attendance for screening may help to provide new strategies to maximize the yield of screening.

In the UK, practice characteristics, such as a large list size, higher prevalence of known diabetes and rural location, were associated with higher uptake of glucose testing, while higher general practitioner whole-time equivalents and higher deprivation score were associated with lower uptake. Patients characteristics, such as

male sex and a higher BMI, were associated with lower attendance for blood testing, whereas older age, prescription of antihypertensive medication and a higher risk score were associated with a higher attendance for blood tests [24].

In The Netherlands, the yield per practice varied widely [25], ranging from 1.1 to 14.1 screen-detected patients per practice adjusted for practice size and age distribution of patients. A lower yield was found in urban practices and in practices with younger general practitioners.

In Denmark, those who attended the screening program were more likely to be older, be unemployed and live in the countryside than nonattenders [26]. No substantial socioeconomic differences were found between attenders and nonattenders.

There has been considerable discussion concerning the content of invitations for screening, particularly mammographic screening [27]. The DICISION trial showed no difference in attendance between brief invitations and more detailed ones when inviting individuals for screening for diabetes [28]. The ADDITION-UK study showed no significant differences in attendance rate, nor in mean anxiety, self-rated health or illness representations 6 weeks after receipt of a loss-framed invitation, which highlights the possible losses of not attending the screening program, or gain-framed invitations, which emphasize the possible gains of attending [29].

■ Psychological effect of screening

A substudy in Cambridge found no evidence of significant psychological harm in people up to 15 months after screening assessed using measures of anxiety, depression and worry about diabetes [30]. There were differences in psychological measures between people who screened positive at the first blood test compared with people who screened negative, but the differences were small and unlikely to be clinically relevant. The more blood tests people had undergone before screening negative, the more worried they became about developing diabetes. The level of worry was, however, low. The number of self-reported symptoms at the first screening test was associated with anxiety and depression at the 1-year follow-up, whereas no relation was found between screening outcomes, and anxiety and depression. Furthermore, a negative test result at diabetes screening did not promote false reassurance [31]. A Danish substudy measuring health-related quality of life, anxiety and worry

indicated that the psychological effects of attending a high-risk screening program for diabetes were minor and without clinical relevance [32].

A qualitative interview study suggested that the stepwise nature of the screening program seemed to help people to adjust their psychological response to their risk of developing diabetes [33]. However, it might be of some concern that participants seemed unaware of their remaining high risk of diabetes and cardiovascular disease when screening test results for diabetes were negative [33].

Patients with screen-detected diabetes reported low emotional distress, low threat perceptions and high self-efficacy but low self-care behavior. Patients vary considerably in their emotional and cognitive outcomes, depending on the time since diagnosis and treatment intensity. Intensively treated patients reported more distress and less self-efficacy in the first year, whereas usual-care patients showed relatively more distress and less self-efficacy 2–3 years after diagnosis [34]. Furthermore, intensified treatment compared with routine treatment did not influence self-rated health status, treatment satisfaction and distress in screen-detected Type 2 diabetic patients [35].

Taken together, these results suggest that any benefits for the minority in which diabetes was detected by screening are unlikely to be outweighed by small harms to the majority with negative screening test results.

■ Screening for diabetes identifies more people at high risk of diabetes & high cardiovascular risk than people with diabetes

In Denmark, for each person identified with diabetes, two were identified as being at high risk of diabetes (impaired fasting glucose or impaired glucose tolerance) and six with a high cardiovascular risk but without diabetes [36]. Approximately one in three people with a high risk of diabetes developed Type 2 diabetes within 3.5 years [37,38]. All-cause mortality over 7 years of follow-up was three- to eight-times higher among people with normal glucose tolerance and high cardiovascular risk (system for cardiac operative risk evaluation [SCORE]: ≥ 5) [39] compared with people with a normal glucose tolerance and low cardiovascular risk (SCORE: < 5) [36]. Most people with a high cardiovascular risk without diabetes did not receive optimal preventive drug treatment [40,41]. In the future, screening for

diabetes should be integrated with screening for a high risk of cardiovascular disease.

■ HbA1c & cardiovascular risk scores identify people who may benefit from preventive treatment

Combining SCORE [39] with either HbA1c or glucose measures was equally effective in identifying people who may benefit from preventive interventions, such as those with excess all-cause mortality within 7 years of follow-up or Type 2 diabetes at screening defined by the old WHO diagnostic criteria [36]. Both combinations identified approximately 97% of people who might benefit from preventive interventions compared with 92, 26 and 20%, respectively, when using cardiovascular risk assessment alone, glucose measures alone or HbA1c alone. Assessment of HbA1c and cardiovascular risk factors is feasible in primary care and may help improve the yield of screening.

■ People with screen-detected diabetes had high but potentially modifiable cardiovascular risk

The median 10-year risk of coronary heart disease evaluated by the UKPDS risk engine was 11% in women and 21% in men [42]. There were differences in distribution of risk factors by country, related to the different screening strategies and the extent to which risk factors had already been detected and treated. The potential for reducing risk was high given that 73% of patients had a blood pressure $\geq 140/90$, 58% of whom were not on antihypertensive medication. Similarly, cholesterol levels were > 5.0 mmol/l in 70% of participants, 91% of whom were not prescribed lipid-lowering drugs. Compared with participants in the UKPDS study [43] participants in the ADDITION study were older, more obese, more hypertensive and had higher levels of serum cholesterol, probably due to the nature of the screening strategies.

■ People with screen-detected diabetes had a low prevalence of diabetic retinopathy

The prevalence of diabetic retinopathy was evaluated in a Danish substudy. Less than 7% had any retinopathy at the time of screening [44]. The majority had minimal retinopathy and no patients had severe nonproliferative diabetic retinopathy. Patients with retinopathy had significantly higher HbA1c, and systolic and diastolic blood pressure than the patients without

retinopathy. The prevalence of any diabetic retinopathy in the UKPDS study was 37% with many having vision-threatening retinopathy [43]. The results suggest that people with screen-detected diabetes in the ADDITION study were identified earlier in their disease trajectory than UKPDS participants.

■ Microalbuminuria

Microalbuminuria was common (18.4%) in people with screen-detected diabetes in the ADDITION study [42]. In the UKPDS study, only 6.5% were found to have microalbuminuria at diagnosis [45]. The criteria and the method used for measuring microalbuminuria in the two studies differed, limiting the interpretation of comparisons.

■ Detection of diabetes & subsequent treatment reduce cardiovascular risk factors

Following diagnosis of diabetes, cardiovascular risk factors, such as weight, smoking, blood pressure, cholesterol and glycemia, improved considerably in the routine care group [17], as shown in Table 2. Most of these risk factors were further improved in the intensive treatment group. However, the change in risk factors from baseline to 5-year follow-up in both groups was more impressive than the difference in risk factors between the two groups at 5 years.

Table 2 also demonstrates the proportion of people prescribed one or more blood pressure-, lipid- and glucose-lowering drugs and aspirin at the time of diagnosis and 5-year follow-up. Considerably more people were prescribed these drugs at follow-up rather than prior to diagnosis by screening, even in the routine care arm. In contrast with the UKPDS study [46], HbA1c in the ADDITION study did not increase in the 5 years following diagnosis. Furthermore, patients lost a mean weight of 2 kg over this period of time. Reductions in BMI and the proportion smoking between baseline and follow-up suggest that lifestyle changes may also have been a consequence of being identified with screen-detected diabetes.

■ Cardiovascular end point: 5-year follow-up comparing routine care with intensive treatment

The ADDITION study was planned as a cluster randomized trial comparing routine care with intensive treatment [14,17]. The composite primary end point was defined as the first of one

of the following events: cardiovascular death, nonfatal myocardial infarction, stroke, revascularization or amputation. We found that the relatively small difference in treatment between intensive treatment and routine care groups (Table 2) in the first 5 years following diagnosis resulted in a nonsignificant 17% reduction in the incidence of the primary end point [17]. The event rate in the routine care arm (8.5% over 5 years) was less than expected, and less than reported for newly diagnosed patients in the UKPDS (12.1%) [47]. Furthermore, mortality in the routine care arm (6.7% over 5 years) was lower than among patients with screen-detected diabetes in the Hoorn study (25% over 10 years) [48] and lower than newly diagnosed people with Type 2 diabetes in Denmark (33% over 7.4 years) [49]. All-cause mortality in the routine care arm in the ADDITION study was much lower than among people with clinically diagnosed diabetes in the Danish diabetes register and not much greater than among the Danish general population without known diabetes. In both comparisons, matching for age and gender were included. It appears that screening may be associated with a reduction in premature mortality among people found to have diabetes. However, it remains unclear whether this difference in mortality is simply a function of the lead time between detection by screening and clinical diagnosis, or whether earlier detection and treatment does alter the trajectory and outcomes of the diabetes. The observations that all-cause mortality among people with screen-detected diabetes and HbA1c >6.5% at screening was near normal [41] and that small increases in treatment were associated with a statistically significant 41% reduction in mortality in the UK [17] suggests that effects are not simply a function of lead time bias.

■ All-cause mortality in people at high risk of diabetes following screening & no screening

Invitation to one round of screening in high-risk individuals was not associated with a reduction in mortality (all-cause, cardiovascular, cancer, diabetes-related or other causes of death) over 10 years [50]. Thus, from a population-based perspective, any adverse effects of screening for the majority of people testing negative did not outweigh the benefits to the small minority (3%) with screen-detected diabetes. The data also suggest that the benefits of screening might

be smaller than expected and restricted only to individuals with screen-detected diabetes. This is not altogether surprising given that no intervention was offered to individuals who tested negative in spite of being at an increased risk of developing both diabetes and cardiovascular disease [51]. Benefits to the population might be increased by detection and management of people at high risk of cardiovascular disease, alongside those at risk of diabetes and those with screen-detected diabetes. Further benefits might also accrue from repeated rounds of screening, identification of nonattenders who tend to be at higher risk and strategies to maximize uptake of screening. However, these proposals would inevitably increase the costs of a screening program.

■ Cohort follow-up study on all-cause mortality in people at high risk of diabetes

In ADDITION-Denmark, compared with those with screen-detected diabetes and HbA1c $\geq 6.5\%$ at screening, all-cause mortality at 7-year follow-up was twice as high among those with screen-detected diabetes and HbA1c $< 6.0\%$ at screening, and even higher among those with an HbA1c $\geq 6.5\%$ but who were not diagnosed with diabetes (Figure 1) [41]. We hypothesized that general practitioners may have been falsely reassured by the exclusion of the diagnosis of diabetes and by low HbA1c levels among people with screen-detected diabetes, and, therefore, did not offer optimal preventive treatment according to guidelines targeting risk factors for cardiovascular disease, including glycemia [41]. During 7 years of follow-up, fewer people with screen-detected diabetes and HbA1c $< 6.0\%$ at screening redeemed prescriptions for lipid-, blood pressure- and glucose-lowering drugs than those with screen-detected diabetes and HbA1c $\geq 6.5\%$ at screening, which supported our hypothesis.

For those at highest risk at screening, such as those with screen-detected diabetes and HbA1c $\geq 6.5\%$ at screening, all-cause mortality was not significantly different from those with normal glucose tolerance and HbA1c $< 6.0\%$ at screening. This suggests that concurrent treatment of multiple risk factors in this group of patients is likely to be beneficial.

By comparison, people with normal glucose tolerance and HbA1c $\geq 6.5\%$ at screening were relatively undertreated during follow-up [40,41]. This group had the highest all-cause mortality

Table 2. Risk factors and drug treatment at diagnosis and 5-year follow-up.

Characteristic	Routine care			Intensive treatment		Difference between RC and IT in change from diagnosis to follow-up**
	At time of diagnosis	5-year follow-up	Change from diagnosis*	At time of diagnosis	5-year follow-up	Change from diagnosis*
Participants† (n)	1379	1285	–	1678	1574	–
SBP (mmHg)	149.8	138.1	-11.7	148.5	134.8	-13.7
DBP (mmHg)	85.5	80.7	-4.8	86.1	79.5	-6.6
Cholesterol (mmol/l)	5.6	4.4	-1.2	5.5	4.2	-1.3
HbA1c (%)	6.6	6.5	-0.1	6.5	6.4	-0.1
Weight (kg)	90.3	88.4	-1.9	90.9	89.1	-1.8
BMI	31.6	31.0	-0.6	31.6	31.1	-0.5
Smokers (%)	27.8	18.4	-9.4	26.9	20.2	-6.7
Blood pressure-lowering drugs (%)	43.7	75.4	31.7	46.7	83.6	36.9
Lipid-lowering drugs (%)	15.4	73.6	58.2	17	81.4	64.4
Blood glucose-lowering drugs (%)	0.5	56.4	55.9	0.5	65	64.5
Aspirin (%)	12.6	41.7	29.1	15.5	70.7	55.2
Aspirin (%)	12.6	41.7	29.1	15.5	70.7	55.2

†The data in the table are given for 86–98% of all people.

*All changes from diagnosis to 5-year follow-up within routine care and intensive treatment is significant with $p < 0.05$.

**The difference between routine care and intensive treatment in change from diagnosis to 5 years are significant ($p < 0.05$) for all parameters except weight and BMI.

DBP: Diastolic blood pressure; IT: Intensive treatment; RC: Routine care; SBP: Systolic blood pressure.

Data taken from [17].

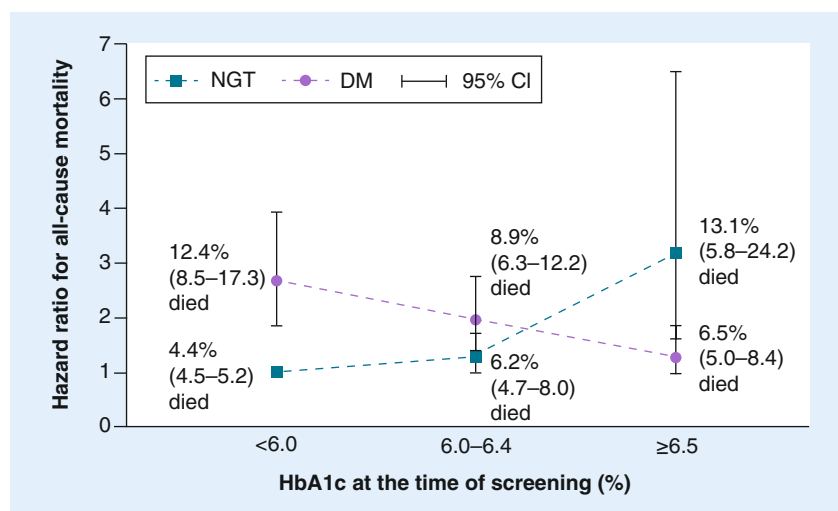


Figure 1. Hazard ratio and absolute values (95% CIs) for all-cause mortality 7 years after screening for diabetes. Individuals are subdivided into categories of HbA1c at screening. Hazard ratios are adjusted for modeled cardiovascular risk at screening and pre-existing ischemic heart disease, stroke and cancer. The results for people with a high risk of diabetes (impaired fasting glucose and impaired glucose tolerance; $n = 2425$) are similar to those for people with NGT, but are omitted from the figure for clarity. For people with NGT, all-cause mortality was higher among those with higher levels of HbA1c at the time of diagnosis ($p = 0.002$). For people with DM, all-cause mortality was lower among those with higher levels of HbA1c at the time of diagnosis ($p = 0.023$). A total of 842 people died in the NGT group and 99 in the DM group. DM: Screen-detected diabetes; NGT: Normal glucose tolerance. Data taken from [41].

(Figure 1) and may in future benefit from the offer of more intensive treatment by being labeled as having diabetes based on the new WHO diagnostic criteria [52].

■ Other findings comparing routine care & intensive treatment

The suggestion of an effect of multifactorial treatment of people with screen-detected diabetes [41] and the 17% nonsignificant reduction in the primary cardiovascular end point when comparing intensive treatment to routine treatment in the ADDITION study [17], is supported by observed reductions in aortic stiffness in the intensive treatment group compared with routine care [53]. Extrapolation of the results for aortic stiffness would correspond to a 7% reduction in modeled cardiovascular risk in favor of intensive treatment.

No significant difference was found in peripheral neuropathy and peripheral arterial disease or in the prevalence of cardiac autonomic neuropathy when comparing routine care with intensive treatment [54,55].

Conclusion & future perspective

Improvements in the quality of diabetes care in general practice meant that in the ADDITION study treatment in the routine care group was better than expected and not very different from the care provided in the intensive treatment group [17]. The small differences in treatment intensity over the first 5-years after diagnosis between the two arms resulted in a nonsignificant 17% reduction in risk for the primary composite cardiovascular end point at 5-year follow-up in favor of the intensive treatment group. Recent trials of intensive treatment of glycemia among patients with long-standing diabetes suggest that adverse effects occur early [56,57] and any benefit in terms of reduction in cardiovascular risk takes longer than 5 years to be achieved [5]. Whether the small difference in the intensity of treatment of multiple risk factors early in the course of the disease in ADDITION will translate into a significant reduction in cardiovascular events and mortality over 10 years will be investigated.

At the population level, all-cause mortality was not reduced as a result of screening for diabetes [50]. There may be several reasons for this. Diabetes was diagnosed in only 3% of the high-risk population invited for screening in Cambridge, thus, even an important benefit for these individuals is unlikely to impact on population mortality within 10 years. Furthermore, the much larger number of individuals at risk of diabetes and at high risk of cardiovascular disease were not offered advice or treatment as part of the intervention program following screening. Therefore, important therapeutic opportunities may have been missed. Better treatment, invitation reminders, repeated rounds of screening and improved methods to attract nonattenders and increase the yield of screening may also increase the overall effectiveness and efficiency of systematic screening.

The results of the ADDITION study have been interpreted as reinforcing the argument against screening [58]. We have suggested that Type 2 diabetes meets many but not all of the criteria for suitability for screening [59], and that the trial evidence indicates that the benefits of earlier detection and treatment appear to outweigh the harms. The recently reported cohort study, showing lower than expected mortality rates over 7 years among people with screen-detected diabetes and HbA1c $\geq 6.5\%$ at screening, presumably due to

more intensive treatment, is consistent with this interpretation [41].

The ADDITION study focused on people with screen-detected diabetes but identified many more without diabetes but at high risk of developing diabetes and cardiovascular disease. Most of these people were not treated optimally according to current guidelines [40,41]. One reason might be a perception of reassurance among general practitioners and people screened if diabetes was not diagnosed and, hence, a reduced perceived need for treatment. This fits well with the finding that people who screened negative for diabetes seemed unaware of their remaining high risk for diabetes and cardiovascular disease [33].

It was reassuring that we could not demonstrate significant harm (direct and via false reassurance) among people following screening [30–35], which is consistent with the results from other studies of similar screening and health promotion interventions.

The yield of screening was low, and fewer people than expected were identified with screen-detected diabetes. This could be due to a number of reasons, such as nonattendance among those at the highest risk at each stage of the stepwise screening program, low sensitivity of screening tests at each stage and a low prevalence of people with undiagnosed diabetes due to opportunistic screening in clinical practice during recent years. The latter explanation seems not to apply, at least not in Denmark, where the estimated prevalence of people with undiagnosed diabetes was 4%, of which only 20% were identified. In Denmark, two people at high risk of developing diabetes and a further six people without diabetes but fulfilling guideline indications for preventive treatment for a high risk of cardiovascular disease were identified for each person with screen-detected diabetes. This highlights the efficiency of combining strategies to identify individuals at high risk of both diabetes and cardiovascular disease.

The inclusion of HbA1c as a diagnostic test for diabetes may help to increase the yield of screening. A combination of HbA1c and SCORE is as effective as measuring blood glucose and cardiovascular risk assessment (SCORE) at identifying people who may benefit from preventive treatment [36].

Future research might focus on ways to increase the yield of programs for earlier detection of diabetes and assessment of

cardiovascular risk, and ways to intensify treatment and adherence.

The main ADDITION study was planned as a randomized trial comparing routine treatment with more intensive treatment in people with screen-detected diabetes. The randomized trial did not deliver conclusive evidence to justify implementation of a systematic screening program. Uncertainties remain, particularly concerning the overall cost-effectiveness of screening for undiagnosed diabetes and individuals with a high risk of diabetes and cardiovascular disease.

However, the overall results of the ADDITION study, including cohort analyses, suggest that earlier detection and treatment of diabetes is associated with net benefit. Thus, primary care teams are encouraged to develop systems to enable earlier detection. This might include opportunistic screening among those known to be at highest risk based either on routinely available information, such as age, BMI and the presence of related conditions such as hypertension, or based on risk questionnaires or scores. Individuals identified in this way should then be offered lifestyle interventions and preventive drug treatment appropriate to their level of risk.

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■ of interest

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