Vascular Outcomes in Patients With Screen-Detected or Clinically Diagnosed Type 2 Diabetes: Diabscreen Study Follow-up

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ABSTRACT

PURPOSE Screening guidelines for type 2 diabetes recommend targeting high-risk individuals. Our objective was to assess whether diagnosis of type 2 diabetes based on opportunistic targeted screening results in lower vascular event rates compared with diagnosis on the basis of clinical signs or symptoms.

METHODS In a prospective, nonrandomized, observational study, we enrolled patients aged 45 to 75 years from 10 family practices in the Netherlands with a new diagnosis of type 2 diabetes, detected either by (1) opportunistic targeted screening (n = 359) or (2) clinical signs or symptoms (n = 206). Patients in both groups received the same guideline-concordant diabetes care. The main group outcome measure was a composite of death from cardiovascular disease (CVD), nonfatal myocardial infarction, and nonfatal stroke.

RESULTS Baseline vascular disease was more prevalent in the opportunistic targeted screening group, mainly ischemic heart disease (12.3% vs 3.9%, $P = .001$) and nephropathy (16.9% vs 7.1%, $P = .002$). After a mean follow-up of 7.7 years (SD = 2.4 years) and 7.1 years (SD = 2.7 years) for the opportunistic targeted screening and clinical diagnosis groups, respectively, composite primary event rates did not differ significantly between the 2 groups (9.5% vs 10.2%, $P = .78$; adjusted hazard ratio 0.67, 95% confidence interval, 0.36-1.25; $P = .21$). There were also no significant differences in the separate event rates of deaths from CVD, nonfatal myocardial infarction, and nonfatal strokes.

CONCLUSIONS Opportunistic targeted screening for type 2 diabetes detected patients with higher CVD morbidity at baseline when compared with clinical diagnosis but showed similar CVD mortality and major CVD morbidity after 7.7 years. Opportunistic targeted screening and guided care appears to improve vascular outcomes in type 2 diabetes in primary care.

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INTRODUCTION

Targeting screening for type 2 diabetes to high-risk individuals is recommended for the prevention of vascular complications.[1] The justification for the promotion of screening is that patients with type 2 diabetes are already at risk for developing microvascular complications before clinical diagnosis[2] and have a twofold higher risk of cardiovascular disease and mortality.[3] The worldwide prevalence of type 2 diabetes is expected to keep rising in the next decade, dramatically increasing the burden of disease and health care costs.[4,5]

Glycemic control and cardiovascular risk management (mainly treatment of hypertension and hypercholesterolemia) decrease vascular disease and mortality in patients with type 2 diabetes.[6,7] It is currently uncertain,

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however, whether treatment of patients with type 2 diabetes detected through screening results in lower vascular event rates when compared with treatment of patients diagnosed by clinical signs or symptoms.[6]

To address this issue, we undertook a study that builds on a type 2 diabetes-screening program performed by the Diabscreen study, in which diabetes screening was conducted during regular primary care in the Netherlands. The Diabscreen study reported a fair yield of opportunistic screening, targeting patients at high risk for undiagnosed type 2 diabetes who visited their family physician.[8] After evaluation, the program was implemented in daily practice. Because of the continuous nature of the primary care setting of the program, we are now able to report a follow-up of up to 10 years after screening.

We compared outcomes in patients with type 2 diabetes that had been diagnosed by opportunistic targeted screening with outcomes of patients given a diagnosis after displaying diabetes signs or symptoms during the same period and in the same family practices. All patients had received the same guideline-concordant diabetes care after diagnosis, ie, the same glycemic control and cardiovascular risk management.[9]

Our main aim was to assess whether opportunistic targeted screening, compared with clinical diagnosis, would beneficially affect the risk of death from cardiovascular disease, myocardial infarction, and stroke.

METHODS

Participants and Setting

For the current Diabscreen study follow-up, data were available from 10 family practices in the Netherlands, all taking part in the Nijmegen Monitoring Project (NMP).[10,11] The NMP is a practice-based research network of the Radboud University Nijmegen Medical Centre, with an audit-enhanced monitoring system for chronic diseases such as type 2 diabetes. Despite this academic alliance, all participants are standard community family practices.

Every individual in the Netherlands is registered with a family physician, and this registration is usually maintained over many years. Type 2 diabetes is commonly treated in primary care, and patients may consult a specialist only upon referral by the family physician.

We included data from all patients, aged 45 to 75 years, with newly diagnosed type 2 diabetes who were enrolled in the monitoring system by their family physician between 1998 and 2005. For the purposes of this study, patients were not randomized into a subgroup but were selected by the detection method of their diabetes, as recorded in the NMP database: (1) type 2 diabetes detected by opportunistic targeted screening; or (2) clinically diagnosed type 2 diabetes based on signs or symptoms. These 2 groups are described in detail.

Type 2 Diabetes by Opportunistic Targeted Screening

The opportunistic targeted screening procedure was based on the Diabscreen study, and some of the current data were derived from that study.[8] In brief, we considered patients to be at high risk for undiagnosed type 2 diabetes if they had 1 or more of the following diabetes risk factors, derived from the American Diabetes Association (ADA) recommendations for screening for type 2 diabetes[1]: a family history of diabetes (defined as diabetes in a parent, brother, sister, or a combination thereof); a history of cardiovascular disease (heart failure, ischemic heart disease, myocardial infarction, transient cerebral ischemia, stroke, or peripheral arterial disease); obesity (body mass index [BMI] >27 kg/m^2); hypertension (blood pressure ≥140/90 mm Hg or taking antihypertensive agents); hypercholesterolemia (total cholesterol >5.0 mmol/L [193 mg/dL] or taking a lipid-lowering agent); or a history of gestational diabetes mellitus.[1,9]

High-risk patients were labeled as such in the electronic medical record. When visiting their family practice for a regular care consultation, high-risk patients were invited for screening using fasting plasma glucose testing. Screening was accepted in 90% of cases.[12] Diagnosis of type 2 diabetes was based on international criteria, requiring 2 fasting plasma glucose measurements on 2 separate days, both with a value ≥7.0 mmol/L (≥126 mg/dL).[13]

Type 2 Diabetes by Clinical Diagnosis

Patients with clinically diagnosed type 2 diabetes had signs or symptoms of diabetes during a practice consultation. If they had classic symptoms of hyperglycemia (polyuria and polydipsia), a single, random, plasma glucose measurement of ≥11.1 mmol/L (≥200 mg/dL) was sufficient for diagnosis. When they had milder symptoms (eg, fatigue, frequent infections, blurred vision), 2 fasting plasma glucose samples, on separate days and both ≥7.0 mmol/L (≥126 mg/dL), were required.[13]

Diabetes Treatment

Patients in both study groups received the same standard of diabetes care and were treated during routine care consultations by their own family physician and practice nurses. Diabetes care was in line with the following Dutch family practice guidelines for type 2

diabetes: recorded on intake and then yearly are family history, smoking status, and comorbidities; a physical examination; an ophthalmologic examination (funduscopy or fundus photography); laboratory testing for fasting blood glucose, hemoglobin A_{1c}, lipids, plasma creatinine, and albuminuria; and education and lifestyle advice. Three times a year patients have weight and blood pressure measured, fasting blood glucose and hemoglobin A_{1c} tested if on insulin; and education and lifestyle advice. Glycemic control is undertaken to reduce hemoglobin A_{1c} to less than 53 mmol/mol (<7.0%), using a stepwise approach with metformin as a first-choice agent when diet is insufficient; a sulphonylurea derivative or insulin is added, if necessary. For cardiovascular risk, the target systolic blood pressure is less than 140 mm Hg. A statin is recommended unless untreated low-density lipoprotein cholesterol is less than 160 mg/dL (2.5 mmol/L) or the absolute 10-year mortality risk is less than 5%. An angiotensin-converting enzyme inhibitor is recommended for microalbuminuria even with normal blood pressure, and a platelet aggregation inhibitor is indicated for secondary prevention only.[9]

Definition of Outcomes

All data were collected from the NMP electronic database. We used all clinical information available up to the end of 2009. The primary group outcome during follow-up was the composite of death from cardiovascular disease (CVD), nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes included microvascular complications (diabetic retinopathy, neuropathy, and nephropathy), any first CVD event (nonfatal myocardial infarction, nonfatal stroke, heart failure, ischemic heart disease, transient cerebral ischemia, or peripheral arterial disease), all-cause death, and non-CVD death. Retinopathy was diagnosed with funduscopy or fundus photography by an ophthalmologist who reported the result to the family physician. Neuropathy was diagnosed by the family physician by physical examination in cases showing loss of monofilament sensation in the toes. Nephropathy was defined as a glomerular filtration rate <60 mL/min/1.73 m^2, estimated by the Modification of Diet in Renal Disease Study equation.[14]

Statistical Analysis

We analyzed participant characteristics at baseline and at the last follow-up visit using the Pearson χ^2 or Fisher exact test for categorical data and the Student *t* test for means where appropriate. The main process and outcome variables of care during follow-up were similarly analyzed.

To compare the primary and secondary outcomes between the 2 study groups, we calculated the incidences of the events and applied the Pearson χ^2 or Fisher exact test for statistical analysis.

In Cox regression models, hazard ratios for the outcomes with their 95% confidence intervals and *P* values were calculated. Time to event was defined as the time between date of diagnosis and date of cardiovascular event or death. For microvascular outcomes, the date of event was the date of diagnosis during follow-up. Patients were followed until death, loss to follow-up, or end of study (December 31, 2009). Hazard ratios were unadjusted and adjusted for 6 baseline variables: age, sex, CVD, fasting plasma glucose, systolic blood pressure, and plasma creatinine.

We conducted all analyses in SPSS 16.0 for Windows (SPSS Inc). All analyses were 2-sided, and we considered a *P* value <.05 to be significant.

RESULTS

Opportunistic targeted screening detected type 2 diabetes in 359 patients. A clinical diagnosis of type 2 diabetes based on signs or symptoms was found in 206 patients (Table 1). Patients with clinically diagnosed type 2 diabetes were more likely to be men and were generally younger than patients with diabetes detected by screening.

At baseline, the prevalence of macrovascular disease was significantly higher in the opportunistic targeted screening group, which could be primarily explained by ischemic heart disease. Prevalence of diabetic retinopathy and neuropathy was similar, but nephropathy was more commonly found with opportunistic targeted screening. Mean systolic blood pressure and plasma creatinine were also significantly higher in the screening group. As expected, fasting blood glucose and hemoglobin A_{1c} levels were significantly elevated in patients with clinically diagnosed diabetes. Other characteristics were similar at baseline.

Follow-up

Mean systolic blood pressure and plasma creatinine no longer differed between the opportunistic targeted screening and clinical diagnosis groups after a mean follow-up of 7.7 years (SD = 2.4 years) and 7.1 years (SD = 2.7 years) , respectively (Table 1). Glucose and cholesterol values had improved and smoking had decreased in both groups.

Process and Outcome Variables of Care

Processes of care were comparable between both study groups after follow-up (Table 2). With regard to outcome variables, we found significantly better glycemic control among patients from the opportunistic targeted

Table 1. Characteristics of Patients with Newly Diagnosed Type 2 Diabetes for Opportunistic Targeted Screening (n = 359) and Clinical Diagnosis (n = 206) Groups at Baseline and After Follow-up

	Baseline			Follow-up		
Characteristic	Opportunistic Targeted Screening	Clinical Diagnosis	*P* Value	Opportunistic Targeted Screening	Clinical Diagnosis	*P* Value
Age, mean (SD), y	61.8 (7.8)	59.0 (8.1)	<.001			
Sex (male), No. (%)	175 (48.7)	118 (57.3)	.05			
Follow-up, mean (SD), y				7.7 (2.4)	7.1 (2.7)	.01
History of macrovascular disease,[a] No. (%)	88 (24.5)	24 (11.7)	<.001			
Ischemic heart disease, No. (%)	44 (12.3)	8 (3.9)	.001			
Myocardial infarction, No. (%)	26 (7.2)	11 (5.3)	.38			
Stroke, No. (%)	12 (3.3)	3 (1.5)	.18			
Other, No. (%)	24 (6.7)	11 (5.3)	.52			
History of microvascular disease,[a] No. (%)	63 (17.5)	24 (11.7)	.06			
Retinopathy, No. (%)	1 (0.3)	3 (1.7)	.12			
Neuropathy, No. (%)	6 (1.7)	8 (3.9)	.10			
Nephropathy, No. (%)	57 (16.9)	13 (7.1)	.002			
Blood glucose control						
FPG, mean (SD), mmol/L	8.8 (2.9)	12.9 (5.0)	<.001	7.9 (1.7)	8.2 (2.2)	.06
HbA_{1c}, mean (SD),[b] mmol/mol	55 (17)	74 (28)	<.001	51 (10)	54 (12)	.001
HbA_{1c}, mean (SD),[b] %	7.2 (1.6)	8.9 (2.5)	<.001	6.8 (0.9)	7.1 (1.1)	.001
CVD risk factors						
Current smoking, No. (%)	66 (19.3)	41 (21.9)	.47	45 (13.5)	29 (15.8)	.48
Systolic blood pressure, mean (SD), mm Hg	153 (20)	147 (21)	.004	145 (18)	144 (17)	.59
Diastolic blood pressure, mean (SD), mm Hg	86 (10)	85 (11)	.33	80 (10)	81 (9)	.16
BMI, mean (SD), kg/m^2	30.5 (4.7)	29.7 (5.0)	.07	29.9 (4.7)	29.6 (4.6)	.51
Total cholesterol, mean (SD), mmol/L	6.0 (1.2)	6.0 (1.4)	.38	4.7 (1.1)	4.7 (1.1)	.58
LDL cholesterol, mean (SD), mmol/L	3.7 (1.1)	3.8 (1.2)	.72	2.6 (1.0)	2.7 (0.9)	.86
Plasma creatinine, mean (SD), mmol/L	88.7 (18.1)	84.1 (17.3)	.004	89.4 (24.5)	87.4 (19.9)	.32

Abbreviations: BMI = body mass index; CVD = cardiovascular disease; FPG = fasting plasma glucose; HbA_{1c} = hemoglobin A_{1c}; LDL = low-density lipoprotein.

[a] Some patients had multiple events.

[b] Missing at baseline = 201 in opportunistic targeted screening group; 126 in clinical diagnosis group.

screening group and less frequent insulin treatment, but a higher use of antihypertensive medications. Other outcomes of care did not differ significantly from those of the clinical diagnosis group.

Primary Outcomes

The composite primary event rates during follow-up did not differ significantly between the opportunistic targeted screening and clinical diagnosis groups (9.5% vs 10.2%, $P = .78$; adjusted hazard ratio [HR] = 0.67, 95% CI, 0.36-1.25; $P = .21$; Table 3). The hazard curves, however, show a more steeply increasing risk for a major macrovascular event in patients with clinically diagnosed diabetes (Figure 1).

Lower incidences and risk for nonfatal myocardial infarction and for nonfatal stroke were observed in the opportunistic targeted screening group, whereas risk for CVD death was higher. Because of the small numbers and a large confidence interval, the differences for CVD death were not statistically significant.

Secondary Outcomes

Microvascular event rates were also not significantly different between the study groups (Table 3), although incidence and risk for diabetic retinopathy were lower after opportunistic targeted screening (1.5% vs 3.9%; $P = .08$; adjusted HR = 0.75, 95% CI, 0.19-3.08; $P = .69$).

Risk for any first CVD event did not differ significantly between the groups (Table 3). Lower incidences and risk were observed in the opportunistic targeted screening group for ischemic heart disease, whereas they were higher for heart failure, transient cerebral ischemia, and peripheral arterial disease, but these differences were not statistically significant or the 95% confidence intervals were large (data not shown).

All-cause death rates did not differ significantly (8.6 vs 10.7%; $P = .42$; adjusted HR = 0.60, 95% CI, 0.31-1.13; $P = .12$), in contrast to non-CVD death (4.2% vs 8.7%; $P = .03$; adjusted HR = 0.33, 95% CI, 0.15-0.71; $P = .01$; Table 3). We observed more deaths caused

by infections or pulmonary disease (2.2% vs 1.5%) in the opportunistic targeted screening group but fewer deaths that were due to cancer (1.9% vs 7.3%). No specific type of cancer could explain the higher prevalence in the clinical diagnosis group (data not shown).

Table 2. Main Process and Outcome Variables of Care, at Last Follow-up for Opportunistic Targeted Screening (n = 359) and Clinical Diagnosis (n = 206) Groups

Variable	Opportunistic Targeted Screening No. (%)	Clinical Diagnosis No. (%)	*P* Value
Process of care			
HbA_{1c} recorded	345 (96.1)	196 (95.1)	.59
Systolic blood pressure recorded	349 (97.2)	197 (95.6)	.32
LDL cholesterol recorded	332 (92.5)	182 (88.3)	.10
Eye examination recorded	344 (95.8)	189 (91.7)	.04
Foot examination recorded	348 (96.9)	192 (93.2)	.04
Outcome of care			
HbA_{1c} <53 mmol/mol (7.0%)	220 (63.8)	99 (50.5)	.003
Systolic blood pressure <140 mm Hg	126 (36.1)	69 (35.0)	.80
LDL cholesterol <2.5 mmol/L	159 (47.9)	81 (44.5)	.46
Glucose-lowering treatment			
Diet only	96 (26.7)	34 (16.5)	.01
Oral agent(s)	231 (64.3)	147 (71.4)	.09
Insulin	19 (5.3)	26 (12.6)	.002
Antihypertensive agent(s)	228 (71.2)	90 (52.3)	<.001
Lipid-lowering agent(s)	216 (67.7)	109 (63.7)	.38

HbA_{1c} = hemoglobin A_{1c}; LDL = low-density lipoprotein.

DISCUSSION

This study is the first to compare patients from the same population with type 2 diabetes detected by either opportunistic targeted screening or by clinical signs or symptoms and observed for long-term vascular outcomes.

For patients with type 2 diabetes detected by opportunistic targeted screening who had higher CVD morbidity at baseline, in particular ischemic heart disease and hypertension-related nephropathy, after up to 10 years follow-up, major macrovascular event rates did not significantly differ between the 2 groups. Secondary vascular event rates were also not significantly different between groups, although the opportunistic targeted screening group did show a lower risk for diabetic retinopathy than the clinical diagnosis group.

Differences at diagnosis between patients with type 2 diabetes detected by screening and clinically were described earlier in the Hoorn Screening Study,[15] a targeted diabetes screening study

Table 3. Events After Diagnosis of Type 2 Diabetes for Opportunistic Targeted Screening (n = 359) and Clinical Diagnosis (n = 206) Groups

Events	Incidence, No. (%)			Unadjusted HR (95% CI)[a]	*P* Value	Adjusted HR (95% CI)[a]	*P* Value
	Opportunistic Targeted Screening	Clinical Diagnosis	*P* Value				
Primary outcomes							
Major macrovascular event[b]	34 (9.5)	21 (10.2)	.78	0.84 (0.49-1.44)	.52	0.67 (0.36-1.25)	.21
CVD death	16 (4.5)	4 (1.9)	.16	2.10 (0.70-6.28)	.19	1.88 (0.41-8.57)	.42
Nonfatal MI	11 (3.1)	11 (5.3)	.18	0.54 (0.23-1.25)	.15	0.43 (0.18-1.02)	.06
Nonfatal stroke	10 (2.8)	9 (4.4)	.32	0.57 (0.23-1.40)	.22	0.68 (0.23-2.02)	.49
Secondary outcomes							
Microvascular event[b]	54 (17.1)	24 (15.2)	.59	1.04 (0.64-1.68)	.88	0.94 (0.55-1.60)	.81
Retinopathy	5 (1.5)	7 (3.9)	.08	0.32 (0.10-1.01)	.05	0.75 (0.19-3.08)	.69
Neuropathy	40 (11.5)	16 (8.3)	.25	1.33 (0.74-2.37)	.34	1.23 (0.63-2.39)	.54
Nephropathy	18 (5.5)	10 (5.9)	.87	0.86 (0.39-1.85)	.69	0.93 (0.38-2.24)	.87
Any first CVD[c]	68 (18.9)	28 (13.6)	.10	1.33 (0.86-2.07)	.21	1.03 (0.63-1.67)	.92
All-cause death	31 (8.6)	22 (10.7)	.42	0.73 (0.42-1.26)	.26	0.60 (0.31-1.13)	.12
Non-CVD death	15 (4.2)	18 (8.7)	.03	0.43 (0.22-0.85)	.02	0.33 (0.15-0.71)	.01

CVD = cardiovascular disease; HR = hazard ratio; MI = myocardial infarction.

[a] Hazard ratios with matching P values compare hazards in type 2 diabetes detected by opportunistic targeted screening with those in clinically diagnosed type 2 diabetes, unadjusted and adjusted for age, sex, and the following baseline characteristics: CVD, systolic blood pressure, fasting plasma glucose, and plasma creatinine.

[b] Some patients had multiple events.

[c] Nonfatal MI, nonfatal stroke, heart failure, ischemic heart disease, transient cerebral ischemia, or peripheral arterial disease.

in the Netherlands. Our data confirmed the findings of the Hoorn Screening Study and showed that glucose levels were higher among patients with signs or symptoms at diagnosis, whereas retinopathy and neuropathy were equally prevalent in the 2 groups. Additionally, these authors already noted strikingly prevalent macrovascular complications in patients with diabetes detected by screening.[16]

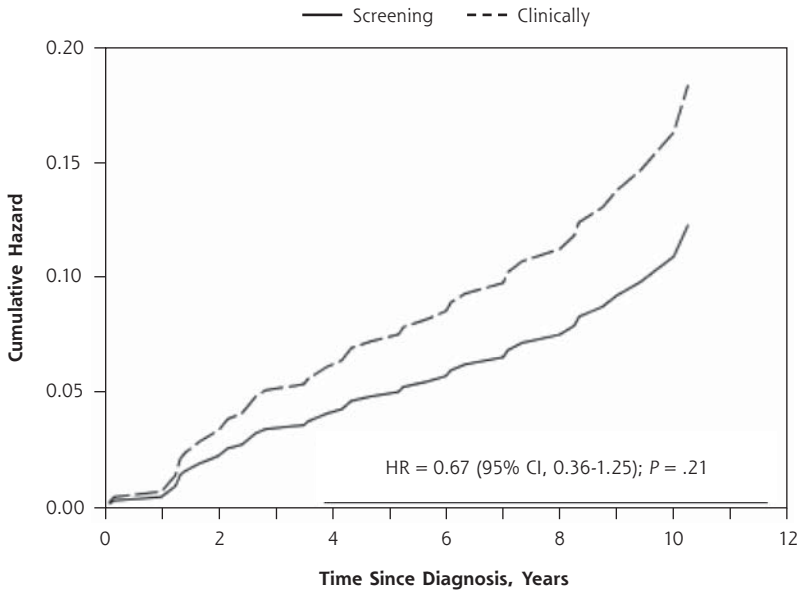
The major strength of our study was its particular setting. Although all NMP practices are affiliated academically with the Radboud University Nijmegen Medical Centre, they are normal community practices with a population representative of the general Dutch population and a diabetes prevalence equal to that anywhere in the Netherlands.[10,17] That the Dutch system of primary health care provides for universal access and continuity of patient registration enabled us to collect and present follow-up data from daily practice. The effectiveness of screening for type 2 diabetes should preferably be investigated in a randomized controlled trial.[18] In the current absence of such trials and with limited evidence found in recent case-control, cross-sectional, and modeling studies,[6] we believe that an observational study can provide important new data. Because we could show that patients in both study groups received the same level of diabetes care,[9] we were able to investigate outcomes related to time of diagnosis and early treatment.

Overall, we found lower vascular event rates than expected in both the opportunistic targeted screening group and the clinical diagnosis group. This finding might reflect the impact of the guideline-concordant diabetes care in the practices, which includes cardiovascular risk management. Diabetes treatment had been successful in reducing blood pressure, smoking, and blood glucose and lipid levels in both groups.

We showed that the hazard curve of the primary outcome was higher for clinically diagnosed diabetes than for opportunistic targeted screening, which might be explained by lead-time bias: the longer interval between diagnosis and development of complications in patients detected by opportunistic targeted screening might be due to earlier detection in the natural history of the disease, instead of earlier treatment.[19] The lower glucose levels at diagnosis and lower risk for retinopathy for patients with diabetes detected by screening suggests that screening detects diabetes at an earlier stage of disease.[2] Patients with diabetes detected by screening also tend to show milder disease and slower progression, with better clinical outcomes after follow-up (length-time bias).[19] Although we screened patients in a high-risk population who had a higher initial prevalence of ischemic heart disease, nephropathy, and hypertension than patients in the clinical diagnosis group, vascular outcomes were similar between the groups upon follow-up. Even adjusted hazard ratios were not significantly different between groups. The opportunistic targeted screening group may have developed diabetes complications caused by longer exposure to hyperglycemia as a result of a slower progression.

A final possibility is that patients who volunteer for screening programs are more health conscious and therefore more likely to have a better disease outcome even without screening (selection bias).[19] The initiation of screening during routine care, the targeting of patients with diabetes risk factors, and the high response rate of 90%,[8] all suggest that selection bias did not play a major role in our study. As previously

Figure 1. Cumulative hazard of primary outcome following diagnosis of type 2 diabetes by opportunistic targeted screening, compared with clinical diagnosis.



CVD = cardiovascular disease; HR = hazard ratio.

Notes: Cumulative hazard of death from CVD, nonfatal myocardial infarction, or nonfatal stroke, adjusted for age, sex, and the following baseline characteristics: CVD, systolic blood pressure, fasting plasma glucose, and plasma creatinine.

stated, however, patients with clinically diagnosed diabetes were more often men and were generally younger than patients with diabetes detected by opportunistic targeted screening. This difference may have been because only patients visiting the family practice were invited for screening, and younger men might be more likely to postpone a primary care consultation. We adjusted data analyses for age and sex to account for this possible bias.

A selection bias that is due to a selective allocation to a group or treatment by the patient's family physician is also unlikely, because patients were not randomized into a group, and although detection method was not blinded, it was recorded in the database for analysis purposes only. Patients from both study groups received the same guided treatment during normal care from their own family physician, independent of the detection method.

A possible limitation may have been the diagnosis of type 2 diabetes by the fasting plasma glucose test rather than the oral glucose tolerance test. The oral glucose tolerance test consists of an fasting plasma glucose test and 2-hour plasma glucose value and is considered to be the reference standard test in the diagnosis of diabetes. The fasting plasma glucose test is more user-friendly, however, faster to perform, more convenient and acceptable to patients, and less expensive. The recent American Diabetes Association recommendation to use hemoglobin A_{1c} for screening was still under debate at the time of our study.[1,20] Although later rectified, there was a large amount of data missing for hemoglobin A_{1c} at baseline, because hemoglobin A_{1c} was not yet registered in the database at the beginning of the study in 1998. The missing hemoglobin A_{1c} values were comparable between groups, reflecting similar care, and the outcome was in line with the mean fasting plasma glucose values at baseline.

With the exception of smoking, we were not able to investigate potential differences in lifestyle between groups, such as exercise or diet, because these data were not collected in the NMP database. Lifestyle advice is, however, an important part of the guided care in the practices.[9]

We have shown that within the first decade after diagnosis, in contrast to our expectations, opportunistic targeted screening for type 2 diabetes resulted in similarly low macrovascular event rates compared with diabetes diagnosed on the basis of signs and symptoms. This central finding of our study might be taken as an argument against screening. Even so, our finding that higher CVD morbidity at baseline did not significantly increase vascular event rates after screening argues in favor of opportunistic targeted screening. We also showed that opportunistic targeted screening identified patients at an earlier stage of diabetes and that these patients had a lower risk for retinopathy during follow-up. Furthermore, we found a trend toward a higher risk for a major macrovascular event in clinically diagnosed type 2 diabetes, and significant differences may yet become apparent over time.[21]

We have no explanation for the higher risk for non-CVD death (mainly caused by various types of cancer) in the group with clinically diagnosed diabetes. Although type 2 diabetes has been associated with an increased cancer risk, hyperglycemia could not be causally linked to this risk.[22]

Even though the overall statistical power of the study may not have been sufficient to detect small differences between groups, our observational study based on daily care did show some interesting results and trends. Further research is needed to investigate our findings in a larger setting and with a longer follow-up.

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