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Population-based screen-detected type 2 diabetes mellitus is associated with less need for insulin therapy after 10 years

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ABSTRACT

Introduction With increased duration of type 2 diabetes, most people have a growing need of glucose-lowering medication and eventually might require insulin. Presumptive evidence is reported that early detection (eg, by population-based screening) and treatment of hyperglycemia will postpone the indication for insulin treatment. A treatment legacy effect of population-based screening for type 2 diabetes of about 3 years is estimated. Therefore, we aim to compare insulin prescription and glycemic control in people with screen-detected type 2 diabetes after 10 years with data from people diagnosed with type 2 diabetes seven (treatment legacy effect) and 10 years before during care-as-usual.

Research design and methods Three cohorts were compared: one screen-detected cohort with 10 years diabetes duration (Anglo-Danish-Dutch study of Intensive Treatment in People with Screen-Detected Diabetes in Primary care (ADDITION-NL): n=391) and two care-as-usual cohorts, one with 7-year diabetes duration (Groningen Initiative to Analyze Type 2 Diabetes Treatment (GIANTT) and Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC): n=4473) and one with 10-year diabetes duration (GIANTT and ZODIAC: n=2660). Insulin prescription (primary outcome) and hemoglobin A1c (HbA1c) of people with a known diabetes duration of 7 years or 10 years at the index year 2014 were compared using regression analyses.

Results Insulin was prescribed in 10.5% (10-year screen detection), 14.7% (7-year care-as-usual) and 19.0% (10-year care-as-usual). People in the 7-year and 10-year care-as-usual groups had a 1.5 (95% CI 1.0 to 2.1) and 1.8 (95% CI 1.3 to 2.7) higher adjusted odds for getting insulin prescribed than those after screen detection. Lower HbA1c values were found 10 years after screen detection (mean 50.1 mmol/mol (6.7%) vs 51.8 mmol/mol (6.9%) and 52.8 mmol/mol (7.0%)), compared with 7 years and 10 years after care-as-usual ($MD_{adjusted}$: 1.6 mmol/mol (95% CI 0.6 to 2.6); 0.1% (95% CI 0.1 to 0.2) and 1.8 mmol/mol (95% CI 0.7 to 2.9); and 0.2% (95% CI 0.1 to 0.3)).

Conclusion Population-based screen-detected type 2 diabetes is associated with less need for insulin after 10 years compared with people diagnosed during care-as-usual. Glycemic control was better after screen detection but on average good in all groups.

Significance of this study

What is already known about this subject?

- With longer duration of type 2 diabetes, most people have a growing need of glucose-lowering medication and eventually require insulin.
- Early treatment of hyperglycemia postpones the indication for insulin treatment.

What are the new findings?

- Targeted population-based diabetes screening is associated with less need for insulin after 10 years compared with people diagnosed during care-as-usual.
- Glycemic control was slightly better after population-based screen detection despite less insulin prescriptions.

How might these results change the focus of research or clinical practice?

- The earlier diabetes is diagnosed and an intervention is initiated, the more favorable results are possible.

INTRODUCTION

In the Anglo-Danish-Dutch study of Intensive Treatment in People with Screen-Detected Diabetes in Primary care (ADDITION) study, 300 000 individuals with a high risk of type 2 diabetes were screened for type 2 diabetes, according to WHO 1999 criteria.[1 2] Subsequently, in more than 3000 screen-detected patients, the effect of an intensive multifactorial treatment (IT) was compared with routine care (RC), according to national guidelines.[3] After 5 years, a reduction in fatal and non-fatal cardiovascular disease (CVD) of 17% (n.s.) was found in favor of the IT group. A remarkable result was the finding that 5 years after screen detection, 37% and 45% of the participants with type 2 diabetes in the IT and RC groups did not use any glucose-lowering medication.[3] After 5 years, the intervention stopped, and the subsequent treatment intensity was up to the general practitioner and the patient.

Results of two recent post hoc analysis with the ADDITION Denmark screening data indicated that after a follow-up of approximately

10 years people diagnosed after population-based screening had a 21% significant lower risk on all-cause mortality and a 16% significant lower risk on CVD events, but no significant risk reduction on CVD mortality compared with unscreened controls.[4 5] Overall, there was little benefit that could be directly related to the screening programme. In part, this was due to the high degree of opportunistic screening in the control group. Based on these results, it was suggested that if opportunistic screening has been well established in a healthcare system, population-based screening might not add additional health benefits.[4 5] In the Netherlands, since two decades, general practitioners are recommended to screen people with a high risk on type 2 diabetes, during surgery hours.[6] This opportunistic screening is likely established differentially across general practices.[7]

Targeted population-based screening as well as opportunistic screening detect people with type 2 diabetes relatively early in the course of their disease. At that time most of them will be asymptomatic. Although evidence is available that early detection is beneficial for disease control, the impact of population-based screening compared with care-as-usual (including not fully implemented opportunistic screening) needs to be explored.

With increased duration of type 2 diabetes, most people have a growing need of glucose-lowering medication and eventually require insulin.[8 9] According to a computer-simulated model based on the ADDITION data, it is speculated that the number of people on insulin therapy would be much higher if they were diagnosed during care-as-usual, an estimated (lead time of) 3–6 years later.[10] Moreover, presumptive evidence is reported that early treatment of hyperglycemia will postpone the indication for insulin treatment due to possible effects on β-cell function.[11–13]

Hence, we hypothesize that, irrespective of age at diagnosis, on the long run, the need for insulin therapy is less in people diagnosed with type 2 diabetes during targeted population-based screening (like in the ADDITION study) compared with people with diabetes diagnosed during care-as-usual. Therefore, we evaluated insulin prescription and glycemic control in Dutch participants from the ADDITION study (both IT and RC) 10 years after being diagnosed with type 2 diabetes. We compared these results with data from Dutch people with a known diabetes duration of 7 years (assuming a lead time of 3 years) and 10 years (since the exact lead time is unknown) from two 'care-as-usual' diabetes cohorts (Groningen Initiative to Analyze Type 2 Diabetes Treatment (GIANTT) and Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC)).[14 15]

RESEARCH DESIGN AND METHODS

Subjects

Participants with type 2 diabetes managed by general practitioners from three cohorts were included. One cohort was the ADDITION-NL cohort (n=391), consisting of people diagnosed with type 2 diabetes between 2002 and 2003 after population-based screening. The two remaining cohorts included participants diagnosed with type 2 diabetes in usual care with opportunistic screening: the GIANTT and ZODIAC[14] cohorts (n=3918).[15] As stated above, opportunistic screening in the Netherlands was definitely not yet widely implemented at the start of the ADDITION study.[15] The guidelines recommended to conduct 3 yearly fasting blood glucose testing in people aged ≥45 years *and* one of the following characteristics: body mass index (BMI) ≥27 kg/m^2, a family history of type 2 diabetes, being known with hypertension, dyslipidemia or CVD, a specific ethnicity (namely Turkish, Moroccan or Surinamese) and a history of gestational diabetes. In 2014, the ADDITION-NL cohort had a diabetes duration of ~10 years. It was estimated that population-based screening would detect people with type 2 diabetes approximately 3 years earlier. Therefore, participants from the care-as-usual cohorts were divided into two groups: people with a known type 2 diabetes duration of 7 years (assuming a lead time of 3 years) and 10 years (because the exact lead time is unknown), respectively.

ADDITION-NL cohort

The ADDITION-Europe study is a cluster-randomised, parallel-group trial evaluating the effect of early IT in people with screen-detected type 2 diabetes. The study was carried out among 343 general practices in Denmark, the UK and the Netherlands. Details of the study have been described previously.[1 3] ADDITION-NL took place in the south western part of the Netherlands, identification of high risk for type 2 diabetes took place in all individuals aged 50–69 years and unknown with type 2 diabetes. High risk for diabetes type 2 was based on the modified version of the Symptom Risk Questionnaire used in the Hoorn study. The questionnaire contained questions on age, sex, BMI, family history of diabetes, frequent thirst, use of antihypertensive medication, shortness of breath, claudication and cycling. Individuals with a score of ≥4 points were invited by their general practitioner for diabetes assessment, using a random blood glucose test, a fasting blood glucose test and an oral glucose tolerance test. The WHO 1999 criteria for type 2 diabetes were used for diagnosis.[1 2]

Exclusion criteria were illness with a life expectancy less than 1 year and psychiatric disorders invalidating informed consent or impeding study participation. Practice-level randomization was carried out in 79 general practices for providing either care-as-usual, according to the 1999 guidelines of the Dutch College of General Practitioners[6] or IT according to the ADDITION-NL protocol. Randomization was performed according to stratification of practice organization (number of patients: 215 IT and 176 RC).[16] In the 5 years following randomization, all patients with screen-detected type 2 diabetes were treated according to the randomly allocated treatment protocol. General practitioners and nurses in practices randomized to intensive multifactorial treatment were

motivated during educational meetings up to twice a year, for providing strict target-driven pharmacological treatment of hyperglycemia as well as promoting healthy lifestyles. After 5 years, the trial ended, and after the trial period, all patients were most likely treated according to the revised Dutch guidelines.[17]

GIANTT cohort

The GIANTT study started in 2004 in the northern part of the Netherlands as a prospective observational study for people with type 2 diabetes with the aim to improve diabetes care through yearly feedback information and advice for participating healthcare professionals. The database contains anonymized longitudinal information retrieved from electronic medical records of general practitioners and is maintained by the University Medical Center Groningen.[18] These records include medical history, prescription data, routine laboratory test results and physical examinations of people with type 2 diabetes (no age restrictions), who did not opt-out for the use of their medical data for scientific research. For scientific research with anonymous data, this opt-out regulation is offered in the Netherlands as option instead of providing full informed consent. Medical history contains date of diabetes diagnosis and comorbidity data based on the International Classification of Primary Care or text descriptions that are coded manually. Data of people with a general practitioner-confirmed diagnosis of type 2 diabetes, exclusively treated in primary care, and a duration of 7 years or 10 years at the index year 2014 were included in the current study.

ZODIAC cohort

The ZODIAC study started in 1998 in the eastern part of the Netherlands as a prospective observational study for people with type 2 diabetes.[19] Study goal was improvement of standard care through addition of extra caregivers, education and at least yearly feedback information and advice for the participating healthcare professionals. At inclusion, the individuals participating in the ZODIAC study were known with or newly diagnosed with type 2 diabetes and exclusively treated in primary care; at inclusion, they provided informed consent for the use of their anonymized data for research purposes. Individuals who were already treated for their diabetes in secondary care, individuals with a very short life expectancy and individuals with insufficient cognitive abilities were excluded. The number of participating general practitioners increased from 53 in 1998 to 459 in 2008. Patient numbers increased from 1622 to 27 438 in this time frame, and nowadays even more than 40 000 patients are participating.

Design of the present comparison

Cohort study, with 2014 as index year. Within the three cohorts, people were treated according to the same national guidelines, with the exception of the ADDITION-IT group. In this group, patients have been treated more strictly during the first 5 years after diagnosis. The frequency of diabetes monitoring, namely four times per year, was equal in all cohorts, all groups and all periods.

Therapy targets

At start of the ADDITION study, hemoglobin A1c (HbA1c) levels were targeted at <64 mmol/mol (8.5%) and <53 mmol/mol (7.0%) for the RC group and IT group, respectively. Moreover, in the IT arm, glucose-lowering medication should be started as soon as the HbA1c level passed 47 mmol/mol (6.5%). Since 2006, the revised Dutch national guidelines set an HbA1c of <53 mmol/mol (7%) as target.[17] In 2013, less strict targets were set for people above 70 years and with a diabetes duration longer than 10 years.[20]

Data assessment

Subject characteristics during the index year: age, sex and disease control characteristics (HbA1c, lipoproteins (serum) – low-density lipoprotein (LDL) cholesterol, systolic blood pressure (SBP), BMI and smoking status) were all retrieved from the electronic medical records of the general practitioners. Assessment dates: GIANTT: January–July, ADDITION: January–December, ZODIAC: January–December, with value and date of last measurement available in the index period.

Glucose-lowering medication

Data of glucose-lowering medication prescribed in the index year were collected from the electronic medical records of the general practitioners using The Anatomical Therapeutic Chemical Classification System code: metformin (A10BA02), sulfonylurea (SU) (A10BB, A10 BB12 and A10BB09), insulin (A10A), and other oral glucose-lowering agents (A10BG, A10BK and A10BJ). Glucose-lowering mediation was categorized according to the Dutch treatment algorithm, with the following steps: (1) lifestyle only; (2) metformin; (3) metformin+SU and (4) insulin±oral agents, using other oral blood glucose-lowering agents or insulin monotherapy in case of intolerance or contraindications for metformin, SU or insulin.[20]

Outcomes

Primary outcome

The primary outcome was prescription of any insulin (either monotherapy or in addition to oral agents) during the index year.

Secondary outcome

The secondary outcome was glycemic control (HbA1c level) during the index year

Statistical analyses

Data of study participants from the former RC and IT groups of the ADDITION-NL cohort were merged and analyzed as one group. Descriptive statistics were performed using SPSS V.24. Categorical variables are reported as counts and percentages, continuous variables as means with SD or medians with IQR for non-normally

distributed variables. Differences with regard to subject characteristics between the population-based screening and care-as-usual groups were determined by analysis of variance for continuous variables and by χ^2 tests for categorical variables. Logistic regression analysis was used to evaluate the difference in insulin prescription 10 years after screen detection compared with care-as-usual, adjusted for the following confounders: age, sex, HbA1c, SBP, LDL cholesterol, BMI and smoking, with cohort as fixed factor. To determine the differences in HbA1c linear regression analyses was used, adjusted for age, sex, BMI and glucose-lowering medication according to the abovementioned classification. All confounders had <7% missing data, except for BMI (10.2% missings) and LDL (13.8% missings). To evaluate the impact of missing data, we performed multiple imputation, with a 10 imputed dataset under the assumption 'missing at random' as sensitivity analysis. To evaluate the impact of population-based screening without the effect of multifactorial intensive treatment during the first 5 years, the ADDITION-NL RC group only was compared with the 7 years and 10 years care-as-usual groups as a sensitivity analysis.

RESULTS

Data of 7524 people with type 2 diabetes and data on glucose-lowering medication were included; 391 participants had population-based screen-detected diabetes (ADDITION-NL cohort) and 7133 people were diagnosed with type 2 diabetes during care-as-usual (GIANTT and ZODIAC combined): 4473 with 7 years (n=2014 GIANTT, n=2459 ZODIAC) and 2660 with 10-year diabetes duration (n=1201 GIANTT, n=1459 ZODIAC). Subject characteristics of the three groups are presented in table 1. People with screen-detected diabetes were on average older and more often male compared with people from the two other cohorts. Ten years after their screen detection, people showed a lower SBP (135 mm Hg vs 138 mm Hg in both care-as-usual groups) and LDL-cholesterol levels (2.1 mmol/L vs 2.5 mmol/L in both care-as-usual groups) but a higher BMI: 30.4 kg/m^2 vs 29.8 kg/m^2 in the 7 years and 29.4 kg/m^2 in the 10 years group.

Insulin prescription

Insulin prescriptions in people with screen-detected diabetes and in people known with diabetes for 7 years and 10 years during care-as-usual were 10.5%, 14.8% and 19.0%, respectively (table 1). After adjustment for confounders, people diagnosed 7 years and 10 years before the index year during care-as-usual had a 1.5 (95% CI 1.0 to 2.1) and 1.8 (95% CI 1.3 to 2.7) times higher chance of getting insulin prescribed compared with those with screen-detected diabetes. Similar results were found after multiple imputation (table 2). Comparing only the ADDITION-NL RC group with the care-as-usual groups, the observed point estimates (mean difference) remained similar in both groups. The broader 95% CIs

Table 1 Subject characteristics of the three groups at the index year

	ADDITION-NL (n=391)	7-years diabetes diagnosis (n= 4473)	10-year diabetes diagnosis (n= 2660)	F-test/χ^2	P value
Age (years)	71.6 (5.3)	68.4 (11)	69.7 (10.6)	22.9	<0.01
Sex, male (n, %)	208 (52.7)	2266 (50.5)	1272 (47.8)	6.2	0.04
Smoking, yes (n, %)	52 (14.2)	706 (16.4)	407 (15.9)	1.2	0.55
BMI (kg/m^2)	30.4 (6.7)	29.8 (5.3)	29.4 (5.2)	7.1	<0.01
HbA1c (%)	6.7 (0.9)	6.9 (0.9)	7.0 (1.0)	NA*	NA*
HbA1c (mmol/mol)	50.1 (9.8)	51.8 (10.1)	52.8 (10.4)	NA*	NA*
SBP (mm Hg)	135 (15.4)	138 (16.1)	138 (16.6)	4.2	0.02
DBP (mm Hg)	74 (9.4)	77 (9.2)	76.1 (9.1)	13.9	<0.01
LDL (mmol/L)	2.1 (0.9)	2.5 (0.9)	2.5 (0.9)	33.7	<0.01
Glucose-lowering medication				NA*	NA*
Lifestyle only	72 (18.4)	795 (17.7)	380 (14.3)		
Metformin	116 (29.7)	1501 (33.4)	736 (27.7)		
Metformin+SU	138 (35.3)	1257 (28.0)	848 (31.9)		
Other oral antidiabetic agents	24 (6.1)	275 (6.1)	192 (7.2)		
Metformin and/or SU+insulin	26 (6.6)	492 (11.0)	377 (14.2)		
Insulin monotherapy	12 (3.1)	138 (3.1)	103 (3.9)		
Insulin+other oral diabetic agents	3 (0.8)	31 (0.7)	24 (0.9)		

*Outcome measures (see table 2).
ADDITION, Anglo-Danish-Dutch study of Intensive Treatment in People with Screen-Detected Diabetes in Primary care; BMI, body mass index; DBP, Diastolic Blood Pressure; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; SBP, systolic blood pressure; SU, sulfonylurea.

Table 2 Chance in getting insulin prescribed and mean difference in HbA1c for people diagnosed during care-as-usual compared with those with screen-detected T2DM

		7 years			10 years		
	ADDITION-NL		Crude	Adjusted		Crude	Adjusted
Insulin	N (%)	N (%)	OR (95% CI)	OR (95% CI)	N (%)	OR (95% CI)	OR (95% CI)
Complete cases	41 (10.5)	661 (14.7)	1.5 (1.1 to 2.1)	1.5 (1.0 to 2.1)	504 (19.0)	2.0 (1.4 to 2.8)	1.8 (1.3 to 2.7)
ADDITION-RC*	17 (9.7)		1.6 (1.0 to 2.7)	1.6 (0.9 to 2.9)		2.2 (1.3 to 3.6)	2.1 (1.2 to 3.7)
MI model†	41 (10.5)	661 (14.7)	1.5 (1.1 to 2.1)	1.5 (1.0 to 2.1)	504 (19.0)	2.0 (1.4 to 2.8)	1.9 (1.3 to 2.7)
HbA1c (%)	**Mean (SE)**	**Mean (SE)**	**Mean difference (95% CI)**		**Mean (SE)**	**Mean difference (95% CI)**	
Complete cases	50.1 (0.5)	51.8 (0.2)	1.7 (0.6 to 2.7)	1.6 (0.6 to 2.6)	52.8 (0.2)	2.7 (1.6 to 3.8)	1.8 (0.7 to 2.9)
	6.7 (0.05)	6.9 (0.01)	0.2 (0.1 to 0.2)	0.1 (0.1 to 0.2)	7.0 (0.02)	0.2 (0.1 to 0.3)	0.2 (0.1 to 0.3)
ADDITION-RC	50.2 (0.8)	51.8 (0.2)	1.6 (0.0 to 3.1)	1.2 (–0.2 to 2.7)	52.8 (0.2)	2.6 (1.0 to 4.2)	1.5 (–0.0 to 2.9)
	6.9 (0.06)	6.9 (0.01)	0.1 (0.0 to 0.3)	0.1 (–0.0 to 0.3)	7.0 (0.02)	0.2 (0.1 to 0.4)	0.1 (–0.0 to 0.3)
MI model†	50.2 (0.8)	51.8 (0.2)	1.7 (0.6 to 2.7)	1.5 (0.5 to 2.5)	52.8 (0.3)	2.7 (1.6 to 3.8)	1.9 (0.9 to 3.0)
	6.7 (0.05)	6.9 (0.01)	0.2 (0.1 to 0.3)	0.2 (0.1 to 0.2)	7.0 (0.02)	0.3 (0.2 to 0.4)	0.2 (0.1 to 0.3)

Model on insulin prescription adjusted for age, sex, HbA1c, SBP, LDL-cholesterol, BMI and smoking; model with HbA1c as outcome, adjusted for sex, age, BMI and glucose-lowering medication.
*Sensitivity analysis with only care-as-usual group (RC) from ADDITION.
†Sensitivity analysis with multiple imputation.
ADDITION, Anglo-Danish-Dutch study of Intensive Treatment in People with Screen-Detected Diabetes in Primary care ; BMI, body mass index; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.

resulted in a non-significant OR compared with the 7 years group ($OR_{adjusted}$=1.6 (95% CI 0.9 to 2.9). The OR compared with the 10 years group ($OR_{adjusted}$=2.1 (95% CI 1.2 to 3.7) was larger and remained significant (table 2).

Glycemic control

Ten years after their screen detection of type 2 diabetes diagnosis, people showed on average a slightly lower HbA1c level compared with those with a 7-year and 10-year diabetes diagnosis based on care-as-usual, namely 50.1 mmol/mol (6.7%) versus 51.8 mmol/mol (6.9%) in those with 7-year and 52.8 mmol/mol (7.0%) with 10-year diabetes diagnosis. The adjusted mean differences between people with screen-detected diabetes and those diagnosed 7 years and 10 years before during care-as-usual were 1.6 mmol/mol (95% CI 0.6 to 2.6) (0.1% (95% CI 0.1 to 0.2)) and 1.8 mmol/mol (95% CI 0.7 to 2.9) (0.2% (95% CI 0.1 to 0.3)), respectively. Similar results were found after multiple imputation (table 2). Comparing only the ADDITION-NL RC group with the care-as-usual groups, the observed mean differences remained similar and were borderline significant with adjusted mean differences of 1.2 mmol/mol (95% CI –0.2 to 2.7) (0.1% (95% CI –0.0 to 0.3)) and 1.5 mmol/mol (95% CI –0.0 to 2.9) (0.1% (95% CI –0.0 to 0.3) (table 2).

CONCLUSION

In this study, we compared 10-year follow-up data after population-based diabetes screening with both 7-year and 10-year follow-up data from care-as-usual. We assumed a lead time of 3 years, based on the results of a computer-simulated model based on the ADDITION Europe data.[8] Since the exact lead time of population-based screening is unknown, we also compared a similar prescribing period (10 years). Our results show that population-based diabetes screening is associated with less need for insulin therapy compared with care-as-usual, which may include but does not guarantee opportunistic screening, in combination with a slightly better long-term glycemic control. Although our findings might seem obvious, because individuals diagnosed during opportunistic screening are likely to have a longer undiagnosed period, they are nevertheless clinically relevant. The ADDITION-DK study suggested that population-based screening has no additional benefits above opportunistic screening on risk reduction on CVD mortality.[4 5] However, our results indicate that population-based screening might result in a delayed need for insulin, which may influence the discussion on population-based versus opportunistic screening for type 2 diabetes.

In people with screen-detected type 2 diabetes, the HbA1c may be lower compared with opportunistic screening and particularly compared with people with symptoms of high glucose levels. In a former study, a high HbA1c at time of diagnosis was strongly associated with early initiation of insulin and poorer glycemic control in the future, independent of the selected glucose-lowering therapy.[21] Therefore, it might be speculated that the delayed need for insulin in the screen-detected people with type 2 diabetes is at least partially related to a difference in HbA1c level at time of diagnosis. Unfortunately, in the GIANNT and ZODIAC cohorts, data on HbA1c at time of diagnosis were not available in the majority of patients. The UK Prospective Diabetes Study demonstrated that a higher glucose level at diagnosis was associated with a decreased likelihood of achieving HbA1c

targets and, subsequently, progressive requirement for pharmacological treatment.[9 22] However, earlier intensive treatment is more likely to result in the achievement of treatment targets, which are more likely thereafter to be maintained. This explanation is in line with the results of a retrospective analysis of the UK Clinical Practice Research Datalink database Study. This study showed that the likelihood of attaining glycemic control was 22% and 28% lower for patients in the intermediate (12–<24 months) and late (24–<36 months) intensification groups, respectively, compared with those whose therapy had been intensified within 12 months.[23]

Considering the type of glucose-lowering medication prescriptions, according to both the ADDITION protocol and the Dutch diabetes guidelines since 2006, metformin as well as SU should be prescribed to the maximally tolerable dose before insulin is prescribed, taken into account a contraindication of metformin for people with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2.[20] Our results could also be partly due to a difference in prescribing behavior of the physicians in the different cohorts, both in terms of type of glucose-lowering medication and in dosages. Alternatively, the people's age at the time of diagnosis could also play a role; people from the ADDITION-NL cohort were, as a result of the inclusion criteria, on average 3 years older when they were diagnosed with type 2 diabetes. It could be that early detection and a diagnosis of type 2 diabetes at older age are associated with a delayed need for more intensive treatment. Finally, the method used for diagnosing type 2 diabetes differs between the cohorts. In the ADDITION-NL cohort, it was based on stepwise screening including risk assessment using the Symptom Risk Questionnaire, followed by random and/or fasting glucose testing and additional an OGTT if needed. In the ADDITION-NL cohort, HbA1c has not been used as a diagnostic marker. In care-as-usual, about 10% of the patients are symptomatic at diagnosis after which a random glucose value will suffice according to the guidelines from the Dutch College of General Practitioners. In the vast majority of asymptomatic people who are diagnosed with type 2 diabetes by care-as-usual, at least one fasting glucose measure in a certified laboratory will have been taken. According to the above-mentioned guidelines, general practitioners were not advised to use HbA1c as a diagnostic marker. Altogether, however, the different diagnosing strategies all result in a diagnosis of diabetes that is considered reliable. So, whereas the diagnostic process and the HbA1c level at diagnosis will likely to be different between the cohorts, they are intrinsically linked to the difference between population-based screening and care-as-usual. Therefore, adjusting for these factors would not be justified, and the results of this study allow conclusions based on the time of detection.

Strengths of this study are the availability of detailed data on glycemic control and glucose-lowering medication over a follow-up period of 10 years after population-based screen detection of type 2 diabetes and data from care-as-usual from the same healthcare system. Several limitations should be mentioned. First, the design of our study does not allow causal interpretation; we adjusted for some patient differences, but bias and confounding are possible. Second, we included three Dutch cohorts from different regions with may be different patients' socioeconomic status, ethnicity and willingness to participate. Finally, we assumed a lead time of 3 years with population-based screen detection, but the higher age at diagnosis in the ADDITION-NL cohort suggests this may not be true.

In conclusion, 10 years after screen-detected type 2 diabetes according to WHO criteria, a lower number of people are in need of insulin compared with individuals diagnosed during care-as-usual, in combination with a slightly better glycemic control. This suggests that the earlier diabetes is diagnosed and an intervention is initiated, the more favorable results are possible.

Contributors GEHMR and RCV designed the study. RCV analyzed the data and drafted the manuscript. RCV and HdO coordinated the data collection of the Anglo-Danish-Dutch study of Intensive Treatment in People with Screen-Detected Diabetes in Primary care-NL data. LAD and HdO were involved in drafting and analysing previous versions of the manuscript. HJGB is responsible for the Zwolle Outpatient Diabetes project Integrating Available Care data and PD for the Groningen Initiative to Analyze Type 2 Diabetes Treatment data. All authors read and approved the final manuscript. RCV is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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