Early Detection and Treatment of Type 2 Diabetes Reduce Cardiovascular Morbidity and Mortality: A Simulation of the Results of the Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen-Detected Diabetes in Primary Care (ADDITION-Europe)

William H. Herman,[1] Wen Ye,[2] Simon J. Griffin,[3] Rebecca K. Simmons,[3] Melanie J. Davies,[4] Kamlesh Khunti,[4] Guy E.H.M. Rutten,[5] Annelli Sandbaek,[6] Torsten Lauritzen,[6] Knut Borch-Johnsen,[7] Morton B. Brown,[2] and Nicholas J. Wareham[3]

Diabetes Care 2015;38:1449–1455 | DOI: 10.2337/dc14-2459

OBJECTIVE

To estimate the benefits of screening and early treatment of type 2 diabetes compared with no screening and late treatment using a simulation model with data from the ADDITION-Europe study.

RESEARCH DESIGN AND METHODS

We used the Michigan Model, a validated computer simulation model, and data from the ADDITION-Europe study to estimate the absolute risk of cardiovascular outcomes and the relative risk reduction associated with screening and intensive treatment, screening and routine treatment, and no screening with a 3- or 6-year delay in the diagnosis and routine treatment of diabetes and cardiovascular risk factors.

RESULTS

When the computer simulation model was programmed with the baseline demographic and clinical characteristics of the ADDITION-Europe population, it accurately predicted the empiric results of the trial. The simulated absolute risk reduction and relative risk reduction were substantially greater at 5 years with screening, early diagnosis, and routine treatment compared with scenarios in which there was a 3-year (3.3% absolute risk reduction [ARR], 29% relative risk reduction [RRR]) or a 6-year (4.9% ARR, 38% RRR) delay in diagnosis and routine treatment of diabetes and cardiovascular risk factors.

CONCLUSIONS

Major benefits are likely to accrue from the early diagnosis and treatment of glycemia and cardiovascular risk factors in type 2 diabetes. The intensity of glucose, blood pressure, and cholesterol treatment after diagnosis is less important than the time of its initiation. Screening for type 2 diabetes to reduce the lead time between diabetes onset and clinical diagnosis and to allow for prompt multifactorial treatment is warranted.

[1]Departments of Internal Medicine and Epidemiology, University of Michigan, Ann Arbor, MI
[2]School of Public Health, University of Michigan, Ann Arbor, MI
[3]Medical Research Council Epidemiology Unit, University of Cambridge School of Clinical Medicine, Institute of Metabolic Science, Cambridge, U.K.
[4]Leicester Diabetes Centre, University of Leicester, Leicester General Hospital, Leicester, U.K.
[5]Department of Primary Care, Julius Center, University Medical Center, Utrecht, the Netherlands
[6]Institute of Public Health, Section of General Practice, Aarhus University, Aarhus, Denmark
[7]Holbaek Hospital, Holbæk Sygehus, Holbaek, Denmark

Corresponding author: William H. Herman, wherman@umich.edu.

Received 16 October 2014 and accepted 23 March 2015.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-2459/-/DC1.

See accompanying article, p. 1399.

The potential health benefits of screening and early treatment for type 2 diabetes have been debated. Clinical trials of screening and early intervention versus screening and delayed intervention could address this question but have not been undertaken because of the ethics of not informing individuals when they are found by screening to have previously undiagnosed diabetes (1). Given that direct observation of the health benefits of screening has not been possible, researchers have used simulation modeling to assess potential benefits but have been limited by the precision of their estimates of the benefits of early intensive treatment (2,3). These benefits were recently reported from a randomized controlled trial (4), thus allowing better quantification of the potential benefits of screening.

The Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (ADDITION-Europe*)* study enrolled people 40–69 years of age without known diabetes from 343 general practices in the U.K., Denmark, and the Netherlands. Its goals were to determine the feasibility, yield, risks, and benefits of primary care–based screening for type 2 diabetes and to determine whether early, intensive, multifactorial treatment of hyperglycemia and cardiovascular risk factors reduced the composite cardiovascular outcome of stroke, myocardial infarction (MI), revascularization, amputation, and cardiovascular death compared with routine care (5). The study demonstrated that stepwise primary care–based screening for type 2 diabetes is feasible and that individuals detected by screening are at high cardiovascular risk (6). The study also showed that screening did not have an adverse psychological impact (7) and that people with negative screening tests were not falsely reassured (8). After 5.3 years of follow-up, the incidence of the composite cardiovascular outcome was 7.2% in the intensive treatment group and 8.5% in the routine care group (hazard ratio 0.83, 95% CI 0.65–1.05) (4). Screening followed by intensive treatment was thus associated with a small, nonsignificant reduction in the incidence of cardiovascular events and death compared with screening followed by routine care.

ADDITION-Europe was designed to estimate the differential impact of intensive compared with routine care in those found to have diabetes by screening—not the impact of screening itself. At the end of the study, BMI and HbA_{1c} did not differ between the treatment groups, and cardiovascular risk factor management improved substantially in both the intensive treatment and routine care groups. The key question that ADDITION-Europe could not answer directly, but which its results may inform, is the magnitude of the risk reduction that would have occurred had screening and treatment for diabetes been compared with no screening (and no treatment) until the time of clinical diagnosis. In this analysis, we use a validated computer simulation model for type 2 diabetes to model the incidence of the ADDITION-Europe composite cardiovascular outcome and all-cause mortality in the intensive treatment group and in the routine care group over 5 and 10 years. In the simulation, we also describe the outcomes that would have occurred after a 3- or 6-year delay in the diagnosis of diabetes and the treatment of glycemia and cardiovascular risk factors.

RESEARCH DESIGN AND METHODS

The Michigan Model for Type 2 Diabetes (Michigan Model) simulates the progression of diabetes and its complications, comorbidities, quality of life, and costs. It is designed to assess the effectiveness and cost-utility of alternative strategies for the prevention and treatment of type 2 diabetes. Since the validation and publication of the model in 2005, we have modified the structure of the cardiovascular disease submodel to accommodate revascularization procedures before and after first MI, to allow repeat revascularization procedures and repeat MIs, and to include congestive heart failure (W.Y., M. Brandle, M.B.B., W.H.H., unpublished data). The cardiovascular disease submodel incorporates the published risk equations from the UK Prospective Diabetes Study (UKPDS) outcomes model for ischemic heart disease, MI, and death after MI (9). As interventions for the prevention and treatment of cardiovascular disease have changed over time, we calibrated the risk equations to generate estimates that matched the incidence of cardiovascular events reported in more recent studies. We then validated the model against the studies used to develop the model and studies not used to develop or calibrate it. The coefficient of variation (R^2) relating the observed incidence of cardiovascular events (validation study results) to the predicted incidence of cardiovascular events (model results) was 0.98 for the studies used to develop and calibrate the model and 0.87 for the studies not used to develop or calibrate it when congestive heart failure was excluded (W.Y., M. Brandle, M.B.B., W.H.H., unpublished data).

Using the updated Michigan Model, we simulated four different scenarios: *1*) intensive treatment as characterized by the treatment parameters (use of medications and reduction in smoking) of the intensive treatment group at the end of ADDITION-Europe; *2*) routine care as characterized by the treatment parameters of the routine care group at the end of the study; *3*) a 3-year delay in diagnosis followed by routine care, i.e., routine care initiated in the fourth year unless there was a cardiovascular event, at which time treatment was initiated; and *4*) a 6-year delay in diagnosis followed by routine care, i.e., routine care initiated in the seventh year unless there was a cardiovascular event. In the latter two scenarios, HbA_{1c} increased by ~0.4% (3 mmol/mol) per year without treatment. Lipid and blood pressure levels increased slightly over time without treatment. By examining the first two scenarios, we were able to assess the model's ability to predict the observed outcomes of ADDITION-Europe and then to project them into the future. By examining the latter two scenarios, we were able to assess the impact of a delay in the initiation of treatment for diabetes and, in the absence of an intercurrent cardiovascular event, no change in the management of cardiovascular risk factors from baseline. Although cardiovascular risk factor management might improve over 3–6 years in the absence of a diagnosis of diabetes or a cardiovascular event, it should be remembered that all subjects enrolled in ADDITION-Europe were recruited from primary care practices and at the time of recruitment had access to and were receiving care according to community standards.

We ran the model for the first two scenarios using cohorts of patients with the demographic and clinical characteristics of the ADDITION-Europe intensive treatment and routine care groups at baseline (Table 1). We repeated each simulation 100 times. Continuous measures were simulated using a Gaussian distribution with the given mean (median) and SD, but truncated at 3 SDs. The only exception

was age, which, in the study, was limited to 40–69 years with a mean of 60 years. Since any symmetric distribution would yield a mean of 55 years, age was simulated by the square root of a uniform random variable that was then mapped into the range from 40 to 69; this distribution provided a mean age of 60 years. Height and weight were simulated with a correlation of 0.51. Systolic and diastolic blood pressure was simulated with a correlation of 0.82. When a measure was dichotomous, it was simulated using a binomial distribution. When a measure was discrete with more than two levels, a uniform random number was generated and divided into ranges that corresponded to the appropriate multinomial probabilities.

At the end of the ADDITION-Europe study, the intensive treatment and routine care groups differed in the frequency of use of glucose-lowering medications, ACE inhibitors and angiotensin receptor blockers (ARBs), β-blockers, statins, and aspirin. We used the baseline characteristics of the routine care group to generate the characteristics of the third and fourth scenarios (Tables 2 and 3). Glycemic management was modeled as progressing from lifestyle intervention, to one oral glucose-lowering medication (metformin), to two oral glucose-lowering medications, to basal insulin, and to basal-plus-bolus insulin. As guideline-recommended care was not appropriate for all patients and because adherence was not perfect, we defined adherence rates for each medication and considered individual patients to be either adherent or nonadherent. Unless there was a cardiovascular event, the nonadherent patients were considered to remain nonadherent even if they passed the threshold for treatment. We applied the guidelines for treatment according to ADDITION-Europe and empirically adjusted adherence rates in our simulations so that simulated treatment rates would match the observed treatment rates at the end of ADDITION-Europe (Supplementary Data). The adherence rates observed in ADDITION-Europe and in the simulations are reported in Table 2, and the theoretical adherence rates used in the simulation and the thresholds for initiating or intensifying treatment are presented in Supplementary Data.

All analyses were performed using the Michigan Model, which is programmed in Python (Python Software Foundation: www.python.org). SDs presented in the tables and figure were calculated from 100 simulations.

RESULTS

Observed and Simulated Baseline Characteristics

Table 1 presents the baseline characteristics observed in the ADDITION-Europe intensive treatment and routine care groups and the baseline characteristics of the four simulated groups. The mean (SD) age at diagnosis was 60 (7) years, 59% were men, and 96% were white (Table 1). Mean BMI was 31.6 (5.6) kg/m^2, median HbA_{1c} was 6.5% (48 mmol/mol), mean systolic blood pressure was 149 (22) mmHg, mean total cholesterol was 213 (43) mg/dL (5.5 [1.1] mmol/L), and 27% of subjects were current smokers. At baseline, 2.9% and 6.8% had a history of stroke and MI, respectively. Pharmacologic treatment was relatively infrequent. Fewer than 1% of the participants were prescribed any glucose-lowering medication, 47% were prescribed any antihypertensive medication, 17% were prescribed any cholesterol-lowering medication, and 16% were prescribed aspirin.

Observed and Simulated Cardiovascular Disease Incidence and All-Cause Mortality in the Intensive Treatment and Routine Care Groups

Table 2 presents the observed 5-year composite cardiovascular outcomes and all-cause mortality in the ADDITION-Europe intensive treatment and routine care groups and the simulated outcomes in the intensive treatment and the routine care group assuming no delay, a 3-year delay, or a 6-year delay in diagnosis of diabetes and implementation of routine care. There was little difference in the incidence of the composite cardiovascular

Table 1—Directly observed and model-simulated risk factors and treatments at baseline in the intensive treatment and routine care groups (with and without diagnostic delay) in the ADDITION-Europe trial

	Intensive observed	Routine observed	Intensive simulation (*N* = 1,678)	Routine simulation (*N* = 1,379)	Routine 3-year delay simulation (*N* = 1,379)	Routine 6-year delay simulation (*N* = 1,379)
Mean age (years)	60	60	60 (0)	60 (0)	60 (0)	60 (0)
Sex (male), %	59	57	59 (1)	57 (1)	57 (1)	57 (1)
Mean BMI (kg/m^2)	31.6	31.6	31.6 (0.1)	31.6 (0.1)	31.6 (0.1)	31.6 (0.1)
Median HbA_{1c} (%)	6.5	6.6	6.5 (0.0)	6.6 (0.0)	6.6 (0.0)	6.6 (0.0)
Median HbA_{1c} (mmol/mol)	48	49	48	49	49	49
Mean systolic blood pressure (mmHg)	149	150	149 (1)	150 (1)	150 (1)	150 (1)
Mean total cholesterol (mg/dL)	213	217	217	220 (0)	220 (0)	220 (0)
Mean total cholesterol (mmol/L)	5.5	5.6	5.6 (0.0)	5.7 (0.0)	5.7 (0.0)	5.7 (0.0)
Current smoker, %	27	28	27 (1)	28 (1)	28 (1)	28 (1)
Metformin or other oral medication, %	*	*	0	0	0	0
Insulin (basal ± bolus), %	0	0	0	0	0	0
ACE inhibitor or ARB, %	21	19	22 (1)	18 (1)	18 (1)	18 (1)
β-Blocker, %	23	19	23 (1)	19 (1)	19 (1)	19 (1)
Statin, %	17	15	17 (1)	15 (1)	15 (1)	15 (1)
Aspirin, %	16	13	16 (1)	12 (1)	13 (1)	12 (1)

Data are means or means (SD) unless otherwise indicated. SDs were calculated from 100 simulations. *The ADDITION-Europe study reported <1%. These medications were initiated after screening but before confirmatory diagnosis.

Table 2—Directly observed and model-simulated risk factors, treatments, and outcomes at 5 years in the intensive treatment and routine care groups (with and without diagnostic delay) in the ADDITION-Europe trial

	Intensive observed	Routine observed	Intensive simulation (*N* = 1,678)	Routine simulation (*N* = 1,379)	Routine 3-year delay simulation (*N* = 1,379)	Routine 6-year delay simulation (*N* = 1,379)
Mean BMI (kg/m^2)	31.1	31.0	30.8 (0.1)	30.8 (0.1)	31.2 (0.1)	32.9 (0.1)
Median HbA_{1c} (%)	6.4	6.5	6.5 (0.0)	6.6 (0.0)	6.7 (0.0)	8.4 (0.0)
Median HbA_{1c} (mmol/mol)	46	48	48	49	50	68
Mean systolic blood pressure (mmHg)	135	138	135 (0)	139 (0)	138 (0)	150 (1)
Mean total cholesterol (mg/dL)	162	170	162 (0)	166 (0)	170 (0)	182 (0)
Mean total cholesterol (mmol/L)	4.2	4.4	4.2 (0.0)	4.3 (0.0)	4.4 (0.0)	4.7 (0.0)
Current smoker, %	20	18	20 (1)	18 (1)	22 (1)	25 (1)
Metformin or other oral medication, %	78	70	70 (1)	65 (1)	58 (1)	1
Insulin (basal ± bolus), %	6	4	9 (1)	11 (1)	1 (0)	0
ACE inhibitor or ARB, %	74	60	74 (1)	64 (1)	48 (1)	18 (1)
β-Blocker, %	30	24	31 (1)	24 (1)	27 (1)	28 (1)
Statin, %	80	72	79 (1)	68 (1)	40 (1)	25 (1)
Aspirin, %	71	42	72 (1)	43 (1)	44 (1)	22 (1)
Composite cardiovascular events, %	7.2	8.5	7.7 (0.7)	7.9 (0.7)	11.2 (0.8)	12.8 (0.8)
All-cause mortality, %	6.2	6.7	6.0 (0.6)	6.0 (0.6)	7.2 (0.7)	7.9 (0.7)

Data are means or means (SD). SDs were calculated from 100 simulations.

outcome (7.7% vs. 7.9%) or in all-cause mortality (6.0% vs. 6.0%) between the simulated intensive treatment and routine care groups. Indeed, at 5 years, the relative risk reduction in the composite outcome was only 3% using the simulation model and the relative risk reduction in all-cause mortality was negligible.

The simulated 10-year composite outcomes and all-cause mortality in the intensive treatment group and the routine care group assuming no delay, a 3-year delay, or a 6-year delay in diagnosis of diabetes and implementation of routine care are presented in Table 3. The absolute benefits of intensive treatment versus routine care increased over time, but the relative risk reduction in the composite cardiovascular outcome and all-cause mortality remained small (6% and 1%) at 10 years (Fig. 1).

Observed and Simulated Cardiovascular Disease Incidence and All-Cause Mortality When Diagnosis and Treatment Are Delayed

The simulated benefits of early diagnosis and routine care were substantially greater than when diagnosis and treatment were delayed by 3 years in the routine care group. If diagnosis and treatment were delayed by 3 years in the routine care group, the simulated incidence of the composite cardiovascular outcome was 11.2% at 5 years compared with 7.9%, and the simulated incidence of all-cause mortality was 7.2% compared with 6.0%. Screening and routine care, compared with a 3-year delay in diagnosis and routine care, was therefore associated with a 3.3% absolute risk reduction (ARR) and a 29% relative risk reduction (RRR) in the composite outcome and a 1.2% ARR and a 17% RRR in all-cause mortality at 5 years (Table 2 and Fig. 1).

If diagnosis and routine care were delayed by 6 years, that is, beyond the 5-year time horizon used for the simulations in Table 2, the simulated median HbA_{1c} would increase progressively from 6.6% (49 mmol/mol) to 8.4% (68 mmol/mol), mean systolic blood pressure would increase progressively from 139 mmHg to 150 mmHg, and total cholesterol would increase progressively from 166 mg/dL (4.3 mmol/L) to 182 mg/dL (4.7 mmol/L) at 5 years (Table 2). In contrast, screening and routine care would result in substantially better risk factor control over 5 years with a 4.9% ARR and a 38% RRR in the composite cardiovascular outcome and a 1.9% ARR and a 24% RRR in all-cause mortality at 5 years (Table 2 and Fig. 1).

At 10 years, the models predict that screening and routine care would be associated with a 7.5% ARR and a 29% RRR in the composite cardiovascular outcome compared with the routine care with a delay of 6 years in diagnosis and treatment (18.4% compared with 25.9%). The comparable change in all-cause mortality was 3.6% ARR and 20% RRR (14.6% compared with 18.2%) (Table 3 and Fig. 1).

CONCLUSIONS

ADDITION-Europe demonstrated that stepwise primary care–based screening for diabetes is feasible and that individuals diagnosed with type 2 diabetes in primary care practices have substantial but potentially modifiable cardiovascular risk. It further demonstrated that after detection by screening, processes of care and intermediate outcomes improved in the intensive therapy group as a consequence of the trial intervention and in the routine care group as a consequence of the generally good quality of diabetes care in routine clinical practice. After 5.3 years of follow-up, intensive treatment was associated with a nonsignificant 17% reduction in the composite cardiovascular disease outcome compared with routine care. This finding was due not so much the ineffectiveness of screening and early intensive treatment as to the effectiveness of screening and routine care.

ADDITION-Europe was not designed to quantify the impact of screening and early treatment compared with no screening, no diagnosis, and no treatment. To address this question, we used a validated computer simulation

Table 3—Model-simulated risk factors, treatments, and outcomes at 10 years in the intensive treatment and routine care groups (with and without diagnostic delay) in the ADDITION-Europe trial

	Intensive simulation (*N* = 1,678)	Routine simulation (*N* = 1,379)	Routine 3-year delay simulation (*N* = 1,379)	Routine 6-year delay simulation (*N* = 1,379)
BMI (kg/m^2)	31.5 (0.1)	31.7 (0.1)	32.0 (0.1)	31.8 (0.1)
HbA_{1c} (%)	6.4 (0.0)	6.6 (0.0)	6.8 (0.0)	7.0 (0.0)
HbA_{1c} (mmol/mol)	46	49	68	70
Systolic blood pressure (mmHg)	138 (0)	142 (0)	141 (0)	140 (0)
Total cholesterol (mg/dL)	159 (0)	162 (0)	162 (0)	162 (0)
Total cholesterol (mmol/L)	4.1 (0.0)	4.2 (0.0)	4.2 (0.0)	4.2 (0.0)
Current smoker, %	15 (1)	12 (1)	15 (1)	17 (1)
Metformin or other oral medication, %	29 (1)	22 (1)	36 (1)	38 (1)
Insulin (basal ± bolus), %	67 (1)	65 (1)	48 (1)	40 (1)
ACE inhibitor or ARB, %	81 (1)	71 (1)	65 (1)	54 (1)
β-Blocker, %	37 (1)	29 (1)	32 (1)	34 (1)
Statin, %	82 (1)	71 (1)	49 (2)	43 (2)
Aspirin, %	74 (1)	47 (1)	48 (1)	49 (1)
Composite cardiovascular events, %	17.3 (0.8)	18.4 (1.0)	22.4 (1.1)	25.9 (1.1)
All-cause mortality, %	14.4 (0.8)	14.6 (1.0)	16.4 (1.0)	18.2 (1.0)

Data are means or means (SD). SDs were calculated from 100 simulations.

model for type 2 diabetes to model the incidence of the composite cardiovascular outcome and all-cause mortality in the intensive treatment group and in the routine care group over 5 and 10 years. In the simulation of the routine care group, we further assumed that there was no delay, a 3-year delay, or a 6-year delay in diagnosis and routine care. We further assumed that without screening and diagnosis, routine care would be delayed and cardiovascular risk factor levels would progressively worsen.

Our results suggest that the benefits of stepwise primary care–based screening and treatment primarily accrue from early diagnosis, that is, by reducing the lead time between diabetes onset and clinical diagnosis and by hastening the treatment of cardiovascular risk factors. The overall high quality of routine diabetes care delivered in general practice during the ADDITION-Europe study years explains our finding that the small differences in the intensity of glycemic and cardiovascular risk factor management between the two trial groups are relatively less important than the impact of early diagnosis and treatment.

Our assumption that screening could move forward the diagnosis of diabetes by 3 or even 6 years is supported by published literature. In a cohort of people 40–65 years of age and free of known diabetes (*n* = 4,936), Rahman et al. (10) randomly selected one-third for screening at 5-year intervals. Another one-third were invited to attend a diabetes screening 10 years later. Screening resulted in diabetes being identified on average 3.3 years earlier. In older studies that examined the relationship between the prevalence of diabetic retinopathy and known duration of type 2 diabetes in Australian and U.S. populations, Harris et al. (11) estimated that the onset of retinopathy occurs 4–7 years before the clinical diagnosis of type 2 diabetes. Similarly, Porta et al. (12) examined diabetic retinopathy data and estimated that the onset of diabetes occurred 6 years before its clinical diagnosis in Europe, and Thompson et al. (13) estimated that the onset of diabetes occurred up to 8 years before its clinical diagnosis in Egypt.

On the basis of our simulations, we conclude that screening and early diagnosis of type 2 diabetes, with prompt initiation of treatment for glycemia and cardiovascular risk factors, are likely to confer substantial health benefits. In ADDITION-Europe, glycemic control, blood pressure control, lipid management, aspirin therapy, and smoking cessation were effective in reducing cardiovascular risk and all-cause mortality in both the intensive treatment and routine care groups. The factor that was most important in contributing to a reduction in the composite cardiovascular outcome and all-cause mortality was the time at which routine care was initiated. If the delay in initiating treatment had been either 3 or 6 years, then clinical outcomes would have been substantially worse at 5 and 10 years of follow-up.

In our analyses, we did not address an additional benefit of screening for diabetes, that is, identifying individuals at risk for diabetes. The U.S. Preventive Services Task Force recently reviewed the evidence on screening and concluded that screening adults at increased risk for diabetes and treating those with prediabetes with lifestyle interventions reduce the incidence of diabetes and cardiovascular and all-cause mortality (14). To the extent that screening for diabetes identifies people at risk for diabetes and provides an opportunity for timely intervention to delay or prevent the development of type 2 diabetes, we have underestimated the benefits of screening.

There are at least two limitations to our study. First, uncertainty is inherent in any study that employs simulation modeling. We have not formally assessed the statistical significance of our results. In general, misspecification of model parameters and model structure

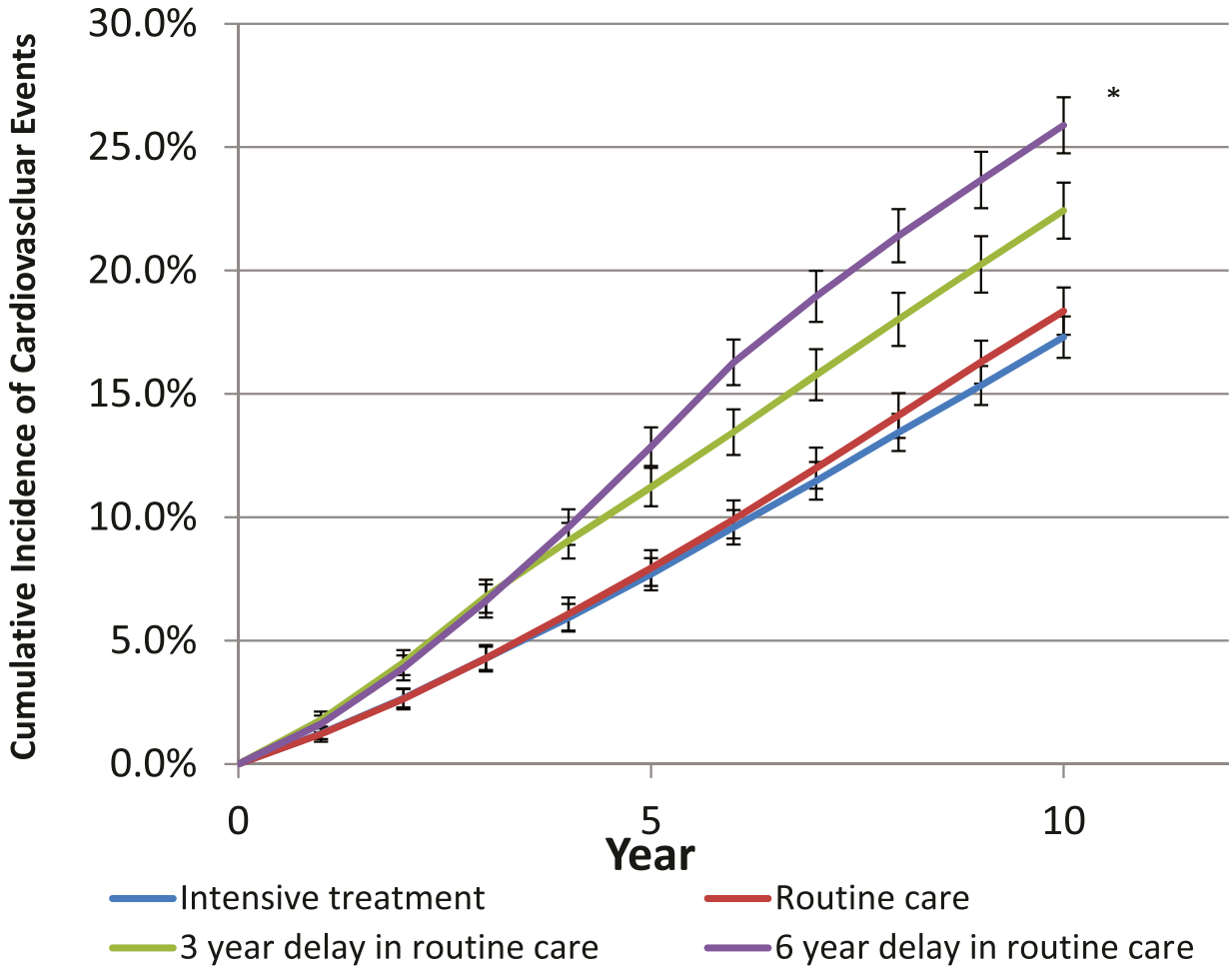

Figure 1—Simulated incidence of the composite cardiovascular outcome by treatment group with and without delays in diagnosis and treatment in the ADDITION-Europe trial. *Outcome defined as stroke, MI, revascularization, amputation, or cardiovascular death. The error bars indicate SDs calculated from 100 simulations.

are the most important sources of uncertainty. For this study, we updated the structure of the Michigan Model, recalibrated the model parameters, and performed both internal and external validation studies to test the model's performance. These studies demonstrated very good performance (W.Y., M. Brandle, M.B.B., W.H.H., unpublished data). In addition, when we programmed the model with the baseline characteristics of the ADDITION-Europe study populations and the treatment goals, the model predicted pharmacologic treatments, risk factor status, the primary composite outcome, and all-cause mortality at 5 years with reasonable accuracy.

Second, our assumption that failure to diagnose diabetes could lead to a 3- or 6-year delay in the treatment of hyperglycemia and the initiation of cardiovascular risk factor management in the absence of an intercurrent cardiovascular event is clearly a worst case scenario. Even in the absence of a diagnosis of diabetes or a cardiovascular event, blood pressure and lipid management might be intensified, aspirin therapy might be prescribed, and smoking cessation encouraged. Nevertheless, participants were identified through primary care and at baseline and had access to and were presumably receiving medical care. Their risk factor profiles were as they were observed to be and worsened over time. To the extent that additional treatments would be applied sooner than 3 years or even 6 years of follow-up and to the extent that cardiovascular risk factors would not worsen over time, the outcomes would be less extreme than we projected but would fall between the outcomes observed for the routine care group and the groups with either a 3-year or 6-year delay in routine care.

We conclude from our modeling that the ADDITION-Europe study results are compatible with a major benefit of early identification of diabetes. Efforts to reduce the delay between the time at which diabetes is first detectable and the time at which it is actually detected and treated are warranted.

Funding. This research was supported by grant P30DK092926 from the Michigan Center for Diabetes Translational Research Methods and Measurement Core from the National Institute of Diabetes and Digestive and Kidney Diseases. R.K.S. reports grants from the Wellcome Trust, Medical Research Council, National Institute for Health Research (NIHR) Health Technology Assessment Programme, and National Health Service (NHS) R&D support funding during the conduct of the study. K.K. is advisor to the Department of Health NHS Health Checks

Programme and was Chair of the National Institute for Health and Care Excellence (NICE) Programme Development Group on "Preventing type 2 diabetes: risk identification and interventions for individuals at high risk." M.J.D. acknowledges support from the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care–East Midlands (NIHR CLAHRC-EM), the Leicester Clinical Trials Unit, and the NIHR Leicester–Loughborough Diet, Lifestyle and Physical Activity Biomedical Research Unit, which is a partnership between University Hospital of Leicester NHS Trust, Loughborough University, and the University of Leicester. N.J.W. is an NIHR Senior Investigator.

Duality of Interest. S.J.G. reports nonfinancial support from Bio-Rad during the conduct of the study and personal fees from Eli Lilly outside the submitted work. M.J.D. has acted as consultant, advisory board member, and speaker for Novartis, Novo Nordisk, Sanofi, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, and Roche and has received grants in support of investigator and investigator-initiated trials from Novartis, Novo Nordisk, Sanofi, Lilly, Pfizer, Merck Sharp & Dohme, and GlaxoSmithKline. A.S. reports grants from Novo Nordisk A/S during the conduct of the study and personal fees from education activities for general practitioners outside the submitted work. T.L. reports grants from Novo Nordisk, AstraZeneca, Pfizer, GlaxoSmithKline, Servier, and HemoCue during the conduct of the study; all aside from Novo Nordisk were outside the submitted work. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. W.H.H. wrote the manuscript. W.Y. and M.B.B. performed the statistical analyses and wrote and edited the manuscript. S.J.G., R.K.S., M.J.D., K.K., G.E.H.M.R., A.S., T.L., and K.B.-J. researched data and reviewed and edited the manuscript. N.J.W. researched data, contributed to discussion, and reviewed and edited the manuscript. W.H.H., W.Y., and M.B.B. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Engelgau MM, Narayan KM, Herman WH. Screening for type 2 diabetes. Diabetes Care 2000;23:1563–1580

2. Gillies CL, Lambert PC, Abrams KR, et al. Different strategies for screening and prevention of type 2 diabetes in adults: cost effectiveness analysis. BMJ 2008;336:1180–1185

3. Kahn R, Alperin P, Eddy D, et al. Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis. Lancet 2010;375:1365–1374

4. Griffin SJ, Borch-Johnsen K, Davies MJ, et al. Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. Lancet 2011;378:156–167

5. Lauritzen T, Griffin S, Borch-Johnsen K, Wareham NJ, Wolffenbuttel BH, Rutten G; Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care. The ADDITION study: proposed trial of the cost-effectiveness of an intensive multifactorial intervention on morbidity and mortality among people with Type 2 diabetes detected by screening. Int J Obes Relat Metab Disord 2000;24(Suppl. 3):S6–S11

6. Sandbaek A, Griffin SJ, Rutten G, et al. Stepwise screening for diabetes identifies people with high but modifiable coronary heart disease risk. The ADDITION study. Diabetologia 2008; 51:1127–1134

7. Eborall HC, Griffin SJ, Prevost AT, Kinmonth AL, French DP, Sutton S. Psychological impact of screening for type 2 diabetes: controlled trial and comparative study embedded in the ADDITION (Cambridge) randomised controlled trial. BMJ 2007;335:486

8. Paddison CAM, Eborall HC, Sutton S, et al. Are people with negative diabetes screening tests falsely reassured? Parallel group cohort study embedded in the ADDITION (Cambridge) randomised controlled trial. BMJ 2009;339: b4535

9. Clarke PM, Gray AM, Briggs A, et al.; UK Prospective Diabetes Study (UKDPS) Group. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia 2004;47:1747–1759

10. Rahman M, Simmons RK, Hennings SH, Wareham NJ, Griffin SJ. How much does screening bring forward the diagnosis of type 2 diabetes and reduce complications? Twelve year follow-up of the Ely cohort. Diabetologia 2012; 55:1651–1659

11. Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. Diabetes Care 1992; 15:815–819

12. Porta M, Curletto G, Cipullo D, et al. Estimating the delay between onset and diagnosis of type 2 diabetes from the time course of retinopathy prevalence. Diabetes Care 2014;37: 1668–1674

13. Thompson TJ, Engelgau MM, Hegazy M, et al. The onset of NIDDM and its relationship to clinical diagnosis in Egyptian adults. Diabet Med 1996;13:337–340

14. U.S. Preventive Services Task Force. Draft recommendation statement. Abnormal glucose and type 2 diabetes mellitus in adults: screening [Internet]. Available from http://www.uspreventiveservicestaskforce.org/page/document/recommendationstatementdraft/screening-for-abnormal-glucose-and-type-2-diabetes-mellitus. Accessed 26 February 2015