Effect of Early Multifactorial Therapy Compared With Routine Care on Microvascular Outcomes at 5 Years in People With Screen-Detected Diabetes: A Randomised Controlled Trial
The ADDITION-Europe Study

OBJECTIVE
To determine the benefit of multifactorial treatment on microvascular complications among people with type 2 diabetes detected by screening.

RESEARCH DESIGN AND METHODS
This study was a multicenter cluster randomized controlled trial in primary care with randomization at the practice level. In four centers in Denmark; Cambridge, U.K.; The Netherlands; and Leicester, U.K., 343 general practices participated in the trial. Eligible for follow-up were 2,861 of the 3,057 people with diabetes detected by screening included in the original trial. Biomedical data on nephropathy were collected in 2,710 (94.7%) participants, retinal photos in 2,190 (76.6%), and questionnaire data on peripheral neuropathy in 2,312 (80.9%). The prespecified microvascular end points were analyzed by intention to treat. Results from the four centers were pooled using fixed-effects meta-analysis.

RESULTS
Five years after diagnosis, any kind of albuminuria was present in 22.7% of participants in the intensive treatment (IT) group and in 24.4% in the routine care (RC) group (odds ratio 0.87 [95% CI 0.72–1.07]). Retinopathy was present in 10.2% of the IT group and 12.1% of the RC group (0.84 [0.64–1.10]), and severe retinopathy was present in one patient in the IT group and seven in the RC group. Neuropathy was present in 4.9% and 5.9% (0.95 [0.68–1.34]), respectively. Estimated glomerular filtration rate increased between baseline and follow-up in both groups (4.31 and 6.44 mL/min, respectively).

CONCLUSIONS
Compared with RC, an intervention to promote target-driven, intensive management of patients with type 2 diabetes detected by screening was not associated with significant reductions in the frequency of microvascular events at 5 years.

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Type 2 diabetes is a common chronic condition associated with a substantial burden of microvascular and macrovascular morbidity. Treatment of individual risk factors, such as blood pressure and glucose, reduces the risk of microvascular complications (1–4). Intensive treatment (IT) of multiple risk factors can halt the risk of retinopathy, neuropathy, and nephropathy among individuals with long-standing diabetes and microalbuminuria (5). However, the effects of starting multifactorial treatment earlier in the course of the disease are uncertain.

Diabetes is frequently asymptomatic, with the true onset occurring several years before diagnosis. When diagnosed, many patients exhibit evidence of microvascular complications (2,3,6). Early detection by screening is not associated with psychological harms (7); therefore, diabetes meets many of the criteria for screening. However, uncertainties still exist about the magnitude of the benefits of early detection and subsequent intensive management. The ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen Detected Diabetes in Primary Care)-Europe trial was set up to investigate whether intensive multifactorial treatment improved outcomes compared with routine care (RC) when commenced in the lead time between detection by screening and clinical diagnosis. IT was associated with a nonsignificant 17% reduction in the composite cardiovascular end point over 5.3 years compared with RC (8). Data from trials of IT of hyperglycemia suggest that beneficial effects can be seen for microvascular outcomes in the short term (9–11), whereas cardiovascular benefits are only evident with longer follow-up (5,12). We report the effect of early intensive multifactorial treatment compared with RC on risk of microvascular complications, including retinopathy, nephropathy, and peripheral neuropathy, at 5 years following screening for diabetes.

RESEARCH DESIGN AND METHODS

The study design and rationale have been reported previously (8). In brief, ADDITION-Europe comprises two phases: 1) a screening phase and 2) a pragmatic cluster randomized parallel group trial in four centers (Denmark; Cambridge, U.K.; The Netherlands; and Leicester, U.K.). The study was approved by the local ethics committee of each center. All participants provided informed consent.

Of 1,312 general practices invited to participate, 379 (29%) agreed, and 343 (26%) were independently randomized to screening plus RC for diabetes or screening followed by intensive multifactorial treatment. Population-based stepwise screening programs among people aged 40–69 years (50–69 years in The Netherlands) without known diabetes were completed between April 2001 and December 2006 (8). The screening phase included an oral glucose tolerance test for all individuals in Leicester and a stepwise screening program using random glucose measurements and HbA1c followed by fasting glucose and oral glucose tolerance test in all other centers. Individuals were given a diagnosis of diabetes based on World Health Organization criteria (13). All patients with newly diagnosed type 2 diabetes were eligible to participate in the treatment study unless their family physician indicated that they had contraindications to the proposed study medication, an illness with a life expectancy of <12 months, or psychological or psychiatric problems that were likely to invalidate informed consent.

The practices were randomly assigned by statisticians independent of measurement teams to provide intensive multifactorial treatment or routine diabetes care according to national guidelines in a 1:1 ratio. Randomization included stratification by county, number of full-time family physicians in Denmark, and single-handed or group practice in The Netherlands. In Cambridge, randomization included minimization for the local district hospital and the number of patients with diabetes per practice. In Leicester, randomization included minimization for practice demographic, deprivation status, and prevalence of type 2 diabetes. Participants were unaware of study group allocation.

Outcome Variables

Prespecified secondary outcomes included measures of kidney function (microalbuminuria, macroalbuminuria, and estimated glomerular filtration rate [eGFR]), retinopathy, and peripheral neuropathy. Health assessments at baseline and follow-up included biochemical, anthropometric, and questionnaire measures and were undertaken by centrally trained staff following standard operating procedures and unaware of study group allocation. Follow-up examinations took place from September 2008 to the end of December 2009 for a mean (SD) follow-up period of 5.3 (1.6) years. All biochemical measures were analyzed in five regional laboratories at baseline and follow-up. Standardized self-report questionnaires were used to collect information on sociodemographic characteristics (age, sex, ethnicity), smoking status, and prescribed medication.
Nephropathy was assessed by the urinary albumin-to-creatinine ratio (ACR) and eGFR. Spot urine ACR was measured with a Roche Hitachi 912 chemistry analyzer at Aarhus Hospital (Aarhus, Denmark) and the Steno Diabetes Centre (Gentofte, Denmark), an Olympus AU400 analyzer at Addenbrooke’s Hospital (Cambridge, U.K.) and the Royal Infirmary (Leicester, U.K.), and a Roche/Hitachi Modular P analyzer at the SHL Centre for Diagnostic Support in Primary Care (Etten-Leur, The Netherlands). Repeated analyses of standardized trial control samples for urine creatinine levels during follow-up confirmed reliability and precision of laboratory methods with coefficients of variation (CVs) <3.4% in all laboratories. Analyses of trial and external quality control samples of urine albumin revealed CVs between 2.0% and 9.8% in Etten-Leur, Leicester, and Gentofte and 4.9% and 3.4% for low and high concentrations, respectively, in Cambridge during the trial testing period. Microalbuminuria was defined as an ACR $\geq 2.5$ mg/mmol for males and $\geq 3.5$ mg/mmol for females, and macroalbuminuria was defined as an ACR $\geq 25$ mg/mmol.

Nephropathy was defined as the presence of either microalbuminuria or macroalbuminuria. eGFR was calculated using data on serum creatinine level, age, sex, and ethnicity for each individual using the Modification of Diet in Renal Disease equation (23) at baseline and follow-up. Change between the two time points was analyzed as a continuous variable. Plasma creatinine level was analyzed with kinetic colorimetric methods at all laboratories at baseline and follow-up except in The Netherlands, where an enzymatic method was used at follow-up. Repeated analyses of standardized control samples for creatinine level during follow-up confirmed reliability and precision of laboratory methods, with CVs between 1.3% and 6.4%.

Retinopathy was assessed using gradable digital images (two from each eye: one with the fovea in the center and one with the macula in the center). In The Netherlands and Leicester, all retinal images were taken as part of the follow-up examination. In Denmark, 81% of the images were taken as part of study follow-up, whereas the remainder were obtained from routine health service records. All retinal images in Cambridge were retrieved from routine medical records. Only images taken in the 2 years preceding the follow-up visit were included in this analysis. Information on retinal photography devices used at the four centers is available on the study website (www.addition.au.dk). Three certified graders unaware of the participants’ study group allocation used a quantitative method to grade retinal images, which were subsequently categorized according to the Early Treatment of Diabetic Retinopathy Study semi-quantitative scale (24). Two binary endpoints were then defined: 1) any retinopathy versus no retinopathy and 2) severe or proliferative retinopathy versus none, mild, or moderate retinopathy.

Peripheral neuropathy was assessed using the self-administered Michigan Neuropathy Screening Instrument (MNSI), which includes 13 questions about neuropathic symptoms (25). Responses to the questions were summed about neuropathic symptoms (25). Responses to the questions were summed according to the Early Treatment of Diabetic Retinopathy Study semi-quantitative scale (24). Two binary endpoints were then defined: 1) any retinopathy versus no retinopathy and 2) severe or proliferative retinopathy versus none, mild, or moderate retinopathy.

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groups in favor of the IT group were seen in the changes for systolic and diastolic blood pressure, HbA1c, and total and LDL cholesterol levels. At follow-up, more patients in the IT group reported using glucose-lowering, antihypertensive, and lipid-lowering medication and aspirin than in the RC group. However, in both groups, the use of these drugs significantly increased. Furthermore, a significantly higher proportion of patients in the IT group met the targets compared with the RC group at follow-up (Table 2).

Of the 2,861 patients still alive at 5 years, 2,493 (87.1%), 2,710 (94.7%), and 2,312 (80.9%) had data for urine ACR, eGFR, and peripheral neuropathy, respectively. Retinal photographs were obtained for 2,190 (76.6%) participants (Fig. 1).

At follow-up, any albuminuria was present in 316 (22.7%) participants in the IT group and 269 (24.4%) in the RC group, whereas macroalbuminuria was present in 56 (4.0%) and 37 (3.4%) patients, respectively. Center-specific ORs for any albuminuria favored the IT group, but the pooled OR was not statistically significant at 0.87 (95% CI 0.72–1.07) (Fig. 2). The pooled OR for macroalbuminuria was 1.15 (0.76–1.74). In both groups ACR increased between baseline and follow-up. In the IT group, the mean (SD) increase was 1.45 (0.60) mg/mmol and in the RC group, 1.30 (0.66) mg/mmol. The overall difference in means was −0.02 (95% CI −0.96 to 0.91 mg/mmol). There were no significant interactions between study group and any of the subgroups.

eGFR increased between baseline and follow-up in both the IT (4.31 [0.49] mL/min) and RC (6.44 [0.90] mL/min) groups, with an overall difference of −1.39 (−2.97 to 0.19). There were no significant interactions between study group and any of the subgroups regarding eGFR. The number of missing values was equally distributed between groups.

Retinopathy was present in 125 (10.2%) patients in the IT group and 116 (12.1%) in the RC group. Center-specific ORs favored the IT group, but the pooled OR was not statistically significant (0.84 [0.64–1.10]) (Fig. 2). Imputation of missing values did not affect the estimates.

Participants without retinal images at follow-up had significantly higher mean

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**Table 1—Effect of intervention on change in clinical and prescribed medication variables: ADDITION-Europe**

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>RC</th>
<th>IT</th>
<th>Estimate (OR)</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smokers (%)</td>
<td>−4.9</td>
<td>−5.2</td>
<td>1.06</td>
<td>0.77</td>
<td>1.45</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>−0.5</td>
<td>−0.5</td>
<td>0.02</td>
<td>−0.17</td>
<td>0.22</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>−11.9</td>
<td>−13.5</td>
<td>−2.86</td>
<td>−4.51</td>
<td>−1.20</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>−6.2</td>
<td>−6.7</td>
<td>−1.44</td>
<td>−2.30</td>
<td>−0.58</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>−0.3</td>
<td>−0.4</td>
<td>−0.08</td>
<td>−0.14</td>
<td>−0.02</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>−1.2</td>
<td>−1.4</td>
<td>−0.27</td>
<td>−0.34</td>
<td>−0.19</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>0.1</td>
<td>0.1</td>
<td>0.00</td>
<td>−0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>1.2</td>
<td>1.3</td>
<td>−0.20</td>
<td>−0.26</td>
<td>−0.13</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>−0.1</td>
<td>−0.1</td>
<td>0.96</td>
<td>0.93</td>
<td>0.99</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>−3.7</td>
<td>−2.2</td>
<td>1.81</td>
<td>0.10</td>
<td>3.53</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>6.4</td>
<td>4.3</td>
<td>−1.39</td>
<td>−2.97</td>
<td>0.19</td>
</tr>
<tr>
<td>ACR</td>
<td>2.5</td>
<td>2.5</td>
<td>0.92</td>
<td>0.82</td>
<td>1.04</td>
</tr>
<tr>
<td>Any albuminuria (%)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.81</td>
<td>0.65</td>
<td>1.03</td>
</tr>
</tbody>
</table>

**Self-reported medication**

| Any glucose-lowering drug (%)     | 56.3  | 64.5  | 1.53          | 1.25   | 1.87   |
| Any antihypertensive drug (%)    | 31.6  | 37.4  | 1.61          | 1.27   | 2.04   |
| Any cholesterol-lowering drug (%)| 58.4  | 64.0  | 1.52          | 1.23   | 1.90   |
| Aspirin (%)                      | 29.9  | 55.5  | 3.37          | 2.76   | 4.12   |

**Table 2—Effect of intervention on percentage of participants meeting treatment targets at follow-up: ADDITION-Europe**

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>RC Baseline (%)</th>
<th>Follow-up (%)</th>
<th>IT Baseline (%)</th>
<th>Follow-up (%)</th>
<th>Estimate (OR)</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure &lt;135/85 mmHg</td>
<td>20.2</td>
<td>38.1</td>
<td>23.8</td>
<td>44.8</td>
<td>1.39</td>
<td>1.14</td>
<td>1.69</td>
</tr>
<tr>
<td>Cholesterol &lt;5 mmol/L (no CVD) or &lt;4.5 mmol/L (with CVD)</td>
<td>28.1</td>
<td>75.1</td>
<td>30.2</td>
<td>82.7</td>
<td>1.69</td>
<td>1.36</td>
<td>2.11</td>
</tr>
<tr>
<td>HbA1c % &lt;7% (53 mmol/mol)</td>
<td>64.6</td>
<td>70.9</td>
<td>66.4</td>
<td>75.3</td>
<td>1.30</td>
<td>1.05</td>
<td>1.61</td>
</tr>
</tbody>
</table>

CVD, cardiovascular disease. *Intervention effect represents the OR of meeting the treatment target at follow-up for IT vs. RC, adjusted for baseline.
HbA1c levels at baseline than those with retinal images (7.18% [55 mmol/mol] and 6.99% [53 mmol/mol], respectively, P = 0.044), but there was no difference between groups (interaction P = 0.78). We found a significant interaction among retinopathy, randomized group, and baseline HbA1c (P = 0.007). It appeared to be more effective among participants with HbA1c ≥6.6% (49 mmol/mol) at baseline (OR 0.65 [0.45–0.93]) than among those with HbA1c <6.6% (49 mmol/mol) (1.17 [0.75–1.82]). There was no evidence of an interaction with either age or sex. Severe retinopathy was present in one participant in the IT group and seven in the RC group. Peripheral neuropathy was present in 63 (4.9%) participants in the IT group and 60 (5.9%) in the RC group (pooled OR 0.95 [0.68–1.34]) (Fig. 2). Nonresponders had higher BMI values (P = 0.055) and were more likely to be from a minority ethnic group (P = 0.004) than responders. Imputation of missing values did not affect the estimates. The overall intracluster correlation coefficient values were 0.024 (95% CI 0.0060–0.095), 0.014 (0.00017–0.55), and 0.011 (4.6 × 10−7 to 1) for albuminuria, retinopathy, and neuropathy, respectively.

**CONCLUSIONS**

An intervention achieving modest changes in prescribed treatment and improvements in cardiovascular risk factors in patients with screen-detected type 2 diabetes was not associated with significant reductions in the frequency of microvascular events at 5 years. Differences between study groups for microvascular end points tended to favor the IT group; differences were greatest for retinopathy and smallest
for neuropathy. However, we cannot rule out the possibility that these findings were due to chance. The frequency of microvascular complications 5 years after diagnosis was lower than expected and lower than that reported among individuals who have had diabetes for a similar length of time. This finding is likely due to early detection and close-to-optimal treatment in both study groups.

Comparison With Previous Literature

Nephropathy

Any albuminuria was common at diagnosis in participants in the ADDITION study (19.9%) (28). The finding of 7.2% with microalbuminuria at baseline in the UK Prospective Diabetes Study (UKPDS) is not directly comparable because a higher level of urinary albumin excretion was used to define microalbuminuria in the UKPDS compared with the ADDITION study (3). Although ADDITION participants were older (mean age 60 years vs. 52 years in UKPDS) and more likely to have hypertension at diagnosis, the rate of progression of albuminuria from 19.9% at baseline to 23.5% (0.7% per year) was one-half that observed in the UKPDS (3). Higher progression rates were also reported in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) (10), ADVANCE (Action in Diabetes and Vascular Disease—Preterax and Diamicron Modified Release Controlled Evaluation) (9), and VADT (Veterans Affairs Diabetes Trial) (11) trials; however, these trials recruited older people with long-standing diabetes.

The increase in eGFR observed in both groups represents a benefit for the patients and is probably a result of the complex treatment regimen, including ACE inhibitors and angiotensin receptor blockers, lipid-lowering treatment, and glucose-lowering treatment.
Retinopathy
The frequency of retinopathy was lower than expected. In the UKPDS, 37% of patients had retinopathy at diagnosis, and retinopathy developed in a further 22% within 6 years (2). In contrast, retinopathy developed in only 12% of patients in the ADDITION RC group within 5 years of diagnosis. Again, this finding is likely to reflect treatment in the lead time between detection by screening and clinical diagnosis.

IT appeared to be more effective among participants with HbA1c ≥6.6% (49 mmol/mol) at baseline than among those with HbA1c ≤6.6% (49 mmol/mol). This finding is likely to be explained by the increased risk of retinopathy at baseline in the former group, which, therefore, had a larger potential for risk reduction by IT.

Neuropathy
The prevalence of peripheral neuropathy was ~5%, with no difference between study groups and substantially lower than the 11% reported in a population having had type 2 diabetes for 16 years (26). However, the MNSI may not be sufficiently sensitive (29) or reliable to detect early features of neuropathy and differences between study groups (30). The heterogeneity in effect size estimates for this outcome across centers supports this view.

Strengths and Limitations
Participants were drawn from large, population-based samples in three European countries. Although recruitment was nonrandom, a large geographical area was covered in each country. The practices randomized (26% of those invited) were nationally representative for key sociodemographic and clinical characteristics. Participants were identified using a range of screening procedures, but all were diagnosed based on World Health Organization criteria. The intervention targeted both patient and practitioner behavior, and treatment algorithms and targets were based on robust trial data.

To minimize the risk of contamination, we randomized general practices rather than individual patients, and the analyses allowed for this cluster design. The intraclass correlation coefficients are small (31) and did not adversely affect study power. They have been reported here for future designs of cluster trials. Both patient and practice characteristics were well matched at baseline. Clinically important outcomes were assessed using standardized equipment and protocols by trained staff unaware of study group allocation. Although screening procedures and intervention delivery varied among centers, there was little heterogeneity in effect size estimates for nephropathy and retinopathy.

There were differences in the proportion of participants with data for the various microvascular end points at 5 years. These ranged from 77% for retinopathy to 95% for eGFR. Examination of characteristics of ADDITION-Europe participants with and without outcome data suggests that some healthy volunteer bias may have been present, although absolute differences were small (e.g., 0.19% [2 mmol/mol] for HbA1c). There were no between-group differences in the proportion of patients with missing data. However, we may have underestimated the prevalence of retinopathy and neuropathy given the adverse risk profile of those with missing data for these outcomes.

Furthermore, the microvascular end points reported here were predefined secondary endpoints in the original trial; therefore, a formal power calculation was not performed for these end points. However, it is still legitimate to report the effects of the intervention on these end points. The CIs show the range of effect sizes, which are compatible with the data and, therefore, are more informative than considerations of power after a trial has been completed, as discussed in the CONSORT (Consolidated Standards of Reporting Trials) sample size reporting guidelines (32).

In this pragmatic trial, outcome assessment and laboratory testing were standardized across participants from both study groups in each center but differed between centers. For example, there was no standardized examination procedure for retinal photography. Some centers collected retinal data as part of the 5-year follow-up examination, whereas others used routine data sources. This variation may have led to differential precision of outcome assessment among centers but not between study groups. Furthermore, only gradable photographs were assessed, and these were coded by three experienced ophthalmologists using a standard scale (Early Treatment of Diabetic Retinopathy Study) while unaware of study group allocation. This may have contributed to some heterogeneity in the results.

Outcomes tended to favor more IT; however, the low frequency of microvascular events means that the 5-year duration of follow-up may have been insufficient to detect potentially clinically important differences between the RC and the IT groups. The trial was conducted during a period in which targets for blood pressure and cholesterol levels became stricter for diabetic patients, which resulted in smaller-than-expected differences between the study groups in terms of cardiovascular risk factors, prescribed medications, and cardiovascular disease outcomes (8). Further follow-up of the trial cohort may be justified to examine whether early intensive multifactorial treatment reduces microvascular risk in the long term as seen in the UKPDS and Steno-2 studies (5,12).

In conclusion, when compared with RC, an intervention to promote target-driven, intensive management of patients with type 2 diabetes detected by screening was associated with modest differences in prescribed treatment and levels of cardiovascular risk factors. However, the intervention was not associated with significant reductions in the frequency of microvascular events at 5 years.

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Microvascular Outcomes

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