Supplementary file S3

Results

Further biochemical outcomes

Three[33 44 41] out of the seven trials included in this review had assessed fasting glucose levels (mmol/l) (see supplementary figure S6). In Swiss patients with prevalent diabetes[44] no difference in change was found between the intervention and control group, while in Dutch patients with diabetes[33] there was a significantly higher reduction in glucose concentrations after one year of intervention, in favour of the control group. In newly diagnosed diabetes patients,[41] the intervention group was observed to have a significantly higher reduction in fasting glucose levels then the control group after six years of intervention.

Six[33 39 41 43 45 46] out of seven trials had measured triglyceride concentrations (mmol/l), yet, multifaceted care did not significantly impact triglyceride levels in any of the studies (see supplementary figure S7).

Creatinine levels were assessed in three[33 41 46] out of the seven trials. Only the pooled five-year results from Addition-Europe[46] showed a significant difference in change between the trial arms, favouring the control arm over the intervention arm (see supplementary figure S8).

Further diabetes complications and related outcomes

Episodes of severe hypoglycaemia were assessed in only one[44] of the three studies with prevalent diabetes patients, in which severe hypoglycaemia was defined as having one or more episodes of hypoglycaemia with clinical symptoms and or requiring hospitalization. Episodes were reported for 19 (11.6%) patients in the intervention group and for eight (5.1%) in the control

group, without further statistical evaluation. In the remaining trials[39 41 43 46] the proportion of individuals reporting hypoglycaemia did not differ between intervention and control arm.

A major aim of the Dutch trial[33] and of the Addition studies[35 39 40 43] was to examine the effect of multifaceted care on cardiovascular risk. To that purpose, authors calculated the 10-year coronary heart disease risk estimate (%) as established by the UK Prospective Diabetes Study (UKPDS). This risk score is calculated using the following variables: the date of diabetes onset, sex, ethnicity, smoking, HbA1c, systolic blood pressure, total cholesterol and HDL-cholesterol. The Dutch authors observed a 1.4% greater decrease in 10-year UKPDS coronary heart disease risk in the intervention group compared to the control group.[33] Within the Addition-Leicester trial,[43] a 5-year UKPDS risk of cardiovascular heart disease was calculated. A significant difference in risk reduction of 1.49% between intervention and control group was found in favour of the intervention group. In the Addition-Europe study,[46] the authors assessed hazard ratios for a composite endpoint of cardiovascular events (any cardiovascular death, myocardial infarction, stroke, revascularization and amputation) at five years of intervention. This endpoint occurred similarly frequent and with similar risk in intervention and control patients. Furthermore, improvements in every singular component of this composite endpoint all favoured the intervention group over the control group, although no comparison reached statistical significance.

Out of the three trials with prevalent diabetes patients, only the Swiss trial[44] reported data on (changes in) medication use. The authors observed no significant changes between the two trial groups in medication use (yes/no variable) concerning antidiabetic therapy, antihypertensive therapy, and lipid-lowering therapy. In contrast to patients with prevalent diabetes, for patients with screen-detected diabetes[43] multifaceted care resulted in a larger number of antihypertensive-, lipid-lowering and anti-platelet therapy after one year, compared to usual care. This was also observed after pooling of the five-year findings from the Addition studies.[46] In

newly diagnosed diabetes patients[41] however, the only between-group difference that was observed with regard to medication intake was the more extensive use of metformin in the intervention group (39 (9%)) compared to the control group (16 (4%)).