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Multifactorial intervention in individuals with type 2 diabetes and microalbuminuria: The Microalbuminuria Education and Medication Optimisation (MEMO) study

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ABSTRACT

Aims: To determine whether tighter cardiovascular risk factor control with structured education in individuals with type 2 diabetes (T2DM) and microalbuminuria benefits cardiovascular risk factors.

Methods: Participants from a multiethnic population, recruited from primary care and specialist clinics were randomised to intensive intervention with structured patient (DESMOND model) education ($n = 94$) or usual care by own health professional ($n = 95$). Primary outcome: change in HbA1c at 18 months. Secondary outcomes: changes in blood pressure (BP), cholesterol, albuminuria, proportion reaching risk factor targets, modelled cardiovascular risk scores.

Results: Mean (SD) age and diabetes duration of participants were 61.5 (10.5) and 11.5 (9.3) years, respectively. At 18 months, intensive intervention showed significant improvements in HbA1c (7.1(1.0) vs. 7.8(1.4)%, $p < 0.0001$), systolic BP (129(16) vs. 139(17) mmHg, $p < 0.0001$), diastolic BP (70(11) vs. 76(12) mmHg, $p < 0.001$), total cholesterol (3.7(0.8) vs. 4.1(0.9) mmol/l, $p = 0.001$). Moderate and severe hypoglycaemia was 11.2 vs. 29.0%; $p = 0.001$ and 0 vs. 6.3%; $p = 0.07$, respectively. More intensive participants achieved ≥ 3 risk factor targets with greater reductions in cardiovascular risk scores.

Conclusions: Intensive intervention showed greater improvements in metabolic control and cardiovascular risk profile with lower rates of moderate and severe hypoglycaemia. Intensive glycaemic interventions should be underpinned by structured education promoting self-management in T2DM.

1. Introduction

Current evidence for the management of diabetic nephropathy suggests a strategy of targeted multiple risk factor control to improve cardiovascular and renal outcomes [1–3]. The Steno-2 study conducted in a Caucasian population within a tertiary care setting, evaluated the effects of intensive multifactorial intervention with behavioural modification in

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individuals with T2DM and microalbuminuria demonstrated significant benefits in microvascular and macrovascular events and mortality [1,2]. The effect of patient education on behavioural changes showed a modest change in nutrient intake with no changes in smoking habits or exercise [4]. In particular, the Steno-2 educational programme did not incorporate a structured education programme and failed to address theoretical principles to guide intervention design [5]. Furthermore, it is not clear if the impressive results from the Steno-2 study are readily achieved and applicable in either a multiethnic population or in different health care settings.

Structured self-management patient education has been shown to induce long lasting behavioural changes which can lead to improvements in biomedical and behavioural outcomes [6,7]. However, no randomised prospective trials have evaluated the potential impact of structured patient education combined with intensive medical therapy in a multiethnic population with established T2DM and nephropathy.

The Microalbuminuria Education and Medication Optimisation study was designed to test the hypothesis that tighter control of cardiovascular risk factors with a structured self-management education programme in high risk individuals with T2DM would result in additional clinical benefits and improvements in long term cardiovascular and renal outcomes. Our aim was to deliver an intensive intervention using tight risk factor targets, medication optimisation and structured education based on the Diabetes Education and Self Management for Ongoing and Newly Diagnosed (DESMOND) model of patient education and self-management in individuals with T2DM [8] and microalbuminuria from a multiethnic population, recruited from primary care and specialist care clinics and determine the efficacy of such a strategy compared to standard care. This paper reports the results after 18 months of an intensive multifactorial intervention on the primary outcome of change in glycated haemoglobin and secondary outcomes which includes changes in other cardiovascular risk factors.

2. Subjects and methods

2.1. Study subjects

Individuals between 25 and 80 years of age with a confirmed diagnosis of T2DM on diet, oral anti-diabetic agents or insulin and microalbuminuria (defined as an albumin creatinine ratio of $\geq$2.5–30 mg/mmol/l in males and $\geq$3.5–30 mg/mmol/l in females) [9] and confirmed by two out of three positive early morning urine samples or overt proteinuria with a serum creatinine of $<$180 μmol/l were eligible. Exclusion criteria were: individuals with a history of malignancy, chronic liver disease or life expectancy of less than five years, learning disability/ mental incapacity or immobility which precluded them from attending educational sessions, serum creatinine $>$180 μmol/l or if participating in another research study.

Individuals were referred both from primary care practices and specialist diabetes clinics in Leicestershire, UK from September 2006 to April 2007. The study protocol was in accordance with the Declaration of Helsinki and was approved by the Leicestershire Research Ethics Committee. All study participants gave written informed consent.

2.2. Study design

The study was a randomised, parallel-group, prospective trial. The intensive intervention was delivered for 18 months and a four year follow-up is planned to allow monitoring of important renal and cardiovascular outcomes including cardiovascular morbidity and mortality. Participants in both groups were followed up at 3 monthly intervals. The control group received standard care by their own clinician according to local guidelines [10], which are consistent with NICE guidance on the management of individuals with T2DM and diabetic nephropathy [11,12], and also provides additional information on management of individuals with T2DM of South Asian ethnicity. Participants in the control group were not seen or treated by the study physician/team and had usual access to education provided as part of standard diabetes care in either primary or secondary care.

Education Medication Optimisation group participants were followed up every three months on a ''one-to-one'' basis. Lifestyle changes, physical activity, medication adherence and self-titration of medication were discussed and written in the participant's record books, which also provided them with general information on T2DM, healthy eating, physical activity and exercise. Treatment targets were: HbA1c $\leq$6.5%, blood pressure of $\leq$130/70 mmHg respectively, total cholesterol of $\leq$3.5 mmol/l and LDL cholesterol of $\leq$2.0 mmol/l or a 30% reduction below baseline lipid levels. Initiation and optimisation of medications was carried out in a step wise manner on an individual basis and as per existing guidelines on the treatment of T2DM [11]. Treatment targets and results were discussed at each visit and participants were supported to pursue these goals and take a pro-active part in decision making and planning lifestyle changes in keeping with the self-efficacy theory of behavioural change [13].

Structured education was based on the DESMOND model of patient education [6]. The content of the educational programmes was underpinned by an empowerment philosophy and sound theoretical principles of adult learning [5,14]. The educational programme was delivered by trained DESMOND educators who are part of an ongoing quality assurance and professional development programme [5]. All participants in groups of 8–10 individuals per session were invited to attend an initial 3 h education session focussing on microalbuminuria. Briefly, the initial educational session explored the different experiences and perceptions of participants pertaining to early kidney disease\microalbuminuria in T2DM. Participants were given clear, concise and easy to understand information on microalbuminuria, potential complications of having microalbuminuria which could be largely avoided by controlling cardiovascular risk factors, working out the roles of blood pressure, lipid profiles, blood glucose and lifestyle issues (weight loss, physical activity, food choices) in reducing cardiovascular risk, identifying their current risk factors and explaining how they could reduce their own cardiovascular risk. Basic information on T2DM and its complications, weight management and physical activity were included within these educational sessions. Participants were offered additional education sessions on blood pressure, cholesterol, glycaemic control and weight management. Individuals on insulin were enrolled into group insulin management sessions conducted

by diabetes educators, to offer pragmatic solutions to problems encountered with insulin therapy.

2.3. Biomedical measurements

Biomedical measures in both groups were obtained at baseline, 6, 12 and 18 months under standard operating procedures, by a trained research assistant who was blinded to the participant's treatment assignment and independent of the study team. Blood samples were analysed at the biochemical laboratory, Leicester Royal Infirmary, UK. HbA1c was measured by ion exchange liquid chromatography (Tosoh, G7), serum creatinine by the kinetic Jaffe enzymatic method, total and high density lipoprotein cholesterol by the cholesterol oxidase method. Low density lipoprotein (LDL) cholesterol was calculated by the Freidwald formula [15]. Urine albumin creatinine ratio was determined by immunoturbidimetry using the Olympus OSR6167 Microalbumin Analyser (sensitivity of 0.46 mg/l) at baseline and 18 months.

Grade 1 (minor) hypoglycaemia was defined as the presence of hypoglycaemic symptoms with a self-measured capillary blood glucose of $\geq$3.1 mmol/l and self-treated, grade 2 (moderate) hypoglycaemia was defined as a self-measured plasma glucose of $<$3.1 mmol/l and self-treated and grade 3 (major) hypoglycaemia was defined as requiring the assistance of another person [16].

Data on adverse events, serious adverse events or relevant clinical outcomes were obtained by self-report and from letters of primary care physicians, specialist clinic letters or hospital discharge summaries. Data was recorded separately and assessed independently by a research physician who was not aware of the study participant's treatment allocation and was not involved with any aspect of the study.

2.4. Outcomes and statistical considerations

The primary outcome was change in mean HbA1c at 18 months. Secondary outcomes were mean changes in blood pressure, total and LDL cholesterol and urine albumin creatinine ratio, proportion of individuals reaching glycaemic, blood pressure and lipid targets, and modelled cardiovascular disease (UKPDS) risk scores [17].

2.5. Sample size

The sample size was based on the primary outcome of change in HbA1c at 18 months using data from multifactorial intervention studies [1,18]. Assuming a standard deviation of 1.8 and a minimal detectable difference of HbA1c of 0.7% with 80% power to detect differences between groups, a sample size of 164 was required. Allowing for a 10% drop out rate, 92 participants were required for each treatment group.

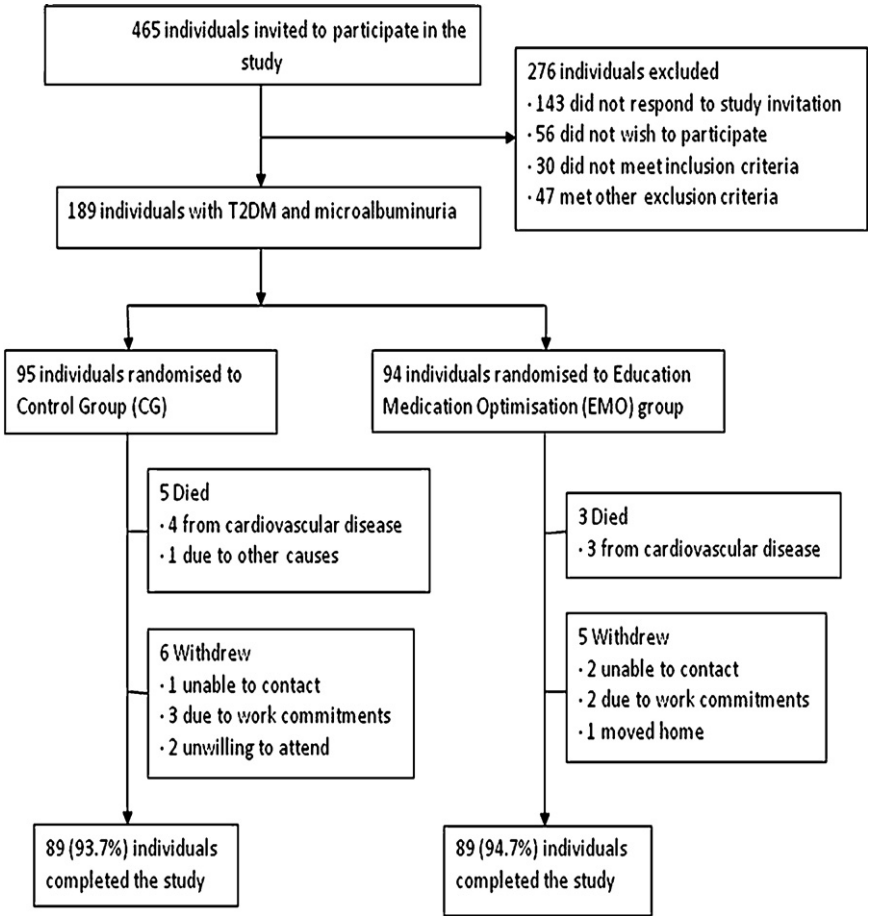

Fig. 1 – Flow of participants in the Microalbuminuria Education and Medication Optimisation (MEMO) study.

2.6. Statistical methods

All data analyses were carried out using SPSS version 16.0 and STATA version 11.0. We report continuous variables as means, standard deviations and categorical variables are reported as counts and percentages. Changes in process variables at 6, 12 and 18 months were analysed by linear regression with adjustments for baseline value of variable. Changes within groups over time were assessed by repeated measures analysis of variance. All p values < 0.05 are considered statistically significant. Urine albumin–creatinine ratios were log transformed due to non-normal distribution. Dosage of medications were calculated as percentage of maximum allowed prescribed dosage and are detailed in the British National Formulary medicines information (September 2007 edition). All results are reported in accordance with CONSORT guidelines for reporting clinical trials [19].

3. Results

The study profile is shown in Fig. 1. 189 individuals were eligible and agreed to participate – 95 were randomised to the control group and 94 to the Education Medication Optimisation group. There were no significant differences in age, gender and ethnicity between the final study sample and individuals who declined to participate. Overall 178 (94.2%) individuals completed the study. The baseline characteristics of study participants by randomised group are shown in Table 1. Ninety (96%) participants in the Education Medication Optimisation group attended the initial educational session, 68 (73%) participants attended at least one additional education session whereas 57 (61%) attended more than one session. Among intensive group participants on insulin therapy, 27/46 (58%) attended the initial insulin management sessions and 34 of 57 (59%) had attended more than five insulin management sessions at 18 months.

Table 1 – Biomedical characteristics of participants in the control group (CG) and Education Medication Optimisation (EMO) group at baseline.

Characteristics	EMO group ($n = 94$)	Control group ($n = 95$)
Age, years	62.6 (10.3)	60.3 (10.7)
Males, *n* (%)	71 (75.5)	72 (75.8)
White European, *n* (%)	68 (72.3)	61 (64.2)
South Asian, *n* (%)	22 (23.4)	30 (31.6)
Duration of diabetes, years	11.0 (9.3)	11.9 (9.4)
HbA1c, %/mmol/mol	7.9 (1.4)/63(8)	8.0 (1.6)/64(6)
Total cholesterol, mmol/l	4.2 (0.8)	4.2 (0.9)
LDL cholesterol, mmol/l	2.1 (0.6)	2.2 (0.8)
HDL cholesterol, mmol/l	1.1 (0.3)	1.0 (0.3)
Triglycerides, mmol/l	2.3 (1.7)	2.6 (1.6)
Urine albumin creatinine ratio, mg/mmol/L[a]	7.6 (2.8–18.8)	5.8 (3.2–17.6)
Estimated GFR, mL/min per 1.73 m^2	66.3 (14.7)	72.0 (19.8)
Systolic blood pressure, mmHg	139 (16)	136 (16)
Diastolic blood pressure, mmHg	76 (12)	77 (12)
Body weight, kg	93.9 (20.1)	93.6 (25.6)
Waist circumference, cms		
Men	112.9 (12.9)	112.6 (16.2)
Women	107.8 (17.0)	108.8 (16.4)
Body mass index, kg/m^2	33.1 (6.8)	32.8 (7.9)
Co-morbidities, n (%)		
Ischemic heart disease	24 (25.5)	14 (14.7)
Congestive cardiac failure	8 (8.5)	7 (7.4)
Cerebrovascular accident/stroke	10 (10.6)	5 (5.3)
Peripheral vascular disease	4 (4.3)	6 (6.3)
Smokers, *n* (%)	13 (13.8)	11 (11.6)
10 year CHD risk score	41.0 (26.7)	43.6 (28.1)
10 year fatal CHD risk score	34.7 (27.0)	37.1 (28.7)
10 year stroke risk score	32.4 (31.8)	33.7 (33.5)
10 year fatal stroke risk score	5.2 (6.0)	4.8 (5.3)
Glucose lowering therapy, n (%)		
Diet alone	11 (11.6)	7 (7.4)
Metformin	53 (56.4)	61 (64.2)
Sulphonyureas	17 (18.0)	21 (22.1)
Glitazones	16 (17)	14 (14.7)
OAD's with insulin	22 (23)	32 (33.7)
Insulin alone	24 (26)	18 (18.9)
Insulin dose, units[a]	79 (51–117)	60 (49–100)
Insulin dose, units per kg	0.78 (0.50)	0.97 (0.55)
Anti-hypertensive therapy, n (%)		
ACE-inhibitors or ARB	77 (81.9)	79 (83.2)
None	5 (5.3)	11 (11.6)
On 1 drug	25 (26.7)	31 (32.6)
On 2 drugs	25 (26.7)	18 (18.9)
On ≥3 drugs	39 (41.5)	35 (36.8)
Lipid lowering therapy, n (%)		
None	12 (12.8)	19 (20.0)
Statins	77 (81.9)	74 (77.9)
Fibrates	3 (3)	0
Aspirin, *n* (%)	80 (85.1)	65 (68.4)

Values are mean (SD) unless indicated otherwise.
[a] Median (inter-quartile range).

3.1. Cardiovascular risk factors

There were significant differences in mean (SD) HbA1c between control and intensive group participants at 6 months (7.4 (1.2) vs. 7.8 (1.4) %, $p < 0.05$), 12 months (7.5 (1.4) vs. 8.0 (1.6) %, $p < 0.05$) and at 18 months (7.1 (1.0) vs. 7.8 (1.4) %, $p < 0.0001$), respectively. Significant improvements were also observed in other cardiovascular risk factors. Intensive group participants had lower systolic and diastolic blood pressure, and greater reductions in total cholesterol and low density lipoprotein cholesterol compared to the control group at 6, 12 and 18 months (Table 2). Overall, there were no significant differences in urine albumin creatinine ratio between randomised groups at 18 months. A small non-significant increase in mean body weight was observed in both intensive (1.15 ± 4.86 kg) and control groups (0.80 ± 3.53 kg) at 18 months, with no differences between groups.

3.2. Modelled cardiovascular risk scores

Mean (95% confidence interval) ten year UKPDS risk of coronary heart disease and stroke at baseline was 41.0 (35.2–46.6) for the control group and 43.6 (37.7–49.5) for intensive group participants ($p = 0.63$). Ten year coronary heart disease and fatal heart disease UKPDS risk estimates for intensive participants improved significantly at 6, 12 and

Table 2 – Changes in biomedical outcomes at 6, 12 and 18 months and treatment differences between participants in the Education Medication Optimisation (EMO) Group and control group.

Variables	Change from baseline[b] (95% CI)		Adjusted model summary[c] Coefficient (95% CI)	P value
	EMO group	Control group		
HbA1c, %				
6 months	−0.40 (−0.62 to −0.17)	−0.08 (−0.37 to 0.21)	−0.39 (−0.70 to −0.08)	0.01
12 months	−0.31 (−0.54 to −0.09)	0.05 (−0.24 to 0.35)	−0.38 (−0.71 to −0.05)	0.02
18 months	−0.75 (−1.04 to −0.47)	−0.12 (−0.43 to 0.18)	−0.68 (−1.00 to −0.37)	<0.0001
Overall	–	–	−0.48 (−0.76 to −0.21)	0.001
Systolic BP, mmHg				
6 months	−4.96 (−9.17 to −0.75)	1.89 (−1.79 to 5.56)	−5.26 (−9.70 to −0.82)	0.02
12 months	−7.01 (−11.38 to −2.65)	−0.04 (−4.15 to 4.08)	−5.57 (− 10.51 to −0.62)	0.03
18 months	−9.00 (−12.64 to −5.36)	2.12 (−1.79 to 6.03)	−10.32 (−14.85 to −5.78)	<0.0001
Overall	–	–	−6.46 (−10.03 to −2.88)	<0.0001
Diastolic BP, mmHg				
6 months	−1.65 (−4.11 to 0.83)	1.43 (−0.95 to 3.81)	−3.33 (−6.05 to −0.61)	0.01
12 months	−3.22 (−6.11 to −0.32)	−0.32 (−3.04 to 2.41)	−2.80 (−6.05 to −0.45)	0.05
18 months	−6.01 (−8.88 to −3.14)	−0.58 (−2.98 to 1.82)	−5.60 (−8.68 to −2.53)	<0.0001
Overall	–	–	−4.00 (−6.33 to −1.66)	0.001
Total cholesterol, mmol/l				
6 months	−0.49 (−0.67 to −0.31)	−0.10 (−0.27 to 0.06)	−0.39 (−0.58 to −0.20)	<0.0001
12 months	−0.50 (−0.70 to −0.31)	−0.07 (−0.25 to 0.11)	−0.45 (−0.67 to −0.23)	<0.0001
18 months	−0.50 (−0.72 to −0.28)	−0.15 (−0.33 to 0.03)	−0.39 (−0.62 to −0.16)	<0.0001
Overall	–	–	−0.38 (−0.56 to −0.20)	<0.0001
Serum triglycerides, mmol/l				
6 months	−0.59 (−0.95 to −0.23)	−0.54 (−0.84 to −0.24)	−0.15 (−0.43 to −0.13)	0.15
12 months	−0.68 (−1.00 to −0.36)	−0.55 (−0.84 to −0.26)	−0.23 (−0.49 to −0.03)	0.04
18 months	−0.65 (−1.02 to −0.28)	−0.72 (−0.99 to −0.44)	−0.13 (−0.38 to 0.11)	0.14
Overall	–	–	−0.22 (−0.43 to −0.001)	0.05
Serum LDL cholesterol, mmol/l				
6 months	−0.33 (−0.47 to −0.18)	−0.01 (−0.15 to 0.14)	− 0.34 (−0.50 to −0.17)	<0.0001
12 months	−0.36 (−0.53 to −0.20)	−0.05 (−0.12 to 0.23)	−0.43 (−0.63 to −0.22)	<0.0001
18 months	−0.43 (−0.61 to −0.24)	−0.03 (−0.22 to 0.15)	−0.41 (−0.61 to −0.20)	<0.0001
Overall	–	–	−0.34 (−0.50 to −0.18)	<0.0001
Serum HDL, mmol/l				
6 months	0.01 (−0.02 to 0.05)	0.08 (0.05 to 0.11)	−0.05 (−0.09 to −0.01)	0.02
12 months	0.12 (0.03 to 0.22)	0.08 (0.01 to 0.15)	−0.03 (−0.14 to 0.09)	0.33
18 months	0.06 (0.02 to 0.11)	0.09 (0.05 to 0.12)	−0.01 (−0.06 to 0.04)	0.35
Overall	–	–	−0.01 (−0.07 to 0.04)	0.65
Estimated GFR, l/min/1.73 m^2				
6 months	0.14 (−1.79 to 2.06)	−0.68 (−2.84 to 1.47)	0.77 (−2.11 to 3.65)	0.60
12 months	1.98 (−0.14 to 4.11)	0.01 (−2.32 to 2.34)	2.08 (−1.08 to 5.24)	0.20
18 months	3.25 (0.49 to 6.01)	2.79 (−0.41 to 5.99)	1.41 (−2.71 to 5.53)	0.50
Overall	–	–	0.90 (−1.96 to 3.76)	0.54
Log albumin creatinine ratio, mg/mmol[a]				
18 months	5.8 (3.0–15.3)	5.6 (2.2–16.9)	−0.03 (−0.72 to 0.62)	0.21
Body weight, kg				
6 months	0.50 (−0.44 to 1.44)	0.34 (−0.32 to 1.00)	0.18 (−1.33 to 0.98)	0.38
12 months	1.21 (0.14 to 2.28)	0.74 (0.06 to 1.42)	0.48 (−1.74 to 0.78)	0.37
18 months	1.15 (0.04 to 2.26)	0.80 (−0.02 to 1.63)	0.40 (−1.80 to 1.00)	0.29
Overall	–	–	0.24 (−0.81 to 1.30)	0.65
Waist circumference, cms				
6 months	−0.40 (−0.62 to −0.17)	−0.08 (−0.37 to 0.21)	0.17 (−1.38 to 1.71)	0.41
12 months	−0.31 (−0.54 to −0.09)	0.05 (−0.24 to 0.35)	0.66 (−2.52 to 1.19)	0.24
18 months	−0.75 (−1.04 to −0.47)	−0.12 (−0.43 to 0.18)	0.16 (−1.89 to 1.57)	0.42
Overall	–	–	0.02 (−1.40 to 1.44)	0.98
10 yr CHD risk score				
6 months	−6.59 (−8.78 to −4.41)	−2.85 (−5.02 to −0.68)	−3.74 (−6.83 to −0.65)	0.009
12 months	−8.54 (−11.08 to −5.99)	−2.81 (−5.39 to −0.23)	−5.73 (−9.36 to −2.10)	0.001
18 months	−23.25(−25.43 to −21.07)	−19.10(−21.2 to −16.92)	−4.15 (−7.23 to −1.01)	0.005
Overall	–	–	−4.02 (−6.90 to −1.16)	0.006
10 yr fatal CHD risk score				
6 months	−5.85 (−7.93 to −3.76)	−2.15 (−4.22 to −0.08)	−3.70 (−6.64 to −0.75)	0.007
12 months	−7.44 (−9.80 to −5.05)	−2.16 (−4.56 to 0.25)	−5.26 (−8.65 to −1.88)	0.002
18 months	−21.75 (−23.63 to −19.88)	−17.91(−19.78 to−16.03)	−3.84 (−6.50 to −1.19)	0.003
Overall	–	–	−3.75 (−6.46 to −1.03)	0.007

Table 2 (*Continued*)

Variables	Change from baseline[b] (95% CI)		Adjusted model summary[c] Coefficient (95% CI)	P value
	EMO group	Control group		
10 yr stroke risk score				
6 months	−2.18 (−3.36 to −1.00)	−0.48 (−1.67 to 0.71)	−1.70 (−3.38 to −0.02)	0.02
12 months	−2.86 (−4.11 to −1.61)	−0.97 (−2.26 to 0.31)	−1.89 (−3.68 to −0.10)	0.02
18 months	−21.12 (−22.73 to −19.50)	−19.24 (−20.86 to −17.62)	−1.88 (−4.17 to 0.42)	0.05
Overall	–	–	−1.31 (−3.48 to 0.9)	0.23
10 yr fatal stroke risk score				
6 months	−0.79 (−1.60 to 0.02)	0.37 (−0.44 to 1.18)	−1.16 (−2.30 to −0.02)	0.02
12 months	−1.46 (−2.18 to −0.73)	0.19 (−0.55 to 0.92)	−1.64 (−2.67 to −0.62)	0.001
18 months	−3.46 (−3.84 to −3.08)	−2.58 (−2.96 to −2.19)	−0.88 (−1.43 to −0.34)	0.001
Overall	–	–	−1.01 (−1.87 to −0.2)	0.02

Values are mean (SD) unless indicated otherwise.
[a] Values reported as median (inter-quartile range).
[b] Change from baseline (95% confidence interval) unadjusted.
[c] Difference between groups adjusted for baseline value of variable.

18 months compared to the control group ($p < 0.05$ at all time points). Ten year risk estimates for fatal stroke also improved significantly at 6, 12 and 18 months ($p < 0.05$, Table 2).

3.3. *Medication use*

Overall use and dose of prescribed oral anti-diabetic agents did not increase significantly between groups during the study intervention, however insulin usage (dose per kg) was greater among intensive group participants at 18 months (1.05 (0.73) vs. 0.96 (0.44), $p < 0.05$). Antihypertensive medication, lipid lowering drugs and aspirin usage were comparable between groups at 18 months. The prescribed dose of lipid lowering medications (statins) increased significantly with intensive intervention ($p = 0.001$, Table 3).

Table 3 – Medication use in the control group (CG) and Education Medication Optimisation (EMO) group.

Therapeutic regime	Baseline		18 months		P value*
	EMO ($n = 94$)	CG ($n = 95$)	EMO ($n = 86$)	CG ($n = 84$)	
Glucose lowering therapy					
On diet alone, *n* (%)	11 (11.6)	7 (7.4)	6 (7.0)	3 (3.6)	0.26
On metformin (MF) therapy, *n* (%)	53 (56.4)	61 (64.2)	62 (72.1)	57 (67.9)	0.33
% (SD) of max allowed MF dose	74.0 (26.0)	86.7 (19.7)	83.1 (26.5)	84.4 (22.5)	0.39
On sulphonyurea (SU) therapy, *n* (%)	17 (18.0)	21 (22.1)	25 (29.1)	24 (28.6)	0.54
%(SD) of max allowed SU dose	55.6 (31.0)	58.4 (30.7)	57.3 (35.6)	51.3 (29.8)	0.31
On thiazolidinediones (TZD) medications, *n* (%)	16 (17)	14 (14.7)	8 (9.3)	14 (16.7)	0.11
% (SD) of max allowed TZD dose	60.3 (28.0)	68.2 (25.2)	60.3 (28.0)	68.2 (25.2)	0.23
OAD's with Insulin, *n* (%)	22 (23)	32 (33.7)	32 (37.2)	29 (34.5)	0.42
Insulin alone, *n* (%)	24 (26)	18 (18.9)	25 (29.1)	22 (26.2)	0.40
Median insulin dose, units (IQR)	79 (51–117)	60 (49–100)	95 (56–124)	76 (44–109)	0.46
Insulin dose, units per kg	0.78 (0.50)	0.97 (0.55)	1.05 (0.73)	0.96 (0.44)	0.03
Anti-hypertensive therapy, n (%)					
ACE-inhibitors or ARB, *n* (%)	77 (81.9)	79 (83.2)	83 (96.5)	75 (89.3)	0.08
Dose of ACEi/ARBs, %(SD)	74.7 (34.1)	68.2 (32.2)	84.2 (27.4)	77.6 (30.7)	0.09
Not taking any antihypertensive drug, *n* (%)	5 (5.3)	11 (11.6)	0	7 (8.3)	0.01
On 1 drug, *n* (%)	25 (26.7)	31 (32.6)	22 (25.9)	23 (27.4)	0.49
On 2 drugs, *n* (%)	25 (26.7)	18 (18.9)	20 (23.3)	21 (25.0)	0.49
On ≥3 drugs, *n* (%)	39 (41.5)	35 (36.8)	44 (51.2)	33 (39.3)	0.21
Lipid lowering therapy					
Not taking any lipid lowering drug *n* (%)	12 (12.8)	19 (20.0)	0	4 (4.8)	0.06
Statins, *n* (%)	77 (81.9)	74 (77.9)	80 (93.0)	74 (88.0)	0.45
% (SD) of max allowed statin dose	34.2 (23.0)	29.1 (18.8)	40.4 (23.8)	29.6 (18.7)	0.001
Fibrates, *n* (%)	3 (3)	0	4 (4.7)	2 (2.4)	0.36
Ezetemibe, *n* (%)	3 (3.2)	4 (4.2)	16 (18.6)	6 (7.1)	0.04
Anti-platelet therapy					
Aspirin, *n* (%)	80 (85.1)	65 (68.4)	82 (95.3)	58 (69.0)	0.10

Values are number (percentage); OADs, oral antidiabetic agents; SD, standard deviation; IQR, interquartile range. Maximal doses of drugs are calculated according to medicines information from British National Formulary, 2007
* Significance between groups at 18 months.

3.4. Adverse events

3.4.1. Hypoglycaemia

The overall incidence of hypoglycemia between intensive and control participants during 18 months was 42.6 vs. 36.9%; $p = 0.20$. Among intensive and control participants, grade 1 hypoglycaemia was reported in 42.4 vs. 32.5%; $p = 0.52$, grade 2 hypoglycaemia was reported in 11.2 vs. 29.0%; $p = 0.001$ and grade 3 (severe) hypoglycaemia was reported in 0% vs. 6.3%; $p = 0.07$, respectively (Table 4).

3.4.2. Cardiovascular and other adverse events (Table 4)

The overall incidence of adverse events (excluding hypoglycaemic events) was 23 (24.5%) in the intensive and 14 (14.7%) among control group participants ($p = 0.07$) (Table 4). Fifteen (16.0%) serious adverse events were reported in the intensive group at 18 months and twenty seven (28.4%) events had occurred in the control group at 18 months follow-up. Two of the six participants with severe hypoglycaemia in the control group were hospitalised for further treatment. In contrast, hypoglycaemia was not reported as a serious adverse event among any intensive group participant. Eight deaths occurred during the study, three in the intensive group (all from cardiovascular causes) and five in the control group (four from cardiovascular and one from a respiratory related illness) ($p = 0.35$, Table 4).

3.5. Risk factor targets

At 18 months, 46.5% participants in the intensive intervention group had achieved greater than three cardiovascular risk factor targets compared to 10.8% in the control group ($p < 0.05$). For individual risk factor targets, nearly 50% of intensive group participants achieved target values of ≤130/70 mmHg and ≤3.5 mmol/l respectively whereas 35% attained an HbA1c of ≤6.5%. In contrast, less than 30% participants who received standard treatment achieved the above mentioned blood pressure and lipid targets and 14% achieved an HbA1c target of ≤6.5% (Data not shown).

Table 4 – Mortality, cardiovascular events and other medical events during 18 months in the control group (CG) and Education Medication Optimisation (EMO) group.

Events	EMO group	CG group
Hypoglycaemic event, n (%)		
Grade 1 (mild)	39 (42.4)	31 (32.5)
Grade 2 (moderate)	11 (11.2)	27 (29)*
Grade 3 (severe)	0	6 (6.3)
Vascular events, n (%)		
Angina	5 (5.3)	3 (3.2)
Heart failure	2 (2.1)	1 (1.1)
Non-fatal myocardial infarction	–	1 (1.1)
Non-fatal stroke	1 (1.1)	–
Coronary revascularization	–	–
Lower limb revascularization	1 (1.1)	–
Other reported medical events, n (%)		
Gastrointestinal	6 (6.4)	3 (3.2)
Respiratory	5 (5.3)	4 (4.2)
Musculoskeletal	3 (3.2)	2 (2.1)
Serious adverse events, n (%)		
Cardiovascular	3 (3.2)	4 (4.2)
Hypoglycaemia	–	2 (2.1)
Any other medical condition	9 (9.6)	16 (16.8)
Cardiovascular mortality	3 (3.2)	4 (4.2)
All cause mortality (cardiovascular causes excluded)	0	1 (1.1)

* Indicates p value < 0.05.

4. Discussion

The results of this study indicate substantial improvements in cardiovascular risk factors and lends credence to our hypothesis that intensive pharmacotherapy with structured patient education compared to standard care can result in additional improvements in blood pressure, lipid and glycaemic control, all of which represent important cardiovascular surrogates known to reliably delay or prevent the progression of cardiovascular and kidney disease [20,21].

Although multifactorial interventions are being increasingly pursued in a conventional manner, the challenge for clinicians is to incorporate comprehensive interventions including structured self-management patient education into routine clinical practice and determine the best ways of achieving success. The MEMO study in part attempts to answer these important issues. Glycaemic control improved significantly at all time points (6, 12 and 18 months) with intensive intervention. Indeed, the degree of glycaemic separation increased between randomised groups during the course of the intervention, with the widest difference observed at 18 months. Significant and wider improvements were also observed with other cardiovascular risk factors (systolic and diastolic blood pressure and lipid fractions) at all time points with intensive intervention. There were significantly greater reductions in ten year UKPDS risk scores for coronary heart disease and fatal stroke at all time points with intensive intervention.

After 18 months of intensive intervention, approximately 60% of intensive group participants achieved a blood target of 130/70 mmHg although nearly 47% participants required more than three blood pressure lowering medications. The mean difference in systolic and diastolic blood pressure was 11 mmHg and 6 mmHg between intensive and control groups at 18 months and are comparable to the results of the STENO-2 study [1].

Medication usage and dose of oral glucose lowering therapies were similar between groups although the dose of insulin used increased significantly among intensive participants compared to the control group at 18 months. This suggests that the effects seen are not due to, or not solely due to, the optimisation of medications. The fact that treatment was equivalent between groups in terms of medication, would suggest that differences in outcomes could be attributed to differences in lifestyle changes and adherence to medications made by intervention participants in response to the education programme. However, despite attempts to achieve lower HbA1c targets and increased insulin usage, severe hypoglycaemia was not reported by any participant with intensive intervention at 18 months and moderate (grade 2) hypoglycaemia was significantly lower in the intensive group. Since the majority of intensive group participants on insulin therapy

had attended multiple insulin management sessions, our results suggest the importance of educating individuals with T2DM on insulin management including self-titration of insulin and avoidance, prompt recognition and treatment of hypoglycaemia. The absence of reported severe hypoglycaemia despite intensive targeted efforts to lower blood glucose further suggests that such interventions underpinned by structured education can offer individuals a better understanding of the complexities of treatment regimes and the need for adherence to treatment, which are crucially important whilst initiating intensive glucose lowering regimes [22,23].

Some criticisms of multifactorial care are that these interventions mainly focus on pharmacotherapy, are not patient-centred and do not adequately address lifestyle and behavioural changes. Self-management education programmes aimed at improving knowledge and self-management skills in diabetes can induce positive effects on behavioural changes and have been widely adopted [24]. The UK Diabetes National Service Framework and NICE guidelines in the UK emphasise that patient education must be structured, ongoing, with a clear theoretical underpinning, delivered by trained educators and become an integral part of good diabetes care [25,26]. Similar enthusiasm has been expressed by international bodies and incorporated in guidelines on the management of T2DM [27,28]. It is pertinent to note that MEMO intensive participants who were not achieving risk factor targets at 3 monthly intervals received optimisation and intensification of treatment in accordance with NICE guidelines on the management of T2DM which is not dissimilar to management strategies received by the control group. Furthermore, intensive participants received structured group education delivered by trained professionals who have been quality assured in the process of delivering the education programme and the programme meets the criteria laid down by NICE guidance on structured patient education [5,25]. This is in contrast to ''education'' per se received by the control group which is delivered in 1:1 consultations, on an ad hoc basis with clinicians in primary or specialist care. Our results therefore suggest that structured education plays a crucial role in achieving sustained improvements in biomedical outcomes in high risk individuals with established T2DM, although it may be argued that whilst delivering such comprehensive care interventions, it is impossible to tease out the separate effects of education per se and intensive medical management.

4.1. *Strengths and limitations of the study*

Our study was adequately randomised with low attrition rates through the trial period and recruited high risk individuals with T2DM including White European and minority ethnic groups from primary care and specialist clinics. As such our results should therefore be generalisable to a majority of people with T2DM and readily applicable under different health-care settings. Our study is also the first trial to assess the effects of combining a DESMOND based model of structured patient self-management education with a multifactorial intervention in individuals with advanced diabetes and related complications. However, some limitations are acknowledged. Since some participants were also recruited from specialist clinic settings, it is conceivable that some participants in the control group would have received aggressive treatment. Additionally, the Pay for Performance targets in UK primary care, an incentive driven system designed to improve the quality of service is also likely to have an impact on the quality of ''standard care'' received by participants during the course of the study [29]. Since we used broad inclusion criteria and did not confine recruitment to any particular range of values around or above preselected study targets, participants who either met study targets or close to achieving them may have lacked motivation to aim for further improvements which could potentially dilute the effects of the intensive intervention. Finally, an intervention involving individuals randomised to intensive targeted pharmacotherapy ''alone'' and in combination with structured education could provide useful information to tease out the individual effects of such interventions on important clinical outcomes. However, within the context of the MEMO study, standard care received by the control group was not dissimilar to a target driven, multifaceted care which is increasingly pursued by general practitioners in the UK [29].

5. Conclusion

A multifactorial intervention using intensive pharmacotherapy with tight risk factor targets and structured education based on self-management care in individuals with T2DM and microalbuminuria resulted in significant benefits in glycaemic control and overall metabolic profile. Importantly, rates of moderate and severe hypoglycaemia were lower and cardiovascular event rate and mortality did not increase despite tight glycaemic targets and increased insulin usage, which underscores the importance of incorporating a structured education programme within intensive glucose lowering regimes.

Furthermore, supplementary education and information on microalbuminuria and chronic kidney disease as incorporated within our education programme should enable such group education interventions to be rolled out to individuals with even more advanced kidney disease. Considering the anticipated increase in the prevalence of diabetic nephropathy, the implications and cost effectiveness of delivering such a service will need to be assessed.

Contributors

MJD, KK and TCS contributed to the concept of the study, designed the study protocol, obtained funding, supervised all phases of the study including educational components and treatment and supervised the writing of the paper. WC recruited, assessed and supervised management of subjects in the intensive arm of the study, planned and carried out data analyses, and drafted the paper. J.J. designed the study protocol, database, designed and delivered the educational components, and assessed study subjects. L.G. supervised all aspects of the data analysis and provided statistical support. J.B. helped in recruitment, carried out biomedical investigations and was involved in data collection and entry. J.T. and H.D. designed and delivered the education sessions and are trained DESMOND educators. I.G.L. and P.G.M. supervised and

contributed to the final writing of the paper. M.E.C. contributed to the design of the DESMOND educational programme and to the final writing of the paper. All authors revised and approved the final version of the manuscript. W.C. is guarantor for the paper.

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Conflict of interest

The authors declare that they have no conflict of interest.

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