Effects of an Electronic Software "Prompt" With Health Care Professional Training on Cardiovascular and Renal Complications in a Multiethnic Population With Type 2 Diabetes and Microalbuminuria (the GP-Prompt Study): Results of a Pragmatic Cluster-Randomized Trial

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OBJECTIVE

Tight, targeted control of modifiable cardiovascular risk factors can reduce cardiovascular complications and mortality in individuals with type 2 diabetes mellitus (T2DM) and microalbuminuria. The effects of using an electronic "prompt" with a treatment algorithm to support a treat-to-target approach has not been tested in primary care.

RESEARCH DESIGN AND METHODS

A multicenter, cluster-randomized trial was conducted among primary care practices across Leicestershire, U.K. The primary outcome was the proportion of individuals achieving systolic and diastolic blood pressure (<130 and <80 mmHg, respectively) and total cholesterol (<3.5 mmol/L) targets at 24 months. Secondary outcomes included proportion of individuals with HbA_{1c} <58 mmol/mol (<7.5%), changes in prescribing, change in the albumin-to-creatinine ratio, major adverse cardiovascular events, cardiovascular mortality, and coding accuracy.

RESULTS

A total of 2,721 individuals from 22 practices, mean age 63 years, 41% female, and 62% from black and minority ethnic groups completed 2 years of follow-up. There were no significant differences in the proportion of individuals achieving the composite primary outcome, although the proportion of individuals achieving the prespecified outcome of total cholesterol <4.0 mmol/L (odds ratio 1.24; 95% CI 1.05–1.47; $P = 0.01$) increased with intensive intervention compared with control. Coding for microalbuminuria increased relative to control (odds ratio 2.05; 95% CI 1.29–3.25; $P < 0.01$).

CONCLUSIONS

Greater improvements in composite cardiovascular risk factor control with this intervention compared with standard care were not achieved in this cohort of high-risk individuals with T2DM. However, improvements in lipid profile and coding can benefit patients with diabetes to alter the high risk of atherosclerotic cardiovascular events. Future studies should consider comprehensive strategies, including patient education and health care professional engagement, in the management of T2DM.

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The presence of microalbuminuria (MA) with type 2 diabetes mellitus (T2DM) identifies people with an increased risk of cardiorenal complications contributing to significant cardiovascular (CV) morbidity and mortality (1). Management of these complications places a huge burden both on the affected individual and the health care system (2). Modifiable risk factors such as hyperglycemia, hypertension, and hypercholesterolemia that predispose to increased CV risk are common in individuals with T2DM and MA (2). Despite unequivocal evidence that the synergistic effects of simultaneous, tight, targeted multifactorial control reduces CV morbidity and mortality, with increased life span free from incident CV disease (3,4), there remains therapeutic inertia in identifying and treating these high-risk individuals with T2DM to mitigate CV risk (5,6). Implementing sophisticated clinical information systems, including point-of-care computer reminders to improve care, have reported mixed effects, whereas combining electronic medical records and computerized physician reminders suggests modest efficacy (7–10).

The General Practitioner Prompt (GP-Prompt) study tested the hypothesis that a health care professional (HCP)-focused multifactorial intervention in individuals with T2DM and MA would result in intensive, targeted control of multiple CV risk factors and an increased proportion of individuals achieving tight CV risk factor targets. The intervention comprised an automated, computerized alert system to provide a screenshot of an individual's risk factor control alongside a treatment algorithm at the clinic consultation, supported by clinician education, audit, and feedback, to prompt HCPs to treat to tight CV risk factor targets. The aim of the pragmatic strategy was to bring about positive changes in health care provider behavior, provide HCPs with easy recall of information, aid decision support, and provide information or guidance in an accessible format during a busy clinic consultation at low marginal cost.

RESEARCH DESIGN AND METHODS

Study Design

The GP-Prompt study was a pragmatic, cluster-randomized controlled, intervention trial with the general practice as the unit of randomization. The design and methods for patient inclusion, randomization, treatment, and initial follow-up have been previously reported (11). Follow-up data were extracted at 12 and 24 months. The study was coordinated in Leicester City and Leicestershire County by the Leicester Diabetes Centre, a collaboration between the University of Leicester and University Hospitals of Leicester.

Ethical Approval

National Health Service ethical approval was granted by the National Research Ethics Service Committee North West–Lancaster (Lancaster, U.K.) on 16 March 2015 (ref: 166517). The trial was sponsored by the University of Leicester, which was responsible for the conduct of the research. Informed consent was given by the lead clinician or practice manager rather than for each individual patient. This approach was adopted because the intervention was implemented across all eligible patients at practices randomized to the intervention arm (12,13). The intervention aimed to improve adherence to current best practice, evidence-based CV risk factor targets, and treatment decisions regarding individual patients remained the responsibility of HCPs at each participating practice.

Randomization

Randomization was conducted at the practice level by an independent statistician using a random number generator with a blocked design stratified for diabetes register size (small practices, $<$600 diabetes patients; large, $>$600 diabetes patients). Practices were randomized before installation of the intervention and HCP training (1:1) to continue to deliver usual care or deliver care aided by the GP-Prompt intervention. Practices were enrolled and assigned randomization by a project manager, with those handling the data blinded to allocation. The nature of the intervention meant it was not possible to blind participants (care providers) after assignment to study group.

Patient Inclusion/Exclusion Criteria

Patient-level data were extracted for individuals aged between 17 and 76 years with a confirmed diagnosis of T2DM and MA or overt proteinuria on their clinical record, or individuals with T2DM and an albumin-to-creatinine ratio (ACR) $>$2.5 in men and $>$3.5 in women on two consecutive occasions $>$90 days and $<$180 days apart, having excluded a urinary tract infection (14). Data were not extracted if patients fulfilling inclusion criteria were pregnant, terminally ill, or excluded from the Pay for Performance–Quality Outcomes Framework (QOF) (whole-domain diabetes) (15).

Procedures

Intervention Group

HCPs from intervention practices were offered a multifactorial intervention that comprised an information technology software prompt and care template that appeared at the time of the consultation for patients with T2DM with a risk factor above target range, supplemented by HCP training delivered in a group format. Participating staff were provided with audit and feedback at 3-month intervals. The intervention has been described in detail previously (11). The intervention was aimed at improving adherence to best-practice CV risk factor targets for patients with T2DM and MA, an approach that has been shown to be effective at significantly reducing CV morbidity and CV event rates in this "high-risk" population but adapted to be delivered at a practice level through decision support tools and HCP training. A generic information leaflet for patients was provided for HCPs to print and give out with information on diabetes and kidney disease, emphasizing the importance of medication adherence. Intensification of treatment was guided by a treatment algorithm (Supplementary Fig. 6).

Educators from the Effective Diabetes Education Now (EDEN) team delivered 3-h group education sessions for general practice staff in primary care and hospital settings. At least two staff from each practice attended one of the sessions, which focused on the evidence base for adherence to tighter risk factor targets, justification for the methods used, and current guidance for managing CV risk in eligible patients. Training on how to use the software prompt was also provided. Participating practices were offered a small financial incentive in the form of backfill pay to cover staff time attending training sessions.

Maintenance of the intervention was promoted through the offer of biannual visits to intervention practices by a specialist diabetologist with expertise in the

management of patients with T2DM and MA. Practices were provided with quarterly performance reports benchmarking their practice's performance in achieving risk factor control for eligible patients against other anonymized participating practices, including levels of prescribing for ACE inhibitors or angiotensin receptor blockers, statins, and antiplatelet agents.

Comparator Group

Staff from control practices continued to deliver usual care according to best practice clinical guidance for management of T2DM and MA (14).

Outcomes

The primary outcome was the proportion (%) of eligible patients meeting both CV risk factor targets: blood pressure (BP) <130/80 mmHg and total cholesterol (TC) <3.5 mmol/L. This was assessed at 12 and 24 months. All CV risk factor measurements extracted relate to blood samples that were collected as part of routine care and analyzed in accordance with relevant regulations and standard operating procedures.

Secondary outcomes included incidence of CV events and all-cause mortality, CV mortality, glycemic control assessed by HbA_{1c}, BP, TC, progression in MA assessed by change in ACR, kidney function measured by change in estimated glomerular filtration rate (eGFR), change in MA coding, and changes in T2DM, BP, and cholesterol-lowering medication prescribing, including contraindications and adverse reactions.

Data Extraction

One line per patient anonymized data were extracted using a standardized Morbidity Information Query and Export SynTax (MIQUEST) query (16) in line with local governance regulations (17,18) and following local research and development governance approval. MIQUEST software allows the collection of individual patient health data from GP clinical systems in a common computer-readable format. These data were extracted at baseline and 12 and 24 months after software prompt installation and every 3 months in intervention practices to allow reporting of performance data and benchmarking. Data extraction was performed remotely using Away from My Desk (AfMD) (19) software, with results uploaded to a secure online database and transferred to the research team via encrypted password protected National Health Service e-mail systems.

Statistical Analysis

Assuming 7.5% of patients with T2DM and MA met enhanced targets for BP (<130/80 mmHg) and TC (<3.5 mmol/L) in the standard care group with an intraclass correlation of 0.05, an average of 118 patients with MA per practice (range, 27–549), data were required from 18 practices (9 in each arm) to detect an increase to ≥18% in the proportion meeting both enhanced targets in the intervention group, with 80% power at the 5% significance level. The inflation for unequal cluster size was based on a coefficient of variation of 1.11 (20).

Descriptive characteristics were compared by group and for the overall population, using mean (SD) or median (interquartile range) for continuous variables and number and percentages for categorical variables. Cluster randomization can give imbalance in individual level covariates; therefore, for presentation of individual level baseline data, we used Pearson χ^2 to analyze differences in proportions and independent samples *t* tests to analyze differences in continuous variables between study groups.

Statistical analysis was performed on intention-to-treat basis. Generalized estimating equation models were fitted for each primary and secondary outcome with an exchangeable correlation structure, accounting for practice-level clustering and adjusting for baseline outcome value. The missing indicator method was used for missing baseline data. The analysis was repeated, additionally adjusting for ethnicity given the high imbalance between groups at baseline. For binary outcomes, we used a logit link with a binomial distribution for the outcome, and for continuous outcomes, we used an identity link with a normal distribution. CV outcomes were analyzed using Cox proportional hazards models with group as the covariate. For all analysis, 95% CIs are presented. Statistical significance was set at 5%. All analyses were conducted using Stata version 14 software (21).

Public and Patient Involvement

Because our intervention was focused on HCPs working in primary care, we sought involvement from local clinicians to develop training materials and technical aspects of the intervention during a development and testing phase. We held a series of focus groups to establish the preferred method of intervention delivery and the visual appearance and functionality of the prompt, and to develop ongoing support and mentorship packages. Further details on public and patient involvement are provided in the previously published study protocol (11).

RESULTS

Overall, 22 practices were randomized with a practice register ranging from 196 to 1,926 people with T2DM (Supplementary Fig. 1). The median number of eligible participants per practice was 98 in the control and 84 in intervention practices. In total, data were extracted for 2,721 participants (1,299 in control and 1,422 in intervention practices).

Eligible participants from ethnic minority groups (Asian, black, mixed ethnic) made up a significantly higher proportion of intervention participants (77.0%) versus control participants (61.7%). At baseline, participants from control practices had significantly higher diastolic BP and a higher prevalence of cerebrovascular events, and a higher proportion were prescribed antihypertensive therapy. Patients from control arm practices had lower eGFR, a lower proportion were coded as MA (Table 1), and a lower proportion of patients were prescribed lipid-lowering therapy (Supplementary Table 4).

Primary Outcome

At the 24-month follow-up, 201 patients met the criteria for the composite primary outcome (106 intervention, 95 control) (Table 1). Odds ratios showed a nonsignificant 7% increased rate of adherence to a composite of BP and TC risk factor targets in patients from intervention practices ($P = 0.647$), which reduced to a nonsignificant 0% when adjusted for ethnicity ($P = 0.967$). At the 24-month follow-up, there were no statistically significant differences between groups in the proportion of patients meeting enhanced targets for CV risk factors, including BP ($P = 0.543$), HbA_{1c} ($P = 0.307$), and TC ($P = 0.709$) (Table 3). Intervention effect did not differ by age, T2DM duration, ethnicity, CV disease (CVD) risk, MA coding, or chronic kidney disease (CKD) stage (Supplementary Fig. 2).

Table 1—Baseline characteristics of eligible study patients

Characteristics	Total (n = 2,721)	Control group (n = 1,299)	Intervention group (n = 1,422)	P value*
Age (years), mean (SD)	62.9 (10.0)	62.8 (10.1)	62.9 (9.9)	0.635
<30 years	7 (0.3)	4 (0.3)	3 (0.2)	
30–44 years	130 (4.8)	67 (5.2)	63 (4.4)	
45–65 years	1,335 (49.1)	623 (48.0)	712 (50.1)	
>65 years	1,249 (45.9)	605 (46.6)	644 (45.3)	
Missing	—	—	—	
Sex				0.273
Male	1,596 (58.7)	776 (59.7)	820 (57.7)	
Female	1,125 (41.4)	523 (40.3)	602 (42.3)	
Missing	—	—	—	
Ethnicity				**<0.001**
White	575 (31.3)	380 (38.3)	195 (23.0)	
Asian	1,136 (61.8)	516 (52.0)	620 (73.2)	
Black	62 (3.4)	45 (4.5)	17 (2.0)	
Mixed	20 (1.1)	14 (1.4)	6 (0.7)	
Other	46 (2.5)	37 (3.7)	9 (1.1)	
Missing	—	—	—	
Smoking status				0.642
Nonsmoker	1,567 (57.6)	750 (57.7)	817 (57.5)	
Current smoker	415 (15.3)	205 (15.8)	210 (14.8)	
Former smoker	739 (27.2)	344 (26.5)	395 (27.8)	
Missing	—	—	—	
T2DM duration (years), median (IQR)	9.9 (5.6–14.8)	10.0 (5.9–14.9)	9.8 (5.3–14.8)	0.386
Missing, n	67	12	55	
HbA_{1c} (mmol/mol), mean (SD)	59.3 (17.4)	59.8 (18.1)	58.9 (16.7)	
<53 mmol/mol	1,164 (42.9)	546 (42.2)	618 (43.6)	0.446
<58.5 mmol/mol	1,604 (59.1)	755 (58.3)	849 (59.9)	0.393
HbA_{1c} (%), mean (SD)	7.6 (1.6)	7.6 (1.7)	7.5 (1.5)	0.069
Missing, n	9	4	5	
TC (mmol/L), mean (SD)	4.1 (0.98)	4.1 (1.0)	4.1 (0.94)	0.055
Missing, n	4	1	3	
Systolic BP (mmHg), mean (SD)	134.3 (14.6)	134.0 (15.0)	134.5 (14.2)	0.821
Missing	—	—	—	
Diastolic BP (mmHg), mean (SD)	76.1 (9.5)	76.7 (9.7)	75.4 (9.2)	**<0.001**
Missing	—	—	—	
BP <130/80 mmHg	640 (23.5)	320 (24.6)	320 (22.5)	0.191
eGFR (mL/min), median (IQR)	83.0 (64.0–90.0)	81.0 (62.0–90.0)	85.0 (66.0–90.0)	**0.047**
Missing, n	3	1	2	
CKD stage 5	33 (1.2)	20 (1.54)	13 (0.9)	0.137
MA/proteinuria code	1,076 (39.5)	410 (31.6)	666 (46.8)	**<0.001**
Medical history				
CVD[a]	519 (19.1)	251 (19.3)	268 (18.8)	0.752
Cerebrovascular disease[b]	189 (6.9)	107 (8.2)	82 (5.8)	**0.011**
Peripheral vascular disease	82 (3.0)	48 (3.7)	34 (2.4)	**0.047**
Drugs: T2DM and other				
ACE inhibitor	1,379 (50.7)	666 (51.3)	713 (50.1)	0.556
Angiotensin receptor blocker	685 (25.2)	349 (26.9)	336 (23.6)	0.052
Antihypertensives	2,355 (86.6)	1,146 (88.2)	1,209 (85.0)	**0.015**
Lipid lowering	2,115 (77.7)	982 (75.6)	1,133 (79.7)	**0.011**
Antiplatelet	1,079 (39.7)	495 (38.1)	584 (41.1)	0.115
Oral antidiabetics				
Monotherapy	962 (43.7)	453 (42.6)	509 (44.7)	0.327
Dual therapy	792 (36.0)	388 (36.5)	404 (35.5)	0.615
Triple therapy	376 (17.1)	186 (17.5)	190 (16.7)	0.611
Four therapies or more	72 (3.3)	36 (3.4)	36 (3.2)	0.766
Insulin	517 (19.0)	235 (18.1)	282 (19.8)	0.248

Data indicate n (%) unless specified otherwise. P values in bold are statistically significant. IQR, interquartile range. *Significant between group difference at baseline. [a]CVD includes myocardial infarction, acute coronary syndrome, angina, ischemic heart disease, bypass graft, cerebrovascular disease, and peripheral vascular disease. [b]Cerebrovascular disease includes transient ischemic attack, stroke.

Secondary Outcomes

The proportion of individuals achieving the secondary outcome of TC <4.0 mmol/L adjusted for baseline values, ethnicity, and cluster effect increased with intensive intervention (odds ratio 1.24; 95% CI 1.05–1.47; $P = 0.012$) (Tables 2 and 3). During the follow-up period, 117 patients died (55 intervention, 62 control) (Supplementary Table 3); however, owing to the way in which these data are stored within practices, we were only able to access cause of death for 53 of 117 patients (23 intervention group, 30 control group). There were no statistically significant between-group differences in total mortality (hazard ratio 0.67; 95% CI 0.35–1.29), CV event rates (Supplementary Table 5), CVD mortality rates (hazard ratio 0.91; 95% CI 0.36–2.29), or medication changes (Table 4).

CONCLUSIONS

A multifaceted, pragmatic intervention using an electronic "prompt" and a stepwise treatment algorithm to support application of a treat-to-target approach did not show further improvements in achieving enhanced risk factor targets for hypertension and hyperlipidemia in a multiethnic population with T2DM and MA. There were increases in the proportion of patients from intervention practices with TC <3.5 mmol/L at 12 months, which was not clinically significant at 24 months. There were no significant improvements in glycemic control with intensive intervention. Prescribing trends related to nephroprotective agents and statin use showed an initial increase, which was not sustained at 24 months. Finally, coding for MA doubled in intervention practices at the 2-year follow-up.

Multifactorial interventions in individuals with T2DM at high risk of CVD are associated with greater reductions in CV risk, morbidity, and mortality. Most studies have been conducted in specialist settings (1,2). Therapeutic inertia resulting in inadequate uptitration of therapy when risk factor targets are not reached, poor implementation of treatment guidelines, inadequate perception of the patient's global risk, poor patient adherence to long-term treatments related in part to polypharmacy and organizational factors,

Table 2—Changes in primary and secondary outcomes at follow-up times and differences in the proportion of patients with MA and T2DM allocated to a software-based intervention or to usual care (control)

Outcomes	Patients, *n* (%)		Difference in proportions* % (95% CI)	Model summary†		Model summary‡	
	Control group	Intervention group		Odds ratio (95% CI)£	*P* values‖	Odds ratio (95% CI)£	*P* values‖
Primary composite outcome§							
24 months	95 (7.31)	106 (7.45)	0.14 (−1.83 to 2.11)	1.07 (0.81–1.41)	0.647	1.00 (0.80–1.26)	0.967
BP <130/80 mmHg							
Baseline	320 (24.63)	320 (22.50)	−2.13 (−5.32 to 1.06)	—			
12 months	335 (25.79)	382 (26.86)	1.07 (−2.24 to 4.39)	1.21 (0.97–1.51)	0.086	1.31 (0.99–1.75)	0.059
24 months	331 (25.48)	361 (25.39)	−0.09 (−3.37 to 3.18)	1.02 (0.85–1.23)	0.827	0.99 (0.83–1.19)	0.953
TC <3.5 mmol/L							
Baseline	335 (25.79)	372 (26.16)	0.37 (−2.92 to 3.67)	—			
12 months	331 (25.48)	405 (28.48)	2.99 (−0.33 to 6.33)	1.18 (0.90–1.54)	0.233	1.25 (1.07–1.45)	**0.004**
24 months	285 (21.94)	337 (23.70)	1.76 (−1.39 to 4.91)	1.04 (0.78–1.39)	0.790	1.09 (0.86–1.38)	0.495
TC <4 mmol/L							
Baseline	624 (48.04)	731 (51.41)	3.37 (−0.39 to 7.13)	—			
12 months	590 (45.42)	733 (51.55)	6.13 (2.38–9.88)	1.21 (0.98–1.50)	0.077	1.20 (1.04–1.40)	**0.015**
24 months	496 (38.18)	623 (43.81)	5.63 (1.94–9.32)	1.09 (0.83–1.44)	0.534	1.24 (1.05–1.47)	**0.012**
HbA_{1c} <53 mmol/mol							
Baseline	546 (42.03)	618 (43.46)	1.43 (−9.29 to 5.15)	—			
12 months	511 (39.34)	587 (41.28)	1.94 (−1.75 to 5.63)	1.10 (0.89–1.36)	0.379	1.21 (0.98–1.49)	0.071
24 months	472 (36.34)	499 (35.09)	−1.24 (−4.85 to 2.36)	0.90 (0.74–1.10)	0.307	0.93 (0.76–1.13)	0.450
HbA_{1c} <58.5 mmol/mol							
Baseline	755 (58.12)	849 (59.70)	1.58 (−2.12 to 5.28)	—			
12 months	720 (55.43)	824 (57.95)	2.52 (−1.21 to 6.25)	1.09 (0.84–1.41)	0.501	1.13 (0.86–1.47)	0.380
24 months	671 (51.66)	715 (50.28)	−1.38 (−5.13 to 2.39)	0.89 (0.71–1.11)	0.288	0.91 (0.74–1.12)	0.369
CKD stage 3 or below							
Baseline	283 (21.79)	258 (18.14)	−3.64 (−6.65 to −0.63)	—			
12 months	307 (23.63)	292 (20.53)	−3.10 (−6.22 to 0.02)	0.92 (0.75–1.13)	0.409	1.06 (0.74–1.53)	0.747
24 months	281 (21.63)	248 (17.44)	−4.19 (−7.18 to −1.21)	0.82 (0.65–1.02)	0.079	0.80 (0.62–1.04)	0.094
MA/proteinuria code							
Baseline	410 (31.56)	666 (46.84)	15.27 (11.65–18.89)	—			
12 months	386 (29.72)	682 (47.96)	18.25 (14.65–21.84)	1.78 (0.94–3.39)	0.078	2.28 (1.11–4.70)	**0.026**
24 months	370 (28.48)	658 (46.27)	17.79 (14.22–21.36)	2.05 (1.29–3.25)	**0.002**	1.99 (1.35–2.95)	**0.001**

P values in bold are statistically significant. *Difference in proportions: (intervention − control). §The primary composite outcome was BP <130/80 mmHg and TC <3.5 mmol/L measured at 24 months. †Estimates are derived using robust generalized estimating equations. Results are adjusted for baseline values and cluster effect. ‡Estimates are derived using robust generalized estimating equations. Results are adjusted for baseline values, ethnicity, and cluster effect. £Odds for outcomes in the intervention group compared with the control group. ‖Significance of intervention term in the model.

Table 3—Changes in CV risk factors at follow-up times and treatment differences between patients with MA and T2DM allocated to a software-based intervention or to usual care (control)

	Mean (SD)		Change from baseline unadjusted (95% CI)		Model summary†		Model summary‡	
Outcomes	Control	Intervention	Control	Intervention	Coefficient (95% CI)	*P* values§	Coefficient (95% CI)	*P* values§
Systolic BP (mmHg)								
12 months	133.37 (14.89)	133.00 (14.43)	−0.65 (−1.53 to 0/0.24)	−1.52 (−2.32 to −0.73)	−0.74 (−2.11 to 0.64)	0.294	−0.57 (−1.93 to 0.78)	0.406
24 months	133.06 (14.72)	132.80 (14.61)	−0.95 (−1.85 to −0.05)	−1.73 (−2.59 to −0.87)	−0.70 (−2.33 to 0.92)	0.397	−0.43 (−1.73 to 0.88)	0.521
Diastolic BP (mmHg)								
12 months	76.14 (9.7)	74.39 (9.4)	0.60 (−1.12 to −0.08)	−1.05 (−1.55 to −0.56)	−1.04 (−2.25 to 0.16)	0.089	−1.13 (−2.48 to 0.22)	0.100
24 months	75.94 (9.8)	74.35 (9.2)	−0.80 (−1.34 to −0.26)	−1.10 (−1.64 to −0.57)	−1.08 (−2.34 to 0.19)	0.096	−1.04 (−2.25 to 0.18)	0.094
TC (mmol/L)								
12 months	4.09 (0.96)	3.98 (0.95)	−0.04 (−0.08 to 0.002)	−0.07 (−0.11 to −0.04)	−0.06 (−0.10 to −0.01)	**0.023**	−0.05 (−0.09 to −0.02)	**0.002**
24 months	4.17 (0.98)	4.07 (0.99)	0.04 (−0.002 to 0.08)	0.01 (−0.03 to 0.05)	−0.04 (−0.11 to 0.03)	0.288	−0.04 (−0.10 to 0.02)	0.153
HbA_{1c} (mmol/mol)								
12 months	58.99 (17.06)	58.08 (16.42)	−0.85 (−1.53 to −0.16)	−0.78 (−1.39 to −0.18)	−0.28 (−1.40 to 0.83)	0.619	−0.73 (−2.16 to 0.70)	0.319
24 months	59.14 (16.68)	58.92 (16.29)	−0.70 (−1.49 to 0.08)	0.06 (−0.69 to 0.81)	0.32 (−1.03 to 1.68)	0.642	0.08 (−1.60 to 1.75)	0.929
ACR								
12 months	27.28 (82.52)	21.70 (77.61)	3.27 (1.11–5.43)	1.13 (−1.48 to 3.75)	−2.11 (−6.35 to 2.14)	0.330	−2.25 (−5.84 to 1.35)	0.220
24 months	26.38 (77.41)	23.89 (78.75)	2.37 (−0.06 to 4.80)	3.33 (0.50–6.15)	0.67 (−3.65 to 4.99)	0.760	0.59 (−3.37 to 4.56)	0.769
eGFR (mL/min)								
12 months	70.84 (20.80)	73.24 (18.98)	−2.73 (−3.17 to −2.29)	−2.73 (−3.13 to −2.33)	0.07 (−0.65 to 0.79)	0.853	0.11 (−0.62 to 0.84)	0.771
24 months	71.41 (21.45)	73.88 (19.45)	−2.15 (−2.66 to −1.64)	−2.09 (−2.54 to −1.64)	0.15 (−0.60 to 0.89)	0.702	0.22 (−0.62 to 1.06)	0.606

P values in bold are statistically significant. †Estimates are derived using robust generalized estimating equations. Differences between treatment groups are adjusted for baseline values and cluster effect. ‡Estimates are derived using robust generalized estimating equations. Results are adjusted for baseline values, ethnicity, and cluster effect. §Significance of intervention term in the model.

Table 4—Changes in medications at follow-up times for patients with MA and T2DM allocated to a software-based intervention or to usual care (control)

Outcomes	Patients, *n* (%)		Difference in proportions*	Model summary†	
	Control group	Intervention group	% (95% CI)	Odds ratio (95% CI)£	*P* values§
Antihypertensives					
Baseline	1,146 (88.22)	1,209 (85.02)	−3.20 (−5.75 to −0.65)	—	
12 months	1,054 (81.14)	1,104 (77.64)	−3.50 (−6.54 to −0.47)	0.84 (0.66–1.06)	0.143
24 months	964 (74.21)	1,018 (71.59)	−2.62 (−5.96 to 0.72)	0.88 (0.66–1.16)	0.364
Lipid lowering					
Baseline	982 (75.60)	1,133 (79.68)	4.08 (0.94–7.22)	—	
12 months	893 (68.75)	1,029 (72.36)	3.62 (0.19–7.05)	0.99 (0.76–1.29)	0.955
24 months	825 (63.51)	944 (66.39)	2.87 (−0.71 to 6.46)	0.89 (0.63–1.26)	0.502
Antiplatelet					
Baseline	495 (38.11)	584 (41.07)	2.96 (−0.71 to 6.64)	—	
12 months	443 (34.10)	514 (36.15)	2.04 (−1.55 to 5.63)	0.99 (0.83–1.19)	0.956
24 months	393 (30.25)	450 (31.65)	1.39 (−2.08 to 4.87)	0.97 (0.77–1.21)	0.769
Oral antidiabetics					
Monotherapy					
Baseline	498 (48.59)	554 (52.17)	3.58 (−0.71 to 7.87)	—	
12 months	454 (48.66)	500 (51.07)	2.41 (−2.07 to 6.89)	1.04 (0.66–1.65)	0.862
24 months	404 (46.92)	477 (52.94)	6.02 (1.36–10.68)	1.23 (0.84–1.79)	0.286
Dual therapy					
Baseline	365 (35.61)	349 (32.86)	−2.75 (−6.82 to 1.32)	—	
12 months	329 (35.26)	321 (32.79)	−2.47 (−6.72 to 1.77)	0.94 (0.71–1.25)	0.678
24 months	312 (36.24)	273 (30.30)	−5.94 (−10.33 to −1.54)	0.83 (0.65–1.06)	0.137
Triple therapy					
Baseline	156 (15.22)	154 (14.50)	−0.72 (−3.77 to 2.33)	—	
12 months	142 (15.22)	147 (15.02)	−0.20 (−3.42 to 3.01)	0.81 (0.49–1.34)	0.406
24 months	139 (16.14)	138 (15.32)	−0.83 (−4.23 to 2.57)	0.79 (0.52–1.22)	0.288
Four or more					
Baseline	6 (0.59)	5 (0.47)	−0.11 (−0.74 to 0.51	—	
12 months	8 (0.86)	11 (1.12)	0.27 (−0.62 to 1.15)	1.24 (0.53–2.87)	0.618
24 months	6 (0.70)	13 (1.44)	0.75 (−0.21 to 1.70)	1.90 (0.42–8.67)	0.406
Insulin					
Baseline	235 (18.09)	282 (19.83)	1.74 (−1.21 to 4.59)	—	
12 months	225 (17.32)	274 (19.27)	1.95 (−0.96 to 4.85)	1.11 (0.83–1.47)	0.494
24 months	201 (15.47)	268 (18.85)	3.37 (0.54–6.20)	1.33 (1.03–1.73)	**0.031**

The bold *P* value indicates statistical significance ($P < 0.05$). *Difference in proportions: (intervention − control). †Estimates are derived using robust generalized estimating equations. Results are adjusted for baseline values and cluster effect. £Odds for medications in intervention group compared with control group. §Significance of intervention term in the model.

are all common, and studies have shown less benefit with such interventions in primary care settings (8,20,22,23). Intervention strategies that place less training and implementation burden on clinics may improve the reach of such intervention strategies in primary care but have not been adequately tested. Furthermore, interventions to alter HCP performance and health outcomes suggest that the benefits accrued are mostly modest and tend to involve process measures only, not patient outcomes. Despite the novel use of a "prompt," it is likely that clinician inertia persists since providers had the opportunity to ignore the "prompt" and continue with the consultation. Furthermore, providers may have been averse to intensify treatment to tighter targets due to lack of professional expertise in diabetes management or concerns about dose escalation causing intolerable adverse effects. Further studies should use objective measures to study physician behavior change (24,25).

The GP-Prompt study was a complex intervention undertaken against a background of general improvements in the delivery of diabetes care, with dissemination of evidence-based guidelines, including National Institute for Health and Care Excellence (NICE) guidelines for T2DM, QOF targets, and national standards of care in the U.K. (14,26,27). Sophisticated information systems were embedded in the form of "alerts" and "care templates" to guide complex diabetes management rather than the use or allocation of extra resources or financial incentives. External accountability was provided by regular meetings held every 6 months between GP clinical leads in intervention practices and the lead physician of the research team to disseminate learning and stimulate change. The intervention was focused on assisting HCPs in their attempts to promote risk factor control, aided by the use of novel technology, looking at the practice as a whole system and at the challenges within primary care. Such strategies have been conceptualized within well-managed health care systems (28–30). However, patient activation strategies (including self-management education), which are vital to aid quality improvement, were not included in the study, which may have impacted on the intervention's strength to deliver change. Structured self-management education is vital since it empowers individuals and facilitates skills-based learning and decision support. Furthermore, high-quality,

structured T2DM self-management programs can improve important biomedical outcomes (31–33).

Achieving "pay for performance" QOF targets is a recognized part of clinical practice in primary care in the U.K. (34). However, payment for performance thresholds are set relatively low and certainly "far off" from the new benchmarks for high-quality care, which are set out in clinical guidelines and shown to be beneficial in people with T2DM and MA. As an example, under the incentivized QOF indicator, the proportion of patients with diabetes achieving a TC value of ≤5 mmol/L is further from "target" compared with our evidence-based study target of <3.5 mmol/L. Furthermore, 40.6% of study participants at baseline had TC values of <5 mmol/L (data not shown). Given that the payment thresholds for the percentage of patients with diabetes on the GP register, whose last measured TC (measured within the preceding 12 months) is ≤5 mmol/L is set at 40–75%, most practices would receive remuneration even without further efforts at improvement. However, it was interesting to note that the proportion of patients achieving a TC target of <4 mmol/L significantly improved with intensive intervention. Individuals with diabetic dyslipidemia are indeed at high risk of atherosclerotic CVD, and any further improvements in lipid lowering are beneficial in mitigating this risk (35).

Strengths and Weaknesses

To our knowledge, this is the largest cluster-randomized trial within a U.K. multiethnic population assessing the effectiveness of a practice-level intervention to support management of a high-risk multiethnic population with T2DM. We used tighter risk factor targets in our study than current national guidance, (e.g., U.K. QOF targets), which may not be pursued by practicing clinicians in primary care as it can be argued that the nature of a high-risk state such as T2DM with MA deserves stricter cardiometabolic control to achieve greater CV mortality and morbidity benefits (4). QOF "pay for performance" targets in U.K. primary care are set at a higher threshold than the targets used for this study, and payment structures do not allow for individualization of risk factor targets in those at high risk. However, it could be argued that individualization of therapy takes precedence, keeping in mind the "risk-benefits" of treatments to minimize CV risk (14,36), and this should be reflected in payment structures. Since the intervention was delivered within routine clinical care in a community setting, we randomized GP practices rather than individual patients to avoid contamination. The practices enrolled were selected based on their willingness to participate, which could limit the generalizability of our findings. However, the cluster randomized design and the large number of patients recruited may partially offset these problems. In addition, we covered a large geographical area, and the participating centers were representative of key characteristics of high-risk individuals with T2DM. One weakness associated with the choice of randomization resulted in unbalancing of groups in ethnicity. The proportion of patients from black, Asian, or mixed ethnicities in the study sample as a whole was broadly reflective of the population demographics in the multiethnic locality from which practices were recruited. Cluster-randomized controlled trials can often result in imbalance between study groups, as seen in our study, and we adjusted for the difference in our analysis.

A further limitation of the study is that targeted risk factor control may already have been occurring in control practices, which would have continued during the study period, thus making it more difficult for the intervention to show effect. Finally, although our study adopted specific strategies to reduce therapeutic inertia, failure to achieve further improvements in prespecified CV risk factor targets at intervention practices may be from implementation burden due to other competing clinical demands or because they were simply not adopted practice-wide.

Despite its mixed results, the study was rigorously designed to provide evidence that a quality improvement intervention delivered to primary care clinics may improve the process of diabetes care. This has negated many issues inherent in other pragmatic trials, which include difficulty in recruiting and consenting individual patients with a relatively narrow inclusion criteria and the volunteer bias arising from obtaining patient consent to use clinical data for research purposes. However, this method of data collection has inherent weaknesses in that it is reliant on accurate record keeping/correct coding on the part of primary care staff. For example, because cause of death is not routinely recorded on GP clinical systems. We could only access cause of death for 53 of 117 individuals (45%) who died during the 24-month follow-up. Finally, we assessed intermediate outcome measures, and no information was collected on the frequency and severity of hypoglycemic events, again due to lack of coding completeness in U.K. primary care. Whether such intervention would effectively reduce the occurrence of CV events can only be inferred from changes in the CV risk profile.

Conclusion

The results of this study demonstrate that this pragmatic intervention applied within a primary care clinic setting was not sufficiently powerful to achieve greater improvements in population-wide diabetes care outcomes within the time frame of our evaluation. It is likely that a combined patient and practice intervention strategy using novel technologies that engage patients directly may accrue more benefit through more intensive intervention. Nonetheless, our study has important implications for future research and primary care management of high-risk patients with T2DM. It can provide policymakers with helpful insight into planning and implementation of such strategies, specifically in regards to organizational structure and resourcing. Clinicians and researchers need to work together in the implementation of such initiatives to design rigorous evaluations from the outset, to demonstrate meaningful impact and maximize success.

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Duality of Interest. W.C. has acted as a consultant, advisory board member, and speaker for Novo Nordisk, Sanofi, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca, Janssen, Napp Pharmaceuticals, and Novartis. M.D. has acted as a consultant, advisory board member, and speaker for Novo Nordisk, Sanofi, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca, and Janssen; as an advisory

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