Effect of a Pharmaceutical Care Program on Vascular Risk Factors in Type 2 Diabetes

The Fremantle Diabetes Study

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OBJECTIVE — To examine the effect of a 12-month pharmaceutical care (PC) program on vascular risk in type 2 diabetes.

RESEARCH DESIGN AND METHODS — We recruited 198 community-based patients randomized to PC or usual care. PC patients had face-to-face goal-directed medication and lifestyle counseling at baseline and at 6 and 12 months plus 6-weekly telephone assessments and provision of other educational material. Clinical, biochemical, and medication-related data were sent regularly to each patient's physician(s). The main outcome measure was change in HbA_{1c}. A diabetes-specific risk engine was used to estimate changes in 10-year coronary heart disease (CHD) and stroke risk in patients without a history of cardiovascular disease.

RESULTS — At total of 180 patients (91%) completed the study. Mean (95% CI) reductions were greater in PC case subjects ($n = 92$) than control subjects ($n = 88$) for HbA_{1c} (−0.5% [95% CI −0.7 to −0.3] vs. 0 [−0.2 to 0.2]) and systolic (−14 mmHg [−19 to −9] vs. −7 [−11 to −2]) and diastolic (−5 mmHg [−8 to −3] vs. −2 [−4 to 1]) blood pressure ($P \leq 0.043$). The improvement in HbA_{1c} persisted after adjustment for baseline value and demographic and treatment-specific variables. The median (interquartile range) 10-year estimated risk of a first CHD event decreased in the PC case subjects (25.1% [15.6–36.2] to 20.3 [14.6–30.2]; $n = 42$, $P = 0.002$) but not in the control subjects (26.1% [17.2–39.4] vs. 26.4 [16.7–38.0]; $n = 52$, $P = 0.17$).

CONCLUSIONS — A 12-month PC program in type 2 diabetes reduced glycemia and blood pressure. Pharmacist involvement contributed to improvement in HbA_{1c} independently of pharmacotherapeutic changes. PC could prove a valuable component of community-based multidisciplinary diabetes care.

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Patients with type 2 diabetes are more likely to die from cardiovascular disease than people without diabetes, and modifiable risk factors such as hyperglycemia, dyslipidemia, and hypertension can be targeted to reduce this risk (1–4). In addition to hospital-based care, there is a need for simple, cost-effective programs implemented in the community that allow the benefits of improved metabolic and blood pressure control to be realized more widely (5). Pharmacists could contribute to such programs through pharmaceutical care (PC). PC comprises the detection, prevention, and solution of drug-related problems (6) and has proved beneficial in diseases such as asthma and cancer (7).

Previous PC studies in type 2 diabetes have involved small samples (8–11), were nonrandomized (9–13), did not report clinically important outcomes such as HbA_{1c} (10–12), had a high attrition rate (13), or did not recruit patients representative of type 2 diabetes in the general population (8–14). Two studies demonstrated some benefits of pharmacist involvement in the diabetes health care team (15,16), but they did not consider vascular risk factors other than glycemia, and in one (16), clinical pharmacist input was only part of the intervention. It has been suggested that rigorously designed PC studies addressing all aspects of diabetes care are of paramount importance (17). Consistent with this aim, we determined the impact of a PC program in a community-based sample of diabetic patients randomized to PC or usual care. We hypothesized that PC would improve glycemic and blood pressure control and dyslipidemia, with a consequent reduction in vascular risk.

RESEARCH DESIGN AND METHODS

— Adults with type 2 diabetes from the Fremantle Diabetes Study (FDS) were eligible for the present study, which was carried out between February 2001 and November 2002. The FDS was a prospective observational study of diabetes in a postcode-defined Australian population of 120,097 (18,19). From April 1993 to July 1996, 2,258 eligible subjects were identified and 1,426 (63%) were recruited, including 1,294 type 2 diabetic patients (91% of the sample). There were no differences in age, sex, country of birth, or diabetes type between FDS subjects and those who were not recruited (18).

All FDS patients had an initial comprehensive assessment and were re-

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Abbreviations: CHD, coronary heart disease; FDS, Fremantle Diabetes Study; PC, pharmaceutical care.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

quested to reattend annually for ≥5 years. In the present study, we recruited type 2 diabetic FDS patients attending for annual review between February and November 2001 who were of self-identified southern European or Anglo-Celt ethnicity and taking at least one prescribed medication. Southern European and Anglo-Celt groups were selected because they were the largest in the FDS, comprising 63.3 and 18.4% of all type 2 patients (18), respectively. Each patient gave informed consent to participate in the FDS, which was approved by the Human Rights Committee, Fremantle Hospital. The Curtin University Human Research Ethics Committee approved the present substudy.

At each FDS visit, demographic and clinical information, including details of diabetes management and cardiovascular risk factors, was documented. A clinical examination was carried out, and biochemical tests were performed on fasting blood and first-morning urine samples (18). Patients were classified as having coronary heart disease (CHD) if there was a self-reported history of myocardial infarction, angina, coronary artery bypass grafting or angioplasty, or if pathological Q waves were present on the electrocardiograph (20). Stroke was determined from self-report and hospital discharge data (21).

The present subset of FDS patients was randomized to PC or usual care by consecutive allocation. All PC patients were assessed by a clinical pharmacist (R.M.C.) at baseline, at 6-weekly intervals by telephone, and at face-to-face meetings at 6 and 12 months. The nine steps of good PC practice (6) were followed in each case, specifically, developing a pharmacist-patient relationship; collecting, analyzing, and interpreting relevant information; listing and ranking drug-related problems; establishing pharmacotherapeutic outcomes with the patient; determining feasible pharmacotherapeutic alternatives; selecting the best pharmacotherapeutic solution; designing a therapeutic monitoring plan; implementing the individual regimen and monitoring plan; and follow-up.

At baseline, each PC subject completed a comprehensive questionnaire relating to pharmacotherapy and diabetes, including use of proprietary and nonproprietary medicines, from which a detailed medication profile was prepared. Self-reported FDS data on diet and exercise levels, home blood glucose monitoring, and compliance with medications were also available to aid assessment. The final PC goals comprised *1*) HbA_{1c} <7.0%, *2*) blood pressure <135/85 mmHg, *3*) use of statin therapy in those with serum total and HDL cholesterol concentrations meeting Australian Pharmaceutical Benefits Scheme criteria (total >4.0 mmol/l with known CHD; total >6.5 mmol/l or >5.5 mmol/l with HDL cholesterol <1.0 mmol/l otherwise; no LDL cholesterol criteria are currently specified) (22), *4*) 30 min of exercise ≥3 times a week, *5*) smoking cessation (if appropriate), and *6*) full medication compliance. If the patient was some way from these goals at study entry, less ambitious targets were set with the involvement of the patient and then revised progressively during regular telephone interview/follow-up visits according to progress. Patient-specific goals, current medication lists, and clinical and biochemical data were sent to the primary care physician and other involved health care professionals after each visit.

Attention to diet (based on National Heart Foundation of Australia recommendations) (23), exercise, and compliance with home blood glucose monitoring and treatment were encouraged initially by the pharmacist, who subsequently advised the patient to consult their doctor for consideration of intensification of pharmacotherapy if there had been insufficient progress at follow-up. Telephone interviews and the PC-related aspects of face-to-face meetings took 5–30 min (average 15 min), the duration largely reflecting the numbers of medications and comorbidities and the level of patient understanding. In addition to scheduled contacts, all PC patients received a bimonthly newsletter on topics based on issues identified at interview. Other relevant educational pamphlets from the National Heart Foundation of Australia and Diabetes Australia were also provided.

The control patients also had a standard FDS assessment immediately before recruitment, a 6-month review at which blood pressure was measured and fasting biochemical tests were performed, and a further-scheduled FDS assessment at 12 months. Lifestyle issues were reinforced at each of these assessments, and the clinical and laboratory results were forwarded to the primary care physician as prescribed under the FDS protocol.

Data analysis

The principal outcome measure was change in HbA_{1c}. Based on previous reports (8,14), 80 PC patients and 80 control subjects were required to demonstrate a 10% difference in HbA_{1c} after 12 months with >80% power and $\alpha = 0.05$. To allow for withdrawals, the sample was increased to 100 subjects per group. Other major end points included changes in fasting plasma glucose, blood pressure, serum lipids, and urinary albumin-to-creatinine ratio. For patients without a history of cardiovascular disease, the 10-year absolute risks of CHD and stroke were estimated at the beginning and end of the study using the U.K. Prospective Diabetes Study (UKPDS) risk engine (24,25).

Statistical analyses were performed using SPSS for Windows (version 11; SPSS, Chicago, IL). Data are summarized as means ± SD, geometric mean (SD range), mean difference (95% CI), or median [interquartile range]. Two-sample comparisons were by Student's or paired *t* tests for normally distributed variables and by Mann-Whitney *U* or Wilcoxon signed-rank tests for nonnormally distributed data. Comparisons of proportions were by χ^2, Fishers' exact, or McNemar's tests. Associations between case-control status and changes in vascular risk factors were assessed by multiple linear regression. A two-tailed significance level of 0.05 was used.

RESULTS

Patient characteristics

Of 489 type 2 diabetic FDS patients assessed during the 10-month screening period, 198 were recruited. There were no age or sex differences between these subjects and FDS patients who were not recruited, but study participants had a shorter diabetes duration at FDS entry (3.0 years [0.5–6.0] vs. 4.0 [1.1–10.0], $P < 0.001$) and more were Anglo-Celt (88 vs. 75%, $P < 0.001$). There were 180 patients who completed the study (91% of recruited subjects), and they were of similar age and sex and had similar diabetes duration to the 18 (7 PC case and 11 control subjects) who withdrew (data not shown). Details of the patients who completed the study are summarized in Table

Table 1— *Baseline values and changes over 12 months in PC case and control subjects*

	PC subjects (n = 92)		Control subjects (n = 88)			
	Baseline	Change over 12 months	Baseline	Change over 12 months	*P* value (baseline)	*P* value (change)
Age (years)	70.5 ± 7.1	—	70.3 ± 8.3	—	0.86	—
Male (%)	47.8	—	56.8	—	0.24	—
Diabetes duration (years)	10.0 [7.6–14.0]	—	8.0 [6.6–12.0]	—	0.009	—
BMI (kg/m^2)	30.0 ± 4.3	−0.6 (−1.0 to −0.3)	30.0 ± 4.5	0.1 (−0.3 to 0.5)	0.98	0.005
Any exercise (%)	75.0	−3.1	76.1	−13.3	0.86	0.55
Fasting serum glucose (mmol/l)	8.8 [7.4–10.5]	−0.8 (−1.3 to −0.4)	8.1 [6.7–9.7]	0.4 (−0.1 to 1.0)	0.11	<0.001
HbA_{1c} (%)	7.5 [6.9–8.1]	−0.5 (−0.7 to −0.3)	7.1 [6.3–7.8]	0 (−0.2 to 0.2)	0.046	0.002
Systolic blood pressure (mmHg)	157 ± 22	−14 (−19 to −9)	156 ± 25	−7 (−11 to −2)	0.63	0.024
Diastolic blood pressure (mmHg)	77 ± 10	−5 (−8 to −3)	77 ± 11	−2 (−4 to 1)	0.91	0.043
Serum total cholesterol (mmol/l)	5.0 ± 1.1	−0.3 (−0.5 to −0.2)	4.9 ± 0.8	−0.2 (−0.3 to 0)	0.50	0.14
Serum HDL cholesterol (mmol/l)	1.19 ± 0.31	0.03 (−0.01 to 0.07)	1.19 ± 0.32	−0.02 (−0.05 to 0.02)	0.93	0.07
Serum triglycerides (mmol/l)	1.7 (0.9–3.0)	−0.6 (−1.3 to 0.1)	1.6 (1.0–2.5)	0 (−0.1 to 0.2)	0.43	0.09
Urinary ACR (mg/mmol)	2.6 (0.6–12.6)	−2.5 (−5.7 to 0.7)	1.7 (0.3–8.1)	1.7 (−3.3 to 6.6)	0.06	0.15
Known CHD/stroke (%)	54.3	0	40.9	0	0.08	—

Data are means ± SD, geometric mean (SD range), median [interquartile range], or percentages. Changes over 12 months are mean difference (95% CI) or percentages. ACR, urinary albumin-to-creatinine ratio.

1. The PC subjects had longer diabetes duration than the control subjects, higher HbA_{1c}, and were taking a greater number of medications. The proportion of patients who had CHD or stroke was similar in the two groups. There were no differences between PC case and control subjects for other variables.

Clinical outcome measures

Changes in key variables over 12 months in the two groups are shown in Table 1. The reduction in BMI, systolic and diastolic blood pressure, fasting plasma glucose, and HbA_{1c} was greater in PC patients than control subjects. There were nonsignificant improvements in serum lipid parameters and urinary albumin-to-creatinine ratio in the PC group. Although most patients in both groups did some exercise, including walking, gardening, and/or more vigorous exertion at baseline, there was no change in either exercise participation during the study (see Table 1) or in the intensity of the exercise in those involved in regular activity (data not shown).

Medication use

There were no differences between the two groups in the percentage change in use of key medications (Table 2), except that ACE inhibitor/angiotensin 2 receptor blocker therapy was more often commenced in the PC group. However, excluding blood glucose–lowering therapies (where starting insulin can mean reducing oral hypoglycemic agents), there was a greater increase in antihypertensive/lipid-lowering/antiplatelet drug use in the PC group.

Predictors of changes in outcome variables

The change in HbA_{1c} may depend on its baseline level, and there was a significant difference in HbA_{1c} between the two groups at study entry. Therefore, we in-

Table 2—*Medication use and changes over 12 months in PC case and control subjects*

	PC subjects (n = 92)		Control subjects (n = 88)			
	Baseline	Change over 12 months	Baseline	Change over 12 months	*P* value (baseline)	*P* value (change)
Number of medications	7 [5–9]	1 (−3 to 4)	5 [3–7]	1 (−2 to 6)	<0.001	0.80
Diabetes treatment						
Oral hypoglycemics only (%)	72.8	0.0	68.2	−2.3	0.52	0.31
Any insulin therapy (%)	8.7	7.6	11.4	3.4	0.62	0.33
Blood pressure treatment						
Any antihypertensive drug (%)	75.0	13.0	75.0	9.1	1.0	0.48
ACE inhibitor/angiotensin 2 receptor blocker therapy (%)	57.6	19.6	53.4	8.0	0.65	0.032
Lipid-lowering therapy (%)	55.4	4.4	56.8	1.2	0.88	0.37
Antiplatelet agents (%)	65.2	16.3	42.0	6.9	0.003	0.06
Drugs for vascular risk factors*	2 [1–3]	1 (0–2)	2 [1–3]	0 (−1 to 2)	0.59	0.002

Data are median [interquartile range], mean difference (95% CI), or percentages of patients in each group taking drugs in each category. *Excluding insulin and oral hypoglycaemic agents (see text).

Table 3—*Multiple linear regression analysis of changes in risk factors after adjustment for key variables*

	Model 1*		Model 2†	
	Regression coefficient for case	*P* value	Regression coefficient for case	*P* value
ΔBMI (kg/m^2)	−0.7	0.008	—	—
ΔSystolic blood pressure (mmHg)	−5	0.09	−4	0.17
ΔDiastolic blood pressure (mmHg)	−3	0.033	−2	0.12
ΔFasting plasma glucose (mmol/l)	−1.1	0.002	−1.0	0.005
ΔHbA_{1c} (%)	−0.3	0.032	−0.3	0.010
ΔTotal serum cholesterol (mmol/l)	−0.1	0.49	−0.1	0.51
ΔSerum HDL cholesterol (mmol/l)	0.04	0.11	0.05	0.11
ΔSerum triglycerides (mmol/l)	−0.5	0.14	−0.5	0.18
ΔACR (mg/mmol)	−3.2	0.26	−2.5	0.40

*Adjustment for age, sex, diabetes duration, baseline value (or ln [value]) for the associated variable, ΔBMI, and change in exercise over 12 months. †Model 1 plus adjustment for intensification of associated pharmacotherapy other than weight-reducing medication. ACR, urinary albumin-to-creatinine ratio.

vestigated associations between PC case-control status and changes in variables of interest, including HbA_{1c}, after adjusting for the baseline value and other potential confounding or explanatory variables (age, sex, diabetes duration, change in BMI, and change in exercise over the study period) in multiple linear regression analysis (model 1). Such analyses showed that PC group allocation remained an independent predictor of changes in fasting plasma glucose, HbA_{1c}, and diastolic blood pressure (Table 3).

We further adjusted for changes in pharmacotherapy in addition to the variables in model 1 (model 2). For glycemic control, model 2 included dose reduction of a hypoglycemic agent, insulin dose reduction, dose increase of a hypoglycemic agent, insulin dose increase, addition of one or two hypoglycemic agents, addition of one insulin, removal of one or two hypoglycemic agents, change in type of hypoglycemic agent, progression from diet to hypoglycemic therapy, and progression to insulin. For the other risk factors, changes in pharmacotherapy were defined as dose reduction or increase of a medication, addition or removal of one or two medications, and/or change of medication. After applying model 2, PC allocation remained an independent predictor of improvement in plasma glucose and HbA_{1c} (Table 3).

Changes in absolute vascular risk

Patients without a previous cardiovascular event ($n = 94$) were more likely to be younger ($P < 0.001$) and female ($P = 0.02$) than those with a cardiovascular history ($n = 86$). For the 42 of these patients who were allocated to PC, the 10-year estimated CHD risk decreased from a median [interquartile range] of 25.1% [15.6–36.2] to 20.3 [14.6–30.2] ($P = 0.002$) over 12 months, while there was no change in the 52 control subjects (26.1% [17.2–39.4] vs. 26.4 [16.7–38.0], $P = 0.17$). The median 10-year estimated risk of stroke did not change during the study in the case subjects (12.8% [9.2–24.2] vs. 14.0 [9.5–26.6], $P = 0.07$) but increased in the control subjects (15.0% [10.7–25.7] vs. 16.8 [10.7–27.2], $P = 0.001$).

CONCLUSIONS — The present study demonstrates that a 12-month PC program implemented in type 2 diabetic patients from the community can produce beneficial reductions in modifiable vascular risk factors, most notably glycemic control and blood pressure. In the case of glycemic control, the improvement persisted after adjustment for key demographic variables and intensification of pharmacotherapy, suggesting that the participation of the pharmacist had a positive impact on medication adherence and other factors that are important in diabetes self-care. In addition, the PC program was associated with a significant reduction in the estimated 10-year risk of CHD in a primary prevention setting.

Our PC program comprised elements that are parts or extensions of existing diabetes management strategies in Australia and other countries, namely *1*) use of the telephone to provide an inexpensive, convenient, and efficient means of communication between face-to-face appointments; *2*) provision of a regularly updated, goal-directed, patient-specific medication profile designed to improve patient compliance and understanding and to communicate drug-related information between patient, pharmacist, primary care physician, and other health care professionals; and *3*) individualized patient education and follow-up reinforcement through additional written educational material. Although the clinical benefits of PC in the present study cannot be assessed in relation to the individual contributions of these three elements, they reflect strategies that have been used successfully in other contexts (7).

The community-based PC patients in our study lowered their HbA_{1c} by a mean of 0.5% over 12 months from a baseline of 7.5%, while there was no change in the control group. Other studies (8,9) have demonstrated a greater reduction (>2.0%) over a shorter period (3–4 months) but from a higher mean baseline HbA_{1c} (>11.0%) and in an outpatient clinic setting. We have previously conducted a 6-month study in clinic patients with mean HbA_{1c} 8.4% that showed no advantage of PC over usual multidisciplinary care (14). Although limited by attrition of most patients, a long-term community-based PC study (13) showed a reduction in mean HbA_{1c} from 7.5 to 7.1% over 4 years. Taken together, these results suggest that the success of PC depends on the combination of patient characteristics, context, and duration. In the present study, we used a sample that reflected type 2 diabetes in an urban Australian context and incorporated one-to-one PC input that could form part of routine care. One indication of the effectiveness of our approach comes from U.K. Prospective Diabetes Study (26) epidemiological analyses that equate a 0.5% HbA_{1c} reduction to an estimated 7% reduction in the risk of myocardial infarction and an estimated 12% reduction in risk of stroke.

Systolic and diastolic blood pressure fell in both groups over 12 months but to a greater extent in PC patients. The mean systolic blood pressure reduction in the PC group was 14 mmHg, double that in the control subjects and equivalent to, in U.K. Prospective Diabetes Study epidemiological analyses, a 17% reduction in myocardial infarction and 27% reduction in stroke (27). Although the greater re-

duction in blood pressure in the PC group was not reflected in beneficial changes in urinary albumin-to-creatinine ratio despite greater use of ACE inhibitor/angiotensin 2 receptor blocker therapy by PC patients (28), the encouraging trends in the data may have become significant had the intervention been longer (3).

PC did not influence use of lipid- lowering therapy. The prescription of subsidized statins and fibrates in Australia is currently restricted in diabetic patients to those with serum lipid concentrations within specified ranges (22). Most patients not receiving lipid-lowering therapy at baseline were ineligible for subsidized therapy, which helps explain why there were similar small increases in statin/fibrate use in both groups during the study period. There was, however, a larger increase in the number of PC patients on antiplatelet agents, consistent with current recommendations (29). The changes in total numbers of medications were similar in the two groups. Informal analysis suggests that the greater increase in use of therapies for vascular risk factors in the PC group was offset by a reduction in oral hypoglycemic therapy in patients commencing insulin together with enhanced identification and discontinuation of unnecessary medications through the PC process.

After adjustment for key demographic variables, the baseline value of the risk factor (important because of the lack of balance in the randomization), change in BMI and in any exercise, and intensification of pharmacotherapy targeting the risk factor (such as oral hypoglycaemic drugs and insulin in the case of HbA_{1c}), PC intervention remained a significant predictor of beneficial changes in glycemic control over the 12 months of the study. This suggests that regular pharmacist contact was independently beneficial perhaps through encouraging adherence with blood glucose–lowering therapy and a prudent diet. Although PC produced reductions in body weight and blood pressure, there was no independent effect of PC involvement in the adjusted models, suggesting that blood glucose control may have had priority over other vascular risk factors.

We used a diabetes-specific vascular risk engine (24,25) so that HbA_{1c} could be included in global risk calculations. In addition, the U.K. Prospective Diabetes Study engine has been developed using data from a largely Anglo-Celt patient cohort similar to that in the FDS. For patients without a history of CHD or stroke (approaching half the sample), PC had a beneficial effect on the 10-year CHD risk over 12 months compared with control subjects (an ~5% reduction) and a lesser effect on risk of stroke. These data highlight the value of PC that targets all conventional risk factors.

Our study had limitations. Although the patients were from a representative community-based cohort, they were survivors who were younger, had a shorter diabetes duration, and were more likely to be Anglo-Celt than those in the full FDS cohort. In addition, they voluntarily returned for annual reviews, which may reflect a stronger interest in self-management. The sustainability of beneficial outcomes beyond 12 months was not assessed. Nevertheless, the randomized nature of the study and the clear differences between the two groups argue for a larger-scale implementation and assessment. As recommended previously (30,31), we assessed quality-of-life and health economic outcomes, but the data will be reported subsequently.

In practical terms, a qualified pharmacist with prior exposure to diabetes-specific medication issues (such as in hospital wards or outpatient clinics) and/or more formal training could implement the present PC model. The PC process is not meant to replace formal diabetes education but rather to complement it. In fact, although the majority of our patients received formal education before recruitment into the FDS (32), our PC program was still beneficial. In addition, we found that the pharmacist developed good relationships with individual doctors and other allied health personnel during the study, a factor that might also have contributed to improved outcomes.

Our PC model could be adapted to a variety of settings. We had a pharmacist working relatively independently of hospital/primary care diabetes facilities, but, as an extension of previous studies (15,16), the strategies we used could be implemented by a similar person located with physicians, diabetes educators, and other health professionals in a clinic. Community pharmacists should also be able to adapt aspects of our PC model to their circumstances (12,13). Our data and those of others (8–16) argue that the pharmacist can be a beneficial addition to integrated care for patients with type 2 diabetes.

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