Determinants of Diabetes-Attributable Non–Blood Glucose–Lowering Medication Costs in Type 2 Diabetes

The Fremantle Diabetes Study

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OBJECTIVE — To prospectively examine the magnitude and predictors of diabetes-attributable non–blood glucose–lowering (non-BGL) medication costs in type 2 diabetes.

RESEARCH DESIGN AND METHODS — Detailed data from 593 community-dwelling patients were available over 4.3 ± 0.4 years. Diabetes-attributable costs (in year 2000 Australian dollars [A$]) were calculated by applying a range of attributable proportions for each complication for which medication was prescribed.

RESULTS — Non-BGL medications accounted for 75% of all prescription medication costs over the study period, and one-third were attributable to diabetes. The median annual cost (in A$) of non-BGL medications per patient increased from A$220 to A$429 over 4 years ($P < 0.001$), whereas the diabetes-attributable contribution increased from A$31 (range 15–40) to A$159 (range 95–219) per patient ($P < 0.001$). Diabetes-attributable hospital costs remained stable during the study. Diabetes-attributable non-BGL costs were skewed and, therefore, square root transformed before regression analysis. Independent baseline determinants of $\sqrt{}$cost/year were coronary heart disease, systolic blood pressure, total serum cholesterol, ln(serum triglycerides), ln(albumin-to-creatinine ratio), serum creatinine, education, and, negatively, male sex and fasting plasma glucose ($P \leq 0.043$; $R^2 = 29\%$). Projected to the Australian population, diabetes-attributable non-BGL medication costs for patients with type 2 diabetes totaled A$79 million/year.

CONCLUSIONS — The median annual cost of diabetes-attributable non-BGL medications increased fivefold over 4 years. This increase was predicted by vascular risk factors and complications at baseline. Better-educated patients had higher costs, probably reflecting improved health care access. Men and patients with higher fasting plasma glucose levels had lower costs, suggesting barriers to health care and/or poor self-care. The contemporaneous containment of hospital costs may be due to the beneficial effect of increased medication use.

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Most patients with type 2 diabetes require drug therapy in addition to that for glycemic control, including medications prescribed for other vascular risk factors. Based on U.S., European, and Australian data, the cost of such non–blood glucose–lowering (non-BGL) medications is significant. In the U.S, the diabetes-attributable cost of outpatient medications, excluding insulin and oral hypoglycemic agents, was estimated to be U.S.$5.5 billion in 2002 or 6% of all diabetes-related health care expenditure (1). In Europe in 1999, total non-BGL outpatient medication costs for people with type 2 diabetes were reported to be €6 billion or 21% of the total health care expenditure (2). The total non-BGL medication costs incurred by Australians with type 2 diabetes in 2002 were estimated to be 26% of total direct health care costs (3).

Available data on non-BGL medication costs have been generated from cross-sectional cost-of-illness studies. It has been proposed that attention should shift from cost-of-illness to more detailed studies that include prospective epidemiological data (4). This approach should promote a better understanding of the factors driving costs and, therefore, improved targeting of expenditure. We have, therefore, investigated the longitudinal cost of diabetes-attributable non-BGL medications in a well-characterized community-based cohort of Australian patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— The Fremantle Diabetes Study (FDS) was a prospective observational study of the care, metabolic control, and complications in diabetic patients recruited from a postcode-defined community of 120,097 people in Western Australia. Descriptions of recruitment, sample characteristics including classification of diabetes type, and details of nonrecruited patients have been published elsewhere (5,6). Of 2,258 diabetic

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Abbreviations: A$, Australian dollars; ACR, albumin-to-creatinine ratio; BGL, blood glucose lowering; CHD, coronary heart disease; DRG, Diagnostic Related Group; FDS, Fremantle Diabetes Study; PBS, Pharmaceutical Benefits Scheme.

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

subjects identified between 1993 and 1996, 1,426 (63%) were recruited and 1,294 had type 2 diabetes. The present study involved the 593 FDS participants with type 2 diabetes who had returned for at least four annual reviews by 30 June 2000.

Clinical assessment

FDS patients attended annually for detailed screening, including medical history, physical examination, and biochemical tests (5). At each visit, FDS participants were asked to bring their current medications, and these were recorded, with all other information, on a confidential computer database. Sources such as hospital case notes were consulted when details of medication regimens were incomplete. Marital status, ethnic background, English-speaking ability, educational attainment, smoking status, exercise in the previous 2 weeks, and alcohol consumption were determined from self-report.

Clinical and/or laboratory data supplemented by hospital morbidity data and self-report were used to identify vascular complications. Patients were classified as having coronary heart disease (CHD) if there was self-reported or hospital history of myocardial infarction, angina, coronary artery bypass grafting, angioplasty, and/or definite ischemic changes on Minnesota coding of the electrocardiogram taken at study entry. Retinopathy (≥1 microaneurysm in either eye) was assessed from direct and/or indirect ophthalmoscopy through dilated pupils and/or more detailed data in patients assessed for photocoagulation. Neuropathy was defined as a score of >2/8 using the Michigan Neuropathy Screening Instrument clinical portion (7). Microalbuminuria was defined as an urinary albumin-to-creatinine ratio (ACR) ≥3.0 mg/mmol (27 μg/mg), and clinical albuminuria was defined as ACR ≥30.0 mg/mmol (265 μg/mg). These figures, in SI units, are consistent with current American Diabetes Association definitions: 30 and 300 μg/mg, respectively (8). A microvascular complication was defined as the presence of retinopathy and/or neuropathy and/or microalbuminuria, and a macrovascular complication was defined as the presence of CHD and/or cerebrovascular disease and/or a diabetes-related lower-extremity amputation.

Costing of prescription medications

In Australia, an uncapped federal government subsidy of approximately A$4.6 billion/year funds the Pharmaceutical Benefits Scheme (PBS), which purchases 90% of all prescription medications (9). The PBS aims to provide equitable access to medicines by limiting their cost through capped copayments and "safety net" provisions. Individuals and families are protected from large overall expenses for PBS-listed medicines by safety nets, whereby expenditure is subsidized or free after an expenditure threshold is exceeded. This monopsony power has resulted in drug prices that are, at most, 54% of those in the U.S. (10). Because of the features of the Australian PBS, relatively accurate estimation of medication cost is possible. On 30 June 2000, A$1 = U.S.$0.60.

The cost of all prescription medications used by FDS participants from recruitment until 30 June 2000 was calculated at patient level as at 30 June 2000, using the Schedule of Pharmaceutical Benefits (11), the quarterly listing of PBS-subsidized drugs. We used the dispensed price (i.e., the cost to both government and patient) to calculate medication cost. Prior and future medication data were, if consistent, used to impute intermediate missing values. For absent dosages, minimum therapeutic doses were assumed. Where a broad term such as "blood pressure tablet" was used, the website of Australia's primary health information management and payment agency, the Health Insurance Commission, was searched and the item with the same dosing schedule reported by the patient that was most prescribed in Western Australia between 1993 and 2000 was used. Medications reported at annual assessment were assumed to be taken at the same rate until the next assessment, unless specifically reported for short-term use. To ascertain whether a medication was prescribed for a diabetes-related reason, all available data were examined. For example, to determine whether digoxin was prescribed for atrial fibrillation or heart failure, baseline electrocardiograms and self-report were used to determine the presence of atrial fibrillation during follow-up. If atrial fibrillation was not present, use of digoxin was attributed to heart failure.

Diabetes complications were defined by reference to previous studies (1,12). We reviewed the literature to ascertain a range of relative risks for each complication, and the corresponding range of diabetes-attributable proportions was calculated (1) (Table 1). Low- and high-cost estimates for diabetes-attributable non-BGL medications and their average were estimated by applying the range of attributable proportions for the complication for which the medication was most likely prescribed.

Projecting diabetes-attributable non-BGL medication costs to the Australian population

The annual cost to the Australian community was calculated using Australian national diabetes prevalence data for individuals aged ≥25 years (13), Australian population data for 2000 (14), FDS age- and sex-specific data on the proportion of diabetic patients diagnosed with type 2 diabetes, and corresponding diabetes-attributable non-BGL medication costs (Table 2). Because of the 4-year follow-up period, we used the mean patient age and mean annual non-BGL medication costs in our projection estimates.

Costing of hospital morbidity data

The Western Australia Health Services Data Linkage System was merged with FDS data to provide Western Australia hospital morbidity data for all patients over the study period (15). The Western Australia Hospital Morbidity Data System records information on all hospital separations, including inpatient and day cases, but not outpatient data. The study straddled the introduction of the ICD-10-AM on 1 July 1999. Therefore, the National Centre for Classification in Health ICD-9-CM/ICD-10-AM mapping tables and handbooks (16,17) were used to maintain coherence in morbidity groupings. The principal diagnosis code was used to define the reason for hospitalization; secondary diagnoses and procedure codes were used as necessary. Hospital costs were derived using a case-mix approach based on Diagnostic Related Group (DRG) version 3.1. Cost ranges for diabetes-attributable hospitalizations during follow-up were estimated.

Statistical analysis

The computer packages SPSS for Windows (version 11.5; SPSS, Chicago, IL) and SAS for Windows (version 8.2; SAS Institute, Cary, NC) were used. Data are presented as proportions, means ± SD,

Table 1—*Proportion of diabetes complications attributable to type 2 diabetes*

Complication	ICD-9-CM principal diagnosis or procedure codes	ICD-10-AM principal diagnosis or procedure codes	Relative risk (RR) compared with RR in individuals without diabetes	Proportion (P) of complication attributable to diabetes*
Diabetes/diabetes complications	250	E10, E11, E13, E14		100
Circulatory disorders				
Hypertension	401–405	I10-I13, I15	1.4–4.0	28.6–75.0
Ischemic heart disease	410–414	I20-I22, I24, I25	1.3–5.6	23.1–82.1
Cerebrovascular disease	430–438, 362.34, 784.3	I60-I67, I69, G45, H34.0, R47.0	2.0–4.6	50.0–78.3
Heart failure	428, 429.2–429.3, 429.9	I50.0-I50.1, I50.9, I51.6-I51.7, I51.9	1.6–2.6	37.5–61.5
Atherosclerosis	440	I70	2.1–5.8	52.4–82.8
Peripheral vascular disease	443, 459.8–459.9, 444, 447.1	I73, I87.2, I99, I74, I77.1	1.7–7.6	41.2–86.8
Visual disorders				
Glaucoma	365	H40, H42.8	1.6–6.9	37.5–85.5
Cataract	366	H25-H26, H28.0	1.6–7.7	37.5–87.0
Blindness	369	H54	5.2–10.3	80.8–90.3
Other disorders				
Nephropathy	580–586, V45.1, V56	N00, N01, N03-N05, N07, N08, N16-N19, Z49, Z99.2	3.0	66.7
Other renal complications				
Infections of kidney	590	N10, N11.8-N11.9, N12, N15.1, N15.9, N28.8	1.2–1.4	16.7–28.6
Cystitis, urinary tract infection	595, 599.0	N30, N39.0	1.1–2.6	9.1–61.5
Proteinuria	791.0	R80	2.8–8.6	64.3–88.4
Neuropathy/other neurologic symptoms	354, 355, 356.8, 729.2	G56-G57, G58.7, G60.8, M79.2, M54.10, M54.11, M54.19	3.4–10.6	70.6–90.6
Chronic skin ulcer	707	L89, L97, L98.4	4.8–13.5	79.2–92.6
Gangrene	785.4	R02	8.1	87.7
Nontraumatic lower-extremity amputation or revision	84.1, 84.3	44338–00, 44358–00, 44361–00, −01, 44364–00, −01, 44367–00, −01, −02, 44376–00	5.9–22.2	83.1–95.5
Other complications				
Candidiasis of vulva and vagina	112.1	B37.3 + N77.1	5.6	82.1
Chronic osteomyelitis of the foot	730.17	M86.37, M86.47, M86.57, M86.67, M86.87	8.7	88.5
Cellulitis	681, 682	L03	2.0–13.7	50.0–92.7
Non–diabetes related	All other codes	All other codes	0	0

Data for RR are range and for P are % and range. *Attributable proportion, P = (RR − 1)/RR.

Table 2—*Estimated age- and sex-specific prevalence and Australian annual direct average cost of diabetes-attributable non-BGL medications for known type 2 diabetes*

	Age (years)		
Classification	25–34	35–44	45–54
Men			
National population (2000)	1,452,706	1,468,730	1,302,037
Prevalence all types of known diabetes (AusDiab) (%)	0.0	1.1	2.8
FDS patients with type 2 diabetes (%)	30.4	67.4	87.2
Prevalence of type 2 diabetes (%)	0	0.74	2.4
No. in Australia with type 2 diabetes	0	10,889	31,791
Average annual cost/patient in 2000 A$	0	77–254	54–165
Total average cost in 2000 A$ (range)	0	1,802,130 (838,453–2,765,806)	3,481,115 (1,716,714–5,245,515)
Women			
National population (2000)	1,444,843	1,472,825	1,285,666
Prevalence all types of known diabetes (AusDiab) (%)	0.3	0.9	3.5
FDS patients with type 2 diabetes (%)	37.5	76.6	87.9
Prevalence of type 2 diabetes (%)	0.11	0.69	3.1
No. in Australia with type 2 diabetes	1,625	10,154	39,554
Average annual cost/patient in 2000 A$	0	46–131	88–250
Total average cost in 2000 A$ (range)	0	898,629 (467,084–1,330,174)	6,684,626 (3,480,752–9,888,500)
Total			
National population (2000)	2,897,549	2,941,555	2,587,703
No. in Australia with type 2 diabetes	1,625	21,043	71,345
Total average cost in 2000 A$ (range)	0	2,700,759 (1,305,537–4,095,980)	10,165,741 (5,197,466–15,134,015)

geometric means (SD range), or, in the case of nonnormally distributed variables, median and interquartile range. Two-sample comparisons for normally distributed variables were by Student's or paired *t* test, and the Mann-Whitney *U* test or Wilcoxon's signed-rank test was used for nonnormal data. Comparisons of proportions were by Fisher's exact, McNemar's, or χ^2 tests. Multiple comparisons of normally distributed repeated measures were by general linear modeling for repeated measures. Multiple comparisons of nonnormally distributed data were by the Kruskal-Wallis H-test for independent samples and Friedman's test for repeated measures. Comparisons of several related dichotomous variables were by Cochran's Q test. In general linear modeling for repeated measures, the score statistic for Type III generalized estimating equation analysis (degrees of freedom = 1) was used for the trend *P* value for multinomial outcome variables. In forward stepwise multiple linear regression, significance levels of $P < 0.05$ and >0.10 were used for entry and removal, respectively. A two-tailed level of significance of 0.05 was used throughout.

RESULTS

Clinical details at entry and during follow-up

The present 593 FDS patients were younger (62.9 ± 9.6 vs. 65.0 ± 12.4 years; $P = 0.001$), had shorter duration of diabetes (3.0 [0.7–7.1] vs 4.0 [1.2–10.0] years; $P < 0.001$), and were more likely to be men (54.5 vs. 44.2%; $P < 0.001$) compared with the 701 FDS participants who had not attended four annual reviews by 30 June 2000. In the latter group, reasons for nonattendance were death (28%), relocation (16%), refusing further participation (49%), delayed fourth review (5%), and unknown (1%). For the present participants, the follow-up period was 4.3 ± 0.4 years (range 3.7–6.5) and totaled 2,556 patient-years. Most patients were Anglo-Celt (68%) or Southern European (17%). One-eighth of the patients did not speak English very well, and 23% had not been educated beyond primary level. Southern Europeans were significantly less likely to have been educated beyond primary level or to speak English very well compared with other participants (33 vs. 87% and 44 vs. 97%, respectively; $P < 0.001$). At study entry, Southern

Table 2—*Continued*

Age (years)			
55–64	65–74	75+	Total 25+
878,626	623,952	414,531	6,140,582
8.6	12.8	13.8	
91.7	97.8	100	
7.9	12.5	13.8	
69,290	78,109	57,205	247,284
86–255	92–273	74–210	
11,813,945	14,254,892	8,123,110	39,475,192
(5,958,940–17,668,950)	(7,186,028–21,323,757)	(4,233,170–12,013,050)	(19,933,305–59,017,078)
860,244	675,349	646,402	6,385,329
4.6	7.3	9.7	
95.5	99.1	100	
4.4	7.2	9.7	
37,791	48,857	62,701	200,681
92–279	117–346	114–328	
7,010,231	11,310,395	13,856,921	39,760,802
(3,476,772–10,543,689)	(5,716,269–16,904,522)	(7,147,914–20,565,928)	(20,288,791–59,232,813)
1,738,870	1,299,301	1,060,933	12,525,911
107,081	126,966	119,906	447,965
18,824,176	25,565,287	21,980,031	79,235,994
(9,435,712–28,212,639)	(12,902,297–38,228,279)	(11,381,084–32,578,978)	(40,222,096–118,249,891)

Europeans had lower total serum cholesterol and serum triglyceride levels than non–Southern Europeans (5.2 ± 1.0 vs. 5.5 ± 1.1 mmol/l [201 ± 39 vs. 213 ± 43 mg/dl], $P = 0.007$; and 1.7 (1.0–2.7) vs. 1.9 (1.1–3.5) mmol/l [151 (89–239) vs. 168 (97–310) mg/dl], $P = 0.016$; respectively). Southern Europeans also had lower HDL cholesterol levels (1.00 ± 0.28 vs. 1.07 ± 0.33 mmol/l [39 ± 11 vs. 41 ± 13 mg/dl]; $P = 0.036$). Baseline systolic and diastolic blood pressures were similar for Southern Europeans and non–Southern Europeans ($P > 0.5$).

Non-BGL medication cost data

The total annual cost of prescription medications for the 593 participants averaged A$409,325, increasing significantly from A$311,480 in the first year to A$511,178 in the fourth year ($P < 0.001$). Non-BGL medications accounted for approximately three-quarters of prescription medicine costs over the study period. The median annual costs per patient of all non-BGL medications nearly doubled, increasing from A$220 to A$429 ($P < 0.001$). The contribution of non-BGL medications attributable to diabetes averaged 26% (range 13–39%) of the total annual cost of all prescription medications or A$107,956 (range A$54,470-A$161,442) per year for the cohort during follow-up. The median annual cost per patient of diabetes-attributable non-BGL medications increased from A$31 (range A$15-A$40) in the year after study entry to A$159 (A$95-A$219) between the third and fourth annual reviews ($P < 0.001$) and comprised 35% (range 18–52%) of all non-BGL medication costs during follow-up.

Changes during follow-up in glycemic control, lipid profiles and blood pressure, blood pressure- and lipid-lowering medication regimens, and the prevalence of diabetes complications are presented in Table 3. The use of blood pressure–lowering medication increased from 48% at study entry to 56% by the end of the fourth year, largely due to increased use of ACE inhibitors. The mean systolic blood pressure did not change during this period, although the mean diastolic blood pressure decreased significantly. Geometric mean ACR decreased during the first 2 years of follow-up but increased thereafter to above baseline by the third year.

Table 3—*Metabolic and blood pressure control and prevalence of diabetes complications during 4 years of annual follow-up* (n = 593)

Variable	Baseline	First review	Second review	Third review	Fourth review	Trend *P* value
BMI (kg/m^2)	29.4 ± 5.2	29.3 ± 5.1	29.1 ± 4.9‡	29.1 ± 5.2†	29.4 ± 5.2	0.21 (linear); <0.001 (quadratic)
Fasting plasma glucose: mmol/l (mg/dl)	8.2 [6.8–10.4] (148 [122–187])	8.3 [6.9–10.4] (149 [124–187])	8.7 [7.2–10.7]† (157 [130–193])	8.9 [7.4–10.9]‡ (160 [133–196])	8.8 [7.2–10.5]* (158 [130–189])	<0.001
HbA_{1c} (%)	7.2 [6.3–8.5]	6.9 [6.0–7.9]‡	7.0 [6.3–8.0]‡	7.1 [6.4–8.1]†	7.3 [6.5–8.2]	<0.001
Systolic blood pressure (mmHg)	148 ± 22	148 ± 22	148 ± 24	148 ± 24	148 ± 24	0.91 (linear); 0.79 (quadratic)
≥130 mmHg	84.6	82.4	78.9†	80.1†	77.4†	0.001
Diastolic blood pressure (mmHg)	81 ± 10	78 ± 11‡	77 ± 11‡	75 ± 12‡	73 ± 12‡	<0.001 (linear); 0.25 (quadratic)
≥80 mmHg	67.4	55.1‡	41.2‡	35.1‡	28.5‡	<0.001
Use of antihypertensive medication	47.6	51.9†	53.0‡	54.6‡	55.6‡	<0.001
ACE inhibitors	19.1	24.7‡	27.7‡	34.1‡	34.9‡	<0.001
β-Blockers	16.7	17.9	17.0	14.0	14.7	0.023
Calcium channel blockers	18.7	20.3	19.4	20.4	20.2	0.70
Total serum cholesterol: mmol/l (mg/dl)	5.5 ± 1.1 (213 ± 43)	5.5 ± 1.0* (213 ± 39)	5.6 ± 1.1* (217 ± 43)	5.5 ± 1.1 (213 ± 43)	5.4 ± 1.0 (209 ± 39)	0.043 (linear); <0.001 (quadratic) 0.024
≥5.0 mmol/l (194 mg/dl)	68.9	72.0	70.2	69.4	65.2	
HDL cholesterol: mmol/l (mg/dl)	1.06 ± 0.32 (41 ± 12)	1.09 ± 0.32‡ (42 ± 12)	1.11 ± 0.32‡ (43 ± 12)	1.14 ± 0.32‡ (44 ± 12)	1.19 ± 0.32‡ (46 ± 12)	<0.001 (linear); 0.016 (quadratic) <0.001
≤1.15 mmol/l (45 mg/dl)	67.2	66.5	61.6†	55.9‡	50.3‡	
LDL cholesterol: mmol/l (mg/dl)§	3.5 ± 0.9 (135 ± 35)	3.5 ± 0.9 (135 ± 35)	3.4 ± 0.9 (132 ± 35)	3.4 ± 0.9 (132 ± 35)	3.3 ± 0.9 (128 ± 35)‡	<0.001 (linear); 0.036 (quadratic) <0.001
≥2.6 mmol/l (101 mg/dl)	87.5	85.3	83.0†	80.3‡	77.2‡	
Serum triglycerides: mmol/l (mg/dl)	1.9 (1.1–3.3) (168 (97–292))	2.0 (1.2–3.4) (177 (106–301))	2.0 (1.2–3.4)† (177 (106–301))	1.9 (1.1–3.3) (168 (97–292))	1.8 (1.0–3.0)‡ (159 (89–266))	<0.001 (linear & quadratic)‖ <0.001
≥1.7 mmol/l (151 mg/dl)	60.1	60.7	62.7	61.4	52.9‡	
On lipid-lowering therapy¶	13.2	19.2‡	24.1‡	28.4‡	36.6‡	<0.001
Statins	8.1	13.0‡	18.5‡	24.5‡	32.0‡	<0.001
Fibrates	4.9	6.1	5.7	4.4	4.9	0.28
Urine albumin–to–urine creatinine ratio: mg/mmol (μg/mg)	2.5 (0.7–9.4) (22 (6–83))	2.4 (0.6–10.0)* (21 (5–88))	2.3 (0.5–11.4) (20 (4–101))	2.6 (0.5–12.8) (23 (4–113))	2.7 (0.5–14.2) (24 (4–126))	0.053 (linear); 0.003 (quadratic)‖
Serum creatinine (mmol/l)	86 ± 23	89 ± 22‡	95 ± 22‡	97 ± 28‡	99 ± 42‡	<0.001 (linear); 0.024 (quadratic) <0.001
Diabetes complications						
None	33.2	26.1	25.0	19.7	15.5	<0.001
Microvascular only	34.2	37.4	35.4	37.6	37.9	
Macrovascular only	12.6	12.0 ‡	10.8 ‡	9.9 ‡	8.6 ‡	
Both	19.9	24.5	28.8	32.7	37.9	

Data are means ± SD, geometric means (SD range), medians [interquartile range], or %. *$P < 0.05$ versus baseline; †$P < 0.01$ versus baseline; ‡$P < 0.001$ versus baseline (uncorrected for multiple comparisons); §LDL cholesterol was calculated using the Friedewald formula (not used when triglycerides ≥4.5 mmol/l [399 mg/dl; 5% of cases]); ‖tests for trend and between each review visit and baseline based on natural logarithm of serum triglycerides or urine albumin–to–urine creatinine ratio; ¶excluding statin and fibrate clinical trial participants from numerator.

Mean serum creatinine level increased steadily during the study period. Only 13% of patients were initially on lipid-lowering therapy, but this figure increased to 36% after 4 years as a result of increased statin prescription. The increase in mean HDL cholesterol level was highly significant. The mean total serum cholesterol and geometric mean serum triglyceride levels increased during the first 2 years after study entry before decreasing to below their respective baseline values by the end of follow-up.

The prevalence of diabetes complications increased during follow-up. The cost of diabetes-attributable non-BGL medications increased significantly as diabetes complication status worsened from no complications to both microvascular and macrovascular complications (within each year, trend $P < 0.001$). Annual costs incurred during follow-up for patients with no complications at baseline were A$44 (A$0–186; range A$23 [A$0–95] to A$64 [A$0–283]) compared with A$260 (A$122–412; range A$133 [A$59–214] to A$384 [A$178–605]) for patients with both microvascular and macrovascular complications. There was evidence of containment in diabetes-attributable hospital costs during the study period (trend $P > 0.56$); the total annual cost averaged A$179,626 (range A$108,583–250,669).

Cost distribution was skewed. In the first year, 43% of patients used no diabetes-related non-BGL medication, decreasing to 31% by study end. Diabetes-attributable non-BGL medication costs were therefore transformed by taking their square root ($\sqrt{}$cost) before further analysis. To be conservative, only results from the multivariate analysis of the lower diabetes-attributable cost estimates are presented. Similar results were found using the higher estimates.

Using forward stepwise multiple linear regression, the $\sqrt{}$cost/year of follow-up was significantly associated with, by order of entry into the model, the presence of CHD at study entry, baseline systolic blood pressure, total serum cholesterol level, ln(ACR), fasting plasma glucose level (negatively), male sex (negatively), serum creatinine level, ln(serum triglycerides), and education beyond primary level ($P \leq 0.043$). This model explained 29% of the variance in cost. Age; duration of diabetes; BMI; presence of retinopathy, neuropathy, or cerebrovascular disease at study entry; smoking status; alcohol consumption; exercise status; marital status; English ability; ethnic background; and calendar year of study entry were not independently associated with $\sqrt{}$cost/year.

The total annual cost of diabetes-attributable non-BGL medications for people aged ≥25 years diagnosed with type 2 diabetes projected to the Australian population in 2000 averaged A$79 million (range A$40–118 million), with no sex difference (Table 2).

CONCLUSIONS — The present study provides estimates of the use and cost of non-BGL medications for patients with type 2 diabetes collected from an Australian community-based cohort. We used prospective data from 593 patients followed for an average of 4 years to examine changes in this cost over time and its relationship to metabolic and blood pressure control. The median annual cost of diabetes-attributable non-BGL medications increased approximately fivefold over 4 years in our patients, due mainly to four- and twofold increases in the proportions treated with statins and ACE inhibitors, respectively. The main baseline predictors of diabetes-attributable non-BGL medication cost were the presence of systolic hypertension, CHD, dyslipidemia, and nephropathy. Patients with higher educational attainment had higher costs, which may reflect better access to health care and/or an awareness-driven demand for medications. Alternatively, this may be due to the confounding effect of patients from a Southern European background who were less well educated but were also less likely to have serum lipid profiles indicating eligibility for PBS-subsidized lipid-lowering therapy. Men had reduced costs, suggesting sex-related barriers to health care. Patients with higher fasting plasma glucose concentrations at baseline had lower costs, which seems paradoxical but may be an indicator of poor diabetes self-management.

Use of statins and antihypertensive medications (especially ACE inhibitors) increased progressively in our cohort. At the same time, there was *1*) a small but statistically significant reduction in total serum cholesterol, LDL cholesterol, and serum triglyceride levels and an increase in HDL cholesterol level; *2*) no improvement in systolic blood pressure; *3*) an increase in the prevalence of both microvascular and macrovascular complications; and *4*) a stabilization of hospital costs. Interpretation of these observations is difficult, especially because statins and ACE inhibitors may have pleiotropic effects on complications beyond lowering serum lipid levels and blood pressure, respectively (18). However, it is likely that more aggressive treatment of vascular risk factors slows the development and progression of chronic vascular complications and thus their severity, in turn decreasing inpatient admissions and hospital costs.

This is the first time in Australia that a cost-of-illness study of type 2 diabetes has been undertaken in a community setting using a bottom-up approach and attributable proportions methodology. We believe this is the first time within Australia and internationally that these costs have been reported longitudinally and related to potential explanatory variables at a patient level. The recently published DiabCost study (3) reported that the total cost of non-BGL prescription medications in 2002 for people with type 2 diabetes was A$1,108 per patient (or A$1,026 in year 2000). The disparity with the current study is due predominantly to the different costing methodologies (total versus diabetes attributable) but may also reflect increased prescription of non-BGL medications between the FDS recruitment period (1993–1996) and 2002. Indeed, the average annual total cost of non-BGL prescription medications at FDS study entry was only A$386 per patient. In the general Australian population, the number of prescriptions filled increased by 30% between 1995 and 2002 from 122 to 158 million, whereas the cost to the commonwealth government increased by 116% (19). Another factor may be that the longitudinal FDS cohort studied in this report comprised survivors and, therefore, may have required less non-BGL therapy. This is unlikely, however, because the average annual total cost of non-BGL prescription medications for the representative FDS baseline cohort of 1,294 patients with type 2 diabetes was similar (A$398).

The present study has limitations. The 593 patients with type 2 diabetes who returned annually for review were younger and healthier than the representative baseline cohort of 1,294 individuals. Therefore, these findings should be generalized with caution. Also, there may have been some misclassification of med-

ications, although all available data were used to establish likely indications. The major limitation of the costing of hospitalizations was the use of DRG costs, which, by definition, represent an average cost of all patients within a particular DRG and may, therefore, underestimate the true cost of hospitalization for a diabetic patient. Nevertheless, the same method was used for the whole study period so that confounding due to financial year and changing hospital reimbursement mechanisms was minimized.

The present study was conducted from April 1993 through June 2000, with recruitment extending over the first 3 years. During recruitment, the landmark trials 4S and CARE (20,21) reported that statin therapy significantly reduced the risk of secondary cardiovascular events in patients with CHD, whereas WOSCOPS showed a similar finding in hypercholesterolemic patients in a primary prevention setting (22). In 1998, the U.K. Prospective Diabetes Study reported that blood pressure reduction in hypertensive patients with type 2 diabetes lowered the risk of both microvascular and macrovascular complications (23). Dissemination of the results of these studies to primary care physicians may have been expected to increase non-BGL medication costs for later recruits, but there was no independent effect of calendar year on costs in our cohort.

With a prospective, patient-level approach, we were able to examine predictors of diabetes-attributable non-BGL medication cost. We have also shown that there is scope for more aggressive non-BGL treatment in our cohort. At study end, relative to recommended targets (24,25), more than three-quarters of patients had elevated systolic blood pressure and LDL cholesterol levels and more than half had increased serum triglycerides and low HDL cholesterol concentrations (Table 3). We found evidence that the direct costs of non-BGL treatment may be partly recovered by subsequent reductions in hospital costs. Reductions in indirect and intangible costs due to the prevention or delay of diabetes complications have not been addressed in this report but are likely to be considerable.

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