Published in final edited form as:

Curr Med Res Opin. 2006 November ; 22(11): 2301–2311.

The incremental costs of recommended therapy versus real world therapy in type 2 diabetes patients

C. Crivera^a, D. C. Suh^a, E. S. Huang^b, E. Cagliero^c, R. W. Grant^{d,e}, L. Vo^a, H. C. Shin^a, and J. B. Meigs^{d,f}

^a Ernest Mario School of Pharmacy, Rutgers University, Piscataway, NJ, USA

^b University of Chicago, Chicago, IL, USA

^c Diabetes Unit, Massachusetts General Hospital and Harvard Medical School Boston, MA, USA

^d General Medicine Division, Massachusetts General Hospital and Harvard Medical School Boston, MA, USA

^e Clinical Research Program, Massachusetts General Hospital and Harvard Medical School Boston, MA, USA

^f Department of Medicine, Massachusetts General Hospital and Harvard Medical School Boston, MA, USA

Abstract

Background—The goals of diabetes management have evolved over the past decade to become the attainment of near-normal glucose and cardiovascular risk factor levels. Improved metabolic control is achieved through optimized medication regimens, but costs specifically associated with such optimization have not been examined.

Objective—To estimate the incremental medication cost of providing optimal therapy to reach recommended goals versus actual therapy in patients with type 2 diabetes.

Methods—We randomly selected the charts of 601 type 2 diabetes patients receiving care from the outpatient clinics of Massachusetts General Hospital March 1, 1996–August 31, 1997 and abstracted clinical and medication data. We applied treatment algorithms based on 2004 clinical practice guidelines for hyperglycemia, hyperlipidemia, and hypertension to patients' current medication therapy to determine how current medication regimens could be improved to attain recommended treatment goals. Four clinicians and three pharmacists independently applied the algorithms and reached consensus on recommended therapies. Mean incremental medication costs, the cost differences between current and recommended therapies, per patient (expressed in 2004 dollars) were calculated with 95% bootstrap confidence intervals (CIs).

Results—Mean patient age was 65 years old, mean duration of diabetes was 7.7 years, 32% had ideal glucose control, 25% had ideal systolic blood pressure, and 24% had ideal low-density lipoprotein cholesterol. Care for these diabetes patients was similar to that observed in recent national studies. If treatment algorithm recommendations were applied, the average annual medication cost/patient would increase from \$1525 to \$2164. Annual incremental costs/patient increased by \$168 (95% CI \$133–\$206) for antihyperglycemic medications, \$75 (\$57–\$93) for antihypertensive medications, \$392 (\$354–\$434) for antihyperlipidemic medications, and \$3 (\$3–\$4) for aspirin prophylaxis. Yearly incremental cost of recommended laboratory testing ranged from \$77–\$189/patient.

Address for correspondence: James B. Meigs, MD, MPH, Assistant Professor of Medicine, General Medicine Division, Massachusetts General Hospital, 50 Staniford St, 9th Floor, Boston, MA 02114, USA. Tel.: +1-617-724-3203; Fax: +1-617-724-3544; email: jmeigs@partners.org.

Limitations—Although baseline data come from the clinics of a single academic institution, collected in 1997, the care of these diabetes patients was remarkably similar to care recently observed nationally. In addition, the data are dependent on the medical record and may not accurately reflect patients' actual experiences.

Conclusion—Average yearly incremental cost of optimizing drug regimens to achieve recommended treatment goals for type 2 diabetes was approximately \$600/patient. These results provide valuable input for assessing the cost-effectiveness of improving comprehensive diabetes care.

Keywords

Cardiovascular disease; Cost studies; Disease management; Health services research; Pharmacoepidemiology; Type 2 diabetes

Introduction

In 2002, \$91.8 billion direct diabetes medical expenditures included \$23.2 billion for diabetes preventive care, \$24.6 billion for chronic diabetes related complications, and \$44.1 billion for excess prevalence of general medical conditions^{1,2}. The most costly type of diabetes complication was cardiovascular, accounting for more than \$17.6 billion². Because of the substantial burden of cardiovascular disease, the emphasis of type 2 diabetes medical management has evolved over the past decade to include not only attainment of near-normal glucose levels but also the intensive management of cardiovascular risk factors such as dyslipidemia, hypertension, and smoking³. While tight glycemic control is important to forestall long-term microvascular complications, intensive control of blood pressure and cholesterol is essential to prevent cardiovascular macrovascular complications⁴. Multiple public health initiatives are underway to improve the delivery of diabetes care in the United States.

Each component of diabetes care has been found to be individually cost-effective for society^{5–8}. For the general population of diabetes patients, treating diabetes, treating hypertension, and treating hyperlipidemia are all cost-effective, based on the traditional incremental cost-effectiveness ratio of \$50 000/quality-adjusted life year (QALY). Less is known about the cost-effectiveness of improving diabetes care comprehensively, which requires accounting for the costs related to simultaneously addressing glucose control, blood pressure control, cholesterol control, and aspirin prophylaxis^{9–11}. Improvements in metabolic control are generally achieved through optimized medication regimens, but costs specifically associated with such optimization have not been examined. The costs of routine diabetes care are important determinants of diabetes cost-effectiveness analyses, and so understanding how much more it costs to improve routine diabetes treatments is essential if we are to understand the social value of multiple large-scale public investments in quality improvement. In this study, we assessed clinical characteristics, metabolic control, and actual medication regimens of a large cohort of type 2 patients in an academic medical center. We estimated incremental medication costs associated with changing medication regimens from actual to idealized care in order to move patients' metabolic control toward current recommended treatment goals.

Patients and methods

Patient selection and data collection

We retrospectively reviewed data from charts and computerized medical records of patients with type 2 diabetes receiving care in outpatient clinics of Massachusetts General Hospital. We randomly selected a subset of 1044 diabetes patients who had an ambulatory claim with

diagnostic code for diabetes (International Classification of Diseases, 9th edition [ICD-9] codes 250.00–250.90) between March 1, 1996 and August 31, 1997. Of these, we identified 789 patients with available records for chart abstraction by trained research nurses (Figure 1)⁹. The distribution of age, sex, race, and insurance status comparing the 789 patients with medical records with the 255 without records were similar (all $p > 0.05$) indicating that the sample study was representative of the background random sample. Abstracted data included the most recent values recorded for glycosylated hemoglobin, systolic blood pressure (SBP), low-density lipoprotein (LDL), and current medications. The study was approved by the Partners/Massachusetts General Hospital Human Research Committee.

Type 2 diagnosis was verified from claims either by physician documentation in the medical chart, or by documentation of insulin or oral hypoglycemic medicines on the medicine list. Patients were excluded for the following reasons: (1) diagnoses were made after March 1, 1996 ($n = 86$); (2) diagnosis could not be confirmed by chart review ($n = 74$); (3) the patient had type 1 diabetes ($n = 23$); or (4) the patient had secondary causes of hyperglycemia (e.g., high-dose glucocorticoid use or alcohol-induced pancreatic insufficiency) ($n = 5$). A total of 601 patients met the inclusion/exclusion criteria⁹.

Recommended treatment algorithms

We developed treatment algorithms for glucose, blood pressure, cholesterol control, and aspirin prophylaxis to hypothetically change current medical therapy to ideal medical therapy, based on current metabolic control and the presence of comorbidities and complications (Table 1). Treatment algorithms were based on 2004 practice recommendations^{12–15} and agreed upon by a study panel of four independent physicians and three pharmacists (the authors of this paper).

Treatment recommendations were based on the following treatment goals: (1) glycosylated hemoglobin (HbA_{1c}) $< 7\%$; (2) LDL-cholesterol < 100 mg/dL; (3) high-density lipoprotein (HDL)-cholesterol > 40 mg/dL; (4) triglycerides (TG) < 150 mg/dL; and (5) blood pressure $< 130/80$ mmHg^{9,10,12,13,16,17}. In addition, all patients were recommended to receive low dose 81 mg aspirin.

Recommended medication dosages

We first classified the dosing of current medications as follows: (1) initial dose; (2) intermediate dose; and (3) maximum dose, after reviewing each patient's current metabolic control, and applied our algorithms to determine the changes in medication therapies needed to move patients toward recommended treatment goals^{18,19}. These medication changes were hypothetical – no actual clinical changes for patients were made in this study. We then determined the type of change that each medication in the patient's regimen underwent. The changes that were applied were: (1) no change; (2) increase dose; (3) add new medication without discontinuation of current medication; (4) add new medication and discontinue one medication; (5) add new medication and discontinue more than one medication; and (6) no recommendation due to missing information.

Therapy algorithm for glucose control

First line therapy for a patient not on any glucose control medication and HbA_{1c} level $> 7\%$ was metformin 500 mg twice daily. If a patient was on metformin or sulfonylurea and had a HbA_{1c} between 7–9%, the dose of the agent was doubled, but if the HbA_{1c} was above 9%, the dose of the agent was maximized or another agent was added if the current agent was already at maximum dose. If a patient had $HbA_{1c} > 7\%$ despite maximum doses of both metformin and a sulfonylurea, these two oral medications were discontinued and NPH insulin 0.2 U/kg was initiated. If a patient was taking less than 150 daily units of NPH, lente, 70/30, or ultralente

insulin and the HbA_{1c} was 7–9%, the dose of insulin was increased by 50%. If HbA_{1c} > 9% and the insulin dose was less than 150 U/d, the dose of insulin was doubled. If a patient was taking between 150 and 200 daily units of NPH, lente, 70/30, or ultralente insulin, rosiglitazone 2 mg/day was added. Type 2 diabetics on regular insulin were continued on the same dose regardless of HbA_{1c} value. HbA_{1c}, microalbumin (urine), and serum creatinine lab tests were hypothetically ordered for patients who had missing values.

Therapy algorithm for blood pressure control

If a patient was not at goal blood pressure level despite being on antihypertensive medicine, the dose of the current medication was doubled. If the maximum dose of the first agent was already reached, a new medication was added. When a new medication was added, we determined which antihypertensive class would be added based on the following sequence: (1) hydrochlorothiazide (HCTZ); (2) angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor antagonist (ARB); (3) beta blocker (BB); (4) calcium channel blocker (CCB); (5) antiadrenergic agent. If a patient was already on the second-step medication without having the first-step medication, the first-step medication was first added before the addition of the third-step medication. The developed algorithms were consistent with practical implementation based on JNC-7 guidelines¹⁵. For patients with gout, hydrochlorothiazide was contra-indicated; however, if a gout patient was already on a thiazide, the thiazide was continued. The ACE inhibitor of choice was lisinopril, starting at 5 mg/day; the BB of choice was atenolol (25 mg/day); the CCB of choice was amlodipine (2.5 mg/day); and the antiadrenergic agent of choice was clonidine (0.05 mg twice daily).

Therapy algorithm for lipid control

We made the assumption that patients with LDL-cholesterol >100 mg/dL had already completed Step 1 and Step 2 diet therapy along with at least 6 months of exercise, thus requiring pharmacotherapy¹⁴. Primary therapy was directed first at lowering LDL-cholesterol levels (goal LDL < 100)¹². If a patient was not on statin therapy, fluvastatin 20 mg daily was first line therapy when LDL-cholesterol was 100–129 mg/dL, and atorvastatin 10 mg daily was first line therapy for LDL ≥ 130. If a patient was already on statin therapy and LDL-cholesterol > 100 mg/dL, the dose of the existing statin was maximized.

If the HDL-cholesterol and TG were within normal limits, but the LDL-cholesterol was >100 mg/dL despite maximum doses of a statin, Questran 4 g three times daily was added. If a patient had an ideal LDL-cholesterol level but HDL < 40 mg/dL or TG > 150 mg/dL, gemfibrozil 600 mg twice daily was initiated. If a patient was already on a maximum dose of a statin and had poor control of LDL-cholesterol, HDL-cholesterol, or TG, gemfibrozil 600 mg twice daily was added. If a patient continued to have poor control of cholesterol despite a combination of a statin and gemfibrozil, both at maximum doses, niacin 500 mg three times daily was added.

Costs of medication and laboratory tests

Costs of current and recommended medications were calculated using the 1997 Average Wholesale prices (AWPs) derived from the 1998 Redbook²⁰. The 1997 prices were selected and reflected prescribing patterns at the time of data collection, taking into consideration the patent status of medications (i.e., some of the medications that were patented in 1997 are no longer patented). Since prices varied for individual medications, three different AWPs were used for each substance – the lowest generic price, highest generic price, and originator price (price of the patented drug medication). If the generic version of the medication was not yet available, the originator AWP alone was used. If more than one originator with different prices existed, the average of the AWPs for these multiple originators was used. AWPs were based on the package size of 100 tablets. Daily insulin cost was based on the price of insulin bottle divided by the total insulin units and then multiplied by the daily-required insulin units.

Costs of current and recommended laboratory tests were calculated using prices charged by the Massachusetts General Hospital in 1997 (i.e., lipid panel = \$74, urine microalbumin = \$24, blood glucose = \$13, blood creatinine = \$11, and HbA_{1c} = \$37). Yearly laboratory costs were calculated based on test frequencies recommended by the study panel (2–4 times for HbA_{1c}, 1–2 times for lipid profile, one time for creatinine, and one time for microalbumin). The 1997 prices of medication and laboratory tests were inflated to the 2004 prices using the prescription and medical care service price indexes accordingly.

Statistical analysis

Daily medication cost per patient was calculated for the two assumptions that the lowest price generic or the highest price of original brand name drug was used, and then projected to a yearly medication cost per patient. Incremental drug therapy cost per patient was calculated by taking the difference in drug costs from current to hypothetical optimized therapies based on our study treatment algorithms. Mean incremental cost per patient was presented with 95% confidence intervals (CIs) calculated by the bootstrap method²¹. Bootstrap method yields CIs robust to the form of the underlying distribution of cost differences from small samples^{21, 22}.

Analysis of covariance was performed to test the differences in incremental costs between stratified study groups after adjusting for baseline costs, and Tukey's HSD test was used for the post-comparisons between the mean incremental costs of the study groups²³. Paired *t*-tests were used to determine whether medication costs of the recommended therapy were significantly different from those of current therapy. We considered a *p*-value of 0.05 to reflect statistical significance. All analyses were performed using SAS version 8.2²⁴.

Results

Characteristics of diabetic patients and current care

The patients whose charts were retrospectively reviewed were on average 65 years old (median age was 66 years), predominantly men (58%) and white (82%) (Table 2). Thirty-six percent received medical coverage from Medicare and 27% had health coverage with a Health Maintenance Organization. The average duration of diabetes diagnosis was 7.65 years, with half having had diabetes for more than 5 years. The most common diabetes-related complications were neuropathy (31%) and retinopathy (22%). At baseline, only 2.7% had ideal control level for glucose, systolic blood pressure, and LDL-cholesterol, and only 32% had ideal glucose control. Twenty-five percent had ideal systolic blood pressure, 24% had ideal LDL-cholesterol, and only 38% were taking aspirin.

Recommendations and costs for comprehensive diabetes care

Currently prescribed antihyperglycemic, antihypertensive, and antihyperlipidemic medications were most commonly used at the intermediate dose, followed by the initial dose (Table 3). Patients were treated with an average of 3.16 medications.

Upon application of the algorithm, almost all patients (98%) were recommended to have changes in some component of diabetes care. Among patients who were recommended to have a change in therapy, 83% of patients had a dose increase in one of their medications, 78% had at least one new medication added, and 4% discontinued one of their current medications. The most common recommendations for antihyperglycemic and antihypertensive medications were either to continue at the current medication(s) dose or increase current medication dosage. For antihyperlipidemic medications, addition of a new medication represented more than half of recommended therapy changes, followed by an increase of current medication.

The cost of current medication therapy ranged from \$1525–\$1999, and the cost of recommended medication therapy ranged from \$2164–\$2884, depending on whether generic or brand name prices were utilized. As a result, the yearly incremental increase in medication costs of recommended therapy ranged from \$639 to \$884 per patient (Table 4). Increasing age did not have a consistent association with incremental medication costs.

Recommended changes and costs by medication therapy

To characterize the movement of patients from current care to recommended care in more detail, we stratified incremental medication costs based on the number of medications a patient was on prior to intensification (Table 5). Most antihyperglycemic regimens were administered as monotherapy and most of these patients were recommended to remain on monotherapy. About 13% of diabetic patients did not take any antihyperglycemic medications and 23% of these patients were recommended to take antihyperglycemics. Approximately 60% of patients who were not taking any antihypertensive medications were recommended to initiate hypertension therapy. Antihyperlipidemic medications were recommended for 50% of patients who were not taking any medications of this class. Notably, the average medication cost for patients who used ≥ 3 drug combinations actually decreased because of the selection of alternative medications or discontinuation of current medications. Average annual incremental cost per patient would be \$3 for aspirin, \$168 for antihyperglycemic medications, \$75 for antihypertensive medications, and \$392 for antihyperlipidemic medications.

Laboratory costs

Current annual rates of laboratory testing were 1.7 tests/year for serum creatinine, 0.7 for HbA_{1c}, 0.4 for lipid profile, and 0.01 for microalbumin. Total costs for current laboratory testing were \$82 (95% CI \$76–\$88) per year. If a patient had tests based on the test frequencies recommended by the study panel, yearly laboratory costs would have ranged from \$158 to \$271 depending on the assumption about the number of lab tests per year. Thus, the incremental costs of recommended laboratory testing ranged from \$77 (95% CI \$71–\$83) to \$189 (95% CI \$183–\$195) per year.

Discussion

In this analysis, the additional medication and laboratory costs of comprehensively improving diabetes management were estimated for patients receiving care at a large academic medical center. At baseline, more than half of the patients had metabolic control values exceeding recommended goals; two-thirds of the patients had a HbA_{1c} $\geq 7\%$, three-quarters had a SBP ≥ 130 mmHg, and half had an LDL ≥ 100 mg/dL. Although the clinical data were collected ending in 1997, these rates are comparable to the quality of care reported more recently (e.g., between 1999–2000, 63% of the patients had HbA_{1c} $\geq 7\%$, 64% had a SBP ≥ 130 mmHg, and 48% had total cholesterol <200 mg/dL) so remain relevant for clinical and policy decisions in 2006^{25,26}. Using a clinically reasonable medication titration algorithm intended to move patient metabolic control toward current national guidelines, we found that the mean number of total medications would increase from 3.16 to 4.36 per patient. We estimated that these medication prescription changes would have resulted in an average annual medication cost increase of \$639, (from \$1525 at baseline to \$2164, if generic agents are used). The average annual incremental cost would be \$3 for aspirin, \$168 for antihyperglycemic medications, \$75 for antihypertensive medications, and \$392 for antihyperlipidemic medications.

These results provide clinicians, payers, health plans, and other healthcare decision makers valuable economic data abstracted from ‘real world’ clinical conditions. An in-depth examination of these incremental costs per patient, and the choices that affect them, are crucial in light of the large-scale disease management initiative that the Center for Medicare and

Medicaid Services (CMS) began in early 2006²⁷. The hope behind such quality improvement initiatives is to improve diabetes care, reduce rates of diabetes complications, and consequently reduce the costs of diabetes-related complications. The study demonstrates that the yearly incremental medication for improving diabetes care ranged from \$600 to \$900 per patient, depending on metabolic control at baseline and whether generics or brand-name drugs were utilized. Our study also illustrates how the distinct components of diabetes care vary widely in their incremental cost increases per patient (i.e., addition of a daily aspirin to patients' profiles was associated with a miniscule incremental cost). These numbers are helpful for communicating with patients who may want to know the additional costs of ideal diabetes care.

This study also provides a valuable cost input that may be used in future cost-effectiveness analysis and our results suggest that therapy in those patients can be optimized with a small incremental treatment cost. Prior cost-effectiveness analyses, such as work conducted by the Centers for Disease Control, Prevention Diabetes Cost-Effectiveness Study Group⁵, and by Eastman *et al.*⁶, have all assessed individual components of diabetes care and relied heavily on cost data from clinical trials. There are very few studies that attempt to assess the cost-effectiveness of improving diabetes care comprehensively and unfortunately data on the costs improving treatments are not routinely estimated in quality improvement studies²⁸. The results help to fill this gap. The findings should be considered with the following limitations. The major limitation of this study is that the baseline data come from the clinics of a single academic institution, collected in 1997, and therefore the characteristics of the patients may not be representative of the entire diabetic population. Despite these concerns, the care of these diabetes patients is surprisingly similar to care currently observed nationally. In particular, national studies of diabetes care trends indicate that the proportion of people who have uncontrolled blood glucose, blood pressure, and lipid levels have remained high over the years, despite the introduction of new therapeutic agents and improved disease management strategies^{25,26,29,30}. In addition, we employed a single treatment algorithm used by diabetologists at the Massachusetts General Hospital and there is not one universally agreed upon algorithm for intensifying care in diabetes. While algorithms for intensifying diabetes care may vary, we suspect that these differences would be unlikely to dramatically alter our main conclusions.

The study is also limited in that our knowledge of prior contraindications was dependent entirely on the medical record, which may not accurately reflect patients' actual experiences. The medication adjustments were also based on current metabolic control and current medication regimen. Since patients were not followed forward over time, this study evaluated only one step in the progression of disease management, and one round of medication adjustment would be unlikely to move all patients from current to ideal metabolic control. Thus, our analysis probably underestimates the true cost of an ideal medication and laboratory testing panel for a typical type 2 diabetes patient. Finally, this hypothetical exercise in medication management for this subset of patients does not take into account the varied barriers to effective care presented by individual patients. These barriers may include medication non-adherence, financial constraints, limited access to care, and significant co-morbidities such as depression³¹.

Conclusion

The yearly incremental cost in medications and laboratory testing, intended to move type 2 diabetes patients from real-world current metabolic control to 'ideal' treatment, was under \$1000 per patient. Although a direct estimate of the cost-effectiveness of these changes is not provided, the modest cost increases may be small relative to the anticipated health benefits of improving diabetes treatment comprehensively. Enhanced diabetes treatment rising costs are important to consider in light of concerns regarding unmanageable health care cost increases

borne by patients, especially by elderly or disabled patients, and society. The federal government is already undertaking efforts to help older patients cover costs of medications via the Medicare Prescription Drug, Improvement, and Modernization Act, but has also implemented large-scale CMS initiatives to examine the financial and health benefits of disease management and quality improvement. The results of these initiatives will help demonstrate whether or not these incremental cost inputs of improved care are as worthwhile as anticipated.

Acknowledgements

Declaration of interest: This research was funded by Aventis Pharmaceuticals, Health Outcomes by an unrestricted research grant from Aventis, the National Pharmaceutical Council, and the MGH Primary Care Operations Improvement and Clinical Research Programs. Dr.Huang is supported by NIA Career Development Award (K23 AG021963-01A1). Dr.Crivera is an employee of Ortho -McNeil Janssen. Dr.Grant is supported by NIDDK Career Development Award (K23 DK067452-01A1). Dr.Meigs is supported in part by American Diabetes Association Career Development Award.

References

1. American Diabetes Association: economic consequences of diabetes mellitus in the US in 1997 Diabetes Care 1998;21:296–309.
2. American Diabetes Association: economic Costs of Diabetes in the US in 2002 Diabetes Care 2003;26:917–32.
3. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. Diabetes Care 1999;22(Suppl 1):S32–41.
4. Huang ES, Meigs JB, Singer DE. The effect of interventions to prevent cardiovascular disease in patients with type 2 diabetes mellitus. Am J Med 2001;111:633–42. [PubMed: 11755507]
5. CDC Diabetes Cost-Effectiveness Study Group, Centers for Disease Control and Prevention. The cost-effectiveness of screening for type 2 diabetes JAMA 1998;280:1757–63.
6. Eastman RC, Javitt JC, Herman WH, et al. Model of complications of NIDDM. II Analysis of the health benefits and cost-effectiveness of treating NIDDM with the goal of normoglycemia. Diabetes Care 1997;20:735–44. [PubMed: 9135935]
7. The CDC Diabetes Cost-effectiveness Group. Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction, for type 2 diabetes. JAMA 2002;287:2542–51. [PubMed: 12020335]
8. UK. Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–53. [PubMed: 9742976]
9. Grant R, Cagliero E, Murphy-Sheehy P. Comparison of hyperglycemia, hypertension and hypercholesterolemia management in patients with type 2 diabetes. Am J Med 2002;112:603–9. [PubMed: 12034408]
10. Bell DS. Current status of diabetes treatment. South Med J 2002;95:24–9. [PubMed: 11829012]
11. Leibovitz H. Oral therapies for diabetic hyperglycemia. Endocrinol Metab Clin North Am 2001;30:909–33. [PubMed: 11727405]
12. American Diabetes Association. Clinical practice recommendations 2004. Diabetes Care 2004;27 (Suppl 1):S1–134.
13. American Diabetes Association. Clinical practice recommendations 1998. Diabetes Care 1998;21 (Suppl 1):S1–98.
14. National Heart Lung and Blood Institute. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Bethesda, MD: National Institute of Health; 2001.
15. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure – the JNC 7 report. JAMA 2003;289:2560–72. [PubMed: 12748199]
16. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. Diabetes Care 2002;25(Suppl 1):S33–49.

17. Mooradian AD. Cardiovascular disease in type 2 diabetes mellitus (current management guidelines). *Arch Intern Med* 2003;163:33–40. [PubMed: 12523914]
18. American Society of Health-System Pharmacists. American hospital formulary service drug information. Bethesda, MD: American Society of Health-System Pharmacists; 2002.
19. Facts and comparisons. Drug facts and comparisons. 58. St. Louis: Facts and comparisons; 2003.
20. Medical Economics Co. Red Book. Montvale: Medical Economics Co; 1998.
21. Efron, B.; Tibshirani, RJ. An introduction to the bootstrap. Boca Raton: Chapman and Hall/CRC; 1993.
22. O'Hagan A, Stevens JW. Assessing and comparing costs: how robust are the bootstrap and methods based on asymptotic normality? *Health Econ* 2003;12:33–49. [PubMed: 12483759]
23. Rosner, B. Fundamentals of Biostatistics. 5. Belmont CA: Duxbury Press; 2000.
24. SAS Institute Inc. The SAS system release 8.2. Cary, NC: SAS Institute;
25. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA* 2004;291:335–42. [PubMed: 14734596]
26. Koro CE, Bowlin SJ, Bourgeois N, et al. Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes. *Diabetes Care* 2004;27:17–20. [PubMed: 14693960]
27. Casalino LP. Disease management and the organization of physician practice. *JAMA* 2005;293:485–8. [PubMed: 15671434]
28. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;348:383–93. [PubMed: 12556541]
29. Cohen FJ, Neslusan CA, Conklin JE, et al. Recent anti-hyperglycemic prescribing trends for U.S. privately insured patients with type 2 diabetes. *Diabetes Care* 2003;26:1847–51. [PubMed: 12766121]
30. Nau DP, Garber MC, Herman WH. The intensification of drug therapy for diabetes and its complications: evidence from 2 HMOs. *Am J Manag Care* 2004;10:118–23. [PubMed: 15005503]
31. Grant RW, Devita NG, Singer DE, et al. Polypharmacy and medication adherence in patients with type 2 diabetes. *Diabetes Care* 2003;26:1408–12. [PubMed: 12716797]

Figure 1.
Study patient selection procedure

Table 1

Treatment recommendations (e.g., for patients whose clinical values are out of the recommended values and did not receive any medications)

Disease state	Treatment goals	Recommended treatment
Glycemic control ^{12,13}	HbA _{1c} < 7%	Add metformin 500 mg twice daily
Cholesterol control ¹⁴	LDL-cholesterol < 100 mg/dL	If LDL 101–130, add Lescol 20 mg daily
		If LDL > 130, add Lipitor 10 mg daily
	HDL-cholesterol > 40 mg/dL	Add gemfibrozil 600 mg twice daily
	TG < 150 mg/dL	Add gemfibrozil 600 mg twice daily
Blood pressure control ¹⁵	BP < 130/80 mmHg	Add HCTZ 12.5 mg daily

HbA_{1c} = glycosylated hemoglobin; LDL = low-density lipoprotein; HDL = high-density lipoprotein; TG = triglyceride; BP = blood pressure; HCTZ = hydrochlorothiazide

Table 2

Characteristics of study patients

Characteristics	Diabetes patients (N = 601)	
	n	(%)
Age, mean $\pm$ SD, years	64.7 $\pm$ 12	
< 55	126	(21)
55–64	148	(25)
65–74	197	(33)
> 74	130	(22)
Female	250	(42)
Race		
White	494	(82)
Black	78	(13)
Other	29	(5)
Insurance		
Fee-for-service	110	(18)
Health maintenance organizations	163	(27)
Medicaid	37	(6)
Medicare	218	(36)
Out of pocket	51	(8)
Blood pressure, mean $\pm$ SD (N = 597)	138.07 $\pm$ 18.62	
Patients with SBP < 130 mmHg	152	(25)
LDL-cholesterol, mean $\pm$ SD (N = 395)	125.98 $\pm$ 37.76	
Patients with LDL < 100 mg/dL	93	(24)
HbA _{1c} , mean $\pm$ SD (N = 552)	8.07 $\pm$ 1.76	
Patients with HbA _{1c} < 7%	174	(32)
Patients using aspirin	230	(38)
Duration of diabetes diagnosis, mean $\pm$ SD, years	7.65 $\pm$ 7.01	
0–1	99	(16)
2–5	201	(33)
6–10	148	(25)
$\geq$ 11	153	(25)
Comorbidities		
Hypertension	439	(73)
Hyperlipidemia	295	(49)
Complications		
Neuropathy	189	(31)
Retinopathy	135	(22)
Nephropathy	72	(12)
Foot ulcers	56	(9)
Amputation	15	(2)

SD = standard deviation; SBP = systolic blood pressure; LDL = low-density lipoprotein; HbA_{1c} = glycosylated hemoglobin

Table 3
Patterns of current medication dosage and recommended therapy by medication therapeutic class

Current therapy	Overall medications	Antihyperglycemic medications	Antihypertensive medications	Antihyperlipidemic medications
Patients who used medications, <i>n</i>	582	520	428	200
Medications per patient, mean $\pm$ SD, <i>n</i>	3.16 $\pm$ 1.62	1.17 $\pm$ 0.69	1.25 $\pm$ 1.04	0.36 $\pm$ 0.55
Classification of individual medication dosages, <i>n</i> (%)				
Total number of medications	1901 (100)	704 (100)	750 (100)	216 (100)
Initial dose	818 (43)	221 (31)	268 (36)	99 (46)
Intermediate dose	903 (48)	429 (61)	372 (50)	101 (47)
Maximum dose	180 (9)	54 (8)	110 (15)	16 (7)
Recommended therapy				
Patients who used medications, <i>n</i>	601	539	533	398
Medications per patient, mean $\pm$ SD	4.36 $\pm$ 1.38	1.22 $\pm$ 0.68	1.46 $\pm$ 0.90	0.75 $\pm$ 0.61
Patients with changes in current regimen, <i>n</i> (%)	589 (98)	378 (70)	464 (87)	368 (92)
Patients without changes in current regimen, <i>n</i> (%)	12 (2)	161 (30)	69 (13)	30 (8)
Types of recommendations for medications, <i>n</i> (%)				
Total number of medications	2621 (100)	734 (100)	877 (100)	453 (100)
No change in medication	1054 (40)	339 (46)	408 (47)	85 (19)
Increased dose in existing medications only	800 (31)	335 (46)	336 (38)	126 (28)
Addition of new medications without discontinuing any medications	745 (28)	38 (5)	133 (15)	242 (53)
Addition of new medications with discontinuation of any medication	22 (1)	22 (3)	0 (0)	0 (0)

Table 4

Yearly drug costs per patient

	Current drug costs		Recommended drug costs		Incremental drug costs			
	Lowest generic		Lowest generic		Lowest generic		Brand name	
	Mean	Brand name	Mean	Brand name	Mean	Brand name	Mean	Brand name
All patients	\$1525		\$2164		\$639		\$884	
Age, years								
<55	\$1454		\$2115		\$662		\$835	
55–64	\$1729		\$2447		\$718		\$973	
65–74	\$1633		\$2270		\$637		\$907	
>74	\$1200		\$1728		\$529		\$798	
Gender								
Male	\$1596		\$2175		\$579		\$821	
Female	\$1426		\$2149		\$723		\$973	
Medications used *								
Aspirin	\$1		\$5		\$3		\$14	
	\$587		\$755		\$168		\$192	
Antihyperglycemics								
Antihypertensives	\$531		\$606		\$75		\$150	
	\$406		\$798		\$392		\$528	
Antihyperlipidemics								

* The costs represent medication costs of therapeutic class (e.g. antihyperglycemic medication) per patient

† The incremental costs are significantly different between study groups stratified by gender at the significance level of 0.05

‡ The incremental costs are significantly different between current and recommended therapy at the significance level of 0.01 CI = confidence interval

Table 5

Yearly incremental drug costs from current drug to recommended therapy

From: current therapy	Patients, <i>n</i>	To: recommended therapy									
		No drug		Monotherapy		2 drug combinations		≥ 3 drug combinations		Brand name	Brand name
		<i>n</i>	All cases*	<i>n</i>	Lowest generic	<i>n</i>	Lowest generic	<i>n</i>	Lowest generic		
Antihyperglycemic medication(s)											
No medication	81	62	\$0	19	\$477	—	—	—	—	—	—
Monotherapy	419	—	—	405	\$214	14	\$446	—	—	\$453	—
2 drug combinations	95	—	—	5	−\$1396	88	\$75	—	—	\$97	\$712
≥ 3 drug combinations	6	—	—	—	—	—	—	—	—	—	−\$276
Sub-total	601	62	\$0	429	\$206	102	\$126	—	—	\$146	−\$29
Antihypertensive medication(s)											
No medication	173	68	\$0	105	\$11	—	—	—	—	—	—
Monotherapy	192	—	—	174	\$149	18	−\$9	—	—	\$19	—
2 drug combinations	165	—	—	—	—	158	\$99	—	—	\$201	\$265
≥ 3 drug combinations	71	—	—	—	—	1	−\$977	—	—	−\$1084	\$147
Sub-total	601	68	\$0	279	\$97	177	\$82	—	—	\$176	\$157
Antihyperlipidemic medication(s)											
No medication	401	203	\$0	198	\$670	—	—	—	—	—	—
Monotherapy	187	—	—	147	\$574	40	\$384	—	—	\$1282	—
2 drug combinations	11	—	—	—	—	11	\$459	—	—	\$559	—
≥ 3 drug combinations	2	—	—	—	—	—	—	—	—	—	−\$874
Sub-total	601	203	\$0	345	\$629	51	\$400	—	—	\$1126	−\$736

* Incremental cost is zero when no medication is recommended for patients who are not taking any medications

Other cells are blank because there are no patients who are recommended to discontinue all of their current medications