The Influence of Insulin Use on Glycemic Control

How well do adults follow prescriptions for insulin?

JOYCE A. CRAMER[1]
MARY JO PUGH, PHD[2,3]

OBJECTIVE — The purposes of this study were to determine the relationship between insulin self-management and glycemic control and to identify patient characteristics associated with better control.

RESEARCH DESIGN AND METHODS — A Department of Veterans Affairs regional database was used to identify patients with diabetes on chronic insulin therapy ($n = 6,222$) with dose defined as number of units and doses. The rate of insulin use during a 2-year period was calculated using pharmacy data. Regression analyses were used *1*) to predict compliance with prescribed insulin regimens using demographic variables, HbA_{1c} levels, and a measure of diabetes management intensity and 2) to predict HbA_{1c} levels using demographic variables and rates of insulin use.

RESULTS — Insulin use was 77.44 ± 17% of prescribed amounts, including wastage; HbA_{1c} levels were 7.98 ± 1.66%. Concomitant oral hypoglycemic agent use (84.89 ± 16%) was higher than insulin use ($P < 0.0001$) but correlated with insulin use ($r = 0.189$, $P < 0.0001$). Ordinary least-squares regression showed that race, HbA_{1c} levels, and intensity of diabetes management were significant predictors of insulin use. Age, race, and insulin use were significant predictors of HbA_{1c} levels.

CONCLUSIONS — Adults prescribed a specific insulin regimen averaged using 77% of prescribed doses, demonstrating good intention to follow the prescription. However, HbA_{1c} higher than the recommended level suggested that the rate of insulin use, the prescribed regimen, or both were inadequate to achieve good glycemic control in patients with long-term insulin use.

Diabetes Care **28:78–83, 2005**

Although the initial treatment in most individuals with type 2 diabetes is an oral hypoglycemic agent (OHA), the progression to insulin is common (28–39% incidence among older men) (1). Insulin may be added to or substitute for an OHA to achieve adequate glycemic control. Regimens range from one to four daily doses (or more), depending on whether an individual can manage with conventional dosing or requires intensive therapy. Despite extensive prescribing of insulin, many patients fail to achieve goals for glycemic control based on HbA_{1c} levels (2).

Numerous barriers to use of insulin have been described (e.g., fear of injections and hypoglycemic events, burden of injections, timing in relation to meals, etc.) (3,4). OHA dosing has been studied by observation with electronic monitors and by prescription refill records, showing that patients take 67–85% of OHAs as prescribed (5). Assessing whether patients follow prescribed insulin regimens is more complicated than assessment of OHA because of the inability to monitor injections and the units needed for each dose and the wastage when filling syringes (6). The effectiveness of insulin treatment may be assessed using an administrative database of prescription records to define the amount of insulin dispensed to patients and laboratory data listing HbA_{1c} levels. These two objective measures can be used to evaluate how well physicians are managing patient's glycemic control. Morris et al. (7) used prescription records in Tayside, Scotland, to determine how much insulin was obtained for use by children and adolescents as a surrogate for insulin self-management. The age of this cohort indicates a preponderance of patients with type 1 diabetes, most of whom probably were responsible for their own injections. They demonstrated a relationship between the amount of insulin obtained and HbA_{1c} levels, adverse events, and hospitalizations. A study of adult type 2 diabetes patients used a health insurance database in the U.S. to determine that patients obtained 63 ± 24% of insulin refills (8).

We proposed to extend these assessments by reviewing the use of insulin by adults followed at Department of Veterans Affairs Medical Centers. We hypothesized that patients who took insulin regularly, as prescribed, would have bet-

From the [1]Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut; the [2]Center for Health Quality, Outcomes, and Economic Research, VA Medical Center, Bedford, Massachusetts; and the [3]Boston University School of Public Health, Boston, Massachusetts.

Address correspondence and reprint requests to Joyce A. Cramer, Yale University School of Medicine, 950 Campbell Ave. (Room 7-127, G7E), West Haven, CT 06516-2770. E-mail: joyce.cramer@yale.edu.

Received for publication 28 July 2004 and accepted in revised form 13 September 2004.

J.A.C. is a member of an advisory board for, serves as a consultant to, and has received honoraria from Novo Nordisk.

M.J.P. is currently affiliated with the Audie L. Murphy VA Hospital, San Antonio, Texas, and was with the Edith Nourse Rogers VA Hospital in Bedford, Massachusetts, during this project.

The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

Abbreviations: OHA, oral hypoglycemic agent.

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

ter glycemic control as measured by HbA_{1c}. These analyses also were designed to identify patient characteristics associated with better outcomes.

RESEARCH DESIGN AND METHODS

— Our population included patients from 12 Veterans Administration medical facilities (eastern U.S. and Puerto Rico) in 2001. We identified patients with two diagnoses of diabetes (International Classification of Diseases, 9th revision, Clinical Modification codes 250.00–250.93 for type 2 diabetes with or without comorbidities) using inpatient or outpatient records, made on two or more occasions (at least 7 days apart). We further selected those receiving insulin with or without concomitant OHA. Outpatient pharmacy data from the Veterans Administration Pharmacy Benefits Management prescription database (2001–2002) were used to assess prescriptions (9). Available data included patient identifier, date dispensed, drug information (drug, dose per unit, route of administration), dosing instructions (as units per day or as needed), days supply (number of days of medications received), and total quantity (number of units) dispensed. These variables allowed determination of the regimen and the duration and stability of regimens in continuous use, as well as concomitant use of insulin with OHA. Analysis methods met Health Insurance Portability and Accountability Act of 1996 requirements for patient privacy (10). All prescription data were "de-identified" but had a unique patient identification number (externally generated) to allow for longitudinal and multiproduct analysis at the individual patient level.

We identified those patients receiving a prescription for any type of insulin with or without OHA during July 2001; insulin dose was defined as the number of units and doses. Medication regimens were classified as insulin-only and OHA-insulin combinations. Use of multiple forms of insulin (e.g., regular and NPH) and multiple OHA were identified. Patients receiving at least one prescription for insulin between 1 January 2001 and 1 July 2001 were selected for the chronic insulin use sample. Patients who did not receive insulin during the 6 months before 1 July 2001 were identified as "new" insulin users and were excluded from most analyses.

Using data only for patients whose prescriptions were defined with specific dosing instructions, we calculated medication use (compliance score) using pharmacy data by continuous multiple interval measures of medication availability described by Steiner and Prochazka (11). We calculated the length of each type of continuous insulin regimen, beginning with the first prescription after 1 January 2001 and continuing through the end of the last prescription before 1 December 2002. The sum of the day supply for each regimen was divided by the total days from the beginning to the end of the period, resulting in a compliance score for each type of insulin. Compliance scores did not differ by insulin type (short acting, long acting, premixed, etc.), so the total days supply of insulin was summed and divided by the sum of the total days in the treatment period. It was understood that wastage occurred during syringe filling from vials, biasing analyses by increasing compliance scores because more insulin was used. Adjustment for wastage was not possible; therefore, it was assumed to be a constant. The small number of patients using pen devices ($n = 50$) precluded analyses of differences between pen versus regular syringe prescriptions. HbA_{1c} levels from a laboratory database were linked to the prescription refill data.

Because intense provider management may be associated with improved patient compliance, we measured diabetes management intensity (12,13). Berlowitz et al. (12,13) defined diabetes treatment intensity as the likelihood of receiving an increase (increased dose, addition of a medication in another drug class, or a change of drug within the same class), decrease (lower dose, discontinuation of medication), or no change in treatment, accounting for variables believed to influence treatment decisions (e.g., HbA_{1c}, cholesterol levels, comorbidities). Observed changes were subtracted from these expected changes in treatment and divided by the number of visits. Scores range from -1 to $+1$, with positive values indicating more intense management and negative values indicating less intense management than expected. For the purposes of this study, we use this measure as a proxy for more or less intensive diabetes management.

Descriptive statistics compared insulin use (compliance scores) and average HbA_{1c} level by age, sex, and race and included correlations between insulin compliance and HbA_{1c} levels (initial and final level). Ordinary least-square regressions were used to predict overall insulin use and the last HbA_{1c} level during the study period.

RESULTS

— Patient files from the 12 Veterans Administration centers included 39,393 patients (98% men) with a diagnosis of diabetes who were taking insulin with or without an OHA. Of these patients, 8,484 received insulin and had at least one HbA_{1c} level recorded. Two-thirds of patients were aged ≥65 years. The racial/ethnic distribution was 41% Caucasian, 7% African American, 30% Hispanic/other, and 22% mixed/undefined (largely African-American mixed) (Table 1). Chronic insulin users ($n = 6,222$) received 8.3 ± 4.7 refills during follow-up; 2,491 patients received insulin alone, 2,431 patients also received one OHA, and 1,300 received more than one OHA with insulin. Diabetes management intensity scores were low, averaging 0.026 ± 0.21. The mean rate of insulin usage was $77.44 \pm 17.1\%$ (median 80.35) of doses prescribed, including wastage, based on the number of units and doses prescribed. Mean for the last HbA_{1c} level was $7.98 \pm 1.66\%$ (median 7.7).

Table 1 shows that older patients had significantly lower HbA_{1c} levels and higher insulin use than younger patients and that there were differences in HbA_{1c} and insulin use by racial/ethnic group. Caucasian and mixed/undefined patients had lower HbA_{1c} levels than African-American or Hispanic/other patients; African-American patients had lower levels of insulin use than all other patients. Among patients taking both an OHA and insulin, use of an OHA ($84.89 \pm 16\%$) was significantly higher than insulin use, even with inflation due to insulin wastage ($P < 0.0001$). Insulin use was not significantly different among groups taking insulin alone or insulin with at least one OHA.

Ordinary least-squares regression analysis showed significantly higher insulin use in Caucasians (versus African Americans and Hispanic/other individuals), those with lower HbA_{1c} levels, and those with higher diabetes management intensity ($R^2 = 0.016$; $F = 65.1$, $P < 0.0001$) (Table 2). Although it is not known what fraction of prescribed insulin is necessary to achieve glycemic control,

Table 1—*Demographic characteristics for chronic insulin users*

	n	HbA_{1c}	Insulin use (%)
All	6,222	7.98 ± 1.66	77.44 (17.14)
Age			
≥65 years	4,053	7.75 ± 1.51*	77.89 (16.95)†
<65 years	2,169	8.41 ± 1.84	76.60 (17.46)
Race/ethnicity			
Caucasian	2,515	7.79 ± 1.53†	78.59 (17.35)†
African American	451	8.28 ± 2.04	70.93 (19.96)‖
Hispanic/other	1,959	8.33 ± 1.74	77.07 (15.44)
Mixed/undefined	1,297	7.71 ± 1.54§	78.02 (17.60)
Insulin alone	2,491	7.67 ± 1.63¶	77.48 (17.22)
Insulin + 1 OHA	2,431	8.08 ± 1.65¶	77.05 (16.95)
Insulin + ≥2 OHAs	1,300	8.39 ± 1.62¶	78.10 (17.35)
Insulin with any OHA	3,731	8.19 ± 1.65	77.41 (17.10)

Data are means ± SD. *$P < 0.0001$, †$P < 0.01$, ‡$P < 0.05$ for Caucasian vs. African American and Hispanic; §$P < 0.05$ for unknown/mixed vs. African American and Hispanic; ‖$P < 0.05$ for African American vs. Hispanic and unknown/mixed; ¶$P < 0.05$ for all group differences.

we used the approximate average rate as a cutoff for categorical analyses (≥80%, $n = 4,793$; <80%, $n = 3,691$) predicting insulin use ≥80%. African Americans were half as likely as Caucasian patients to have higher insulin use (odds ratio [OR] 0.582, 95% CI 0.49–0.70) as well as greater treatment intensity (1.31, 1.05–1.64). Patients recently starting insulin because of elevated HbA_{1c} followed their prescribed regimen better than chronic insulin users (OR 2.49).

Regression analyses predicting the last HbA_{1c} levels indicate that when controlling for other variables, women, African Americans, Hispanic/other patients, those on OHAs, and those with higher diabetes management intensity had significantly higher HbA_{1c} levels than men, Caucasians, patients on insulin only, and patients with lower levels of diabetes management intensity (Table 3). Older patients and those with higher insulin use had significantly lower HbA_{1c} levels than younger, less compliant patients.

CONCLUSIONS — These data show that adults chronically prescribed a specific insulin management regimen used ~77% of prescribed amounts of insulin, based on prescription refills. Insulin use was less than prescribed across all groups but consistent with current and previous findings for OHAs, wherein most patient groups took approximately three-fourths of medication as prescribed (5). This reflects the good overall diabetes care, including patient education and communication with clinicians, in the Veterans Administration system (14). Although patients seen in the Veterans Administration system generally have more comorbidities than non–Veterans Administration diabetes patients, they receive equal or higher levels of preventive care services (15). Nonetheless, their resulting mean HbA_{1c} levels were higher than the American Diabetes Association guideline target (16). This result suggests that insulin self-management (injection compliance), the prescribed regimen, or both were inadequate to achieve good glycemic control. Newly developed Veterans Administration guidelines encourage targeting HbA_{1c} at <7% but allow for higher levels for older, sicker patients (17). Providers might be more lenient with high HbA_{1c} levels because of inconvenience, syringe-filling inaccuracy, wastage, or other dosing problems for these patients as long as patients did not become hypoglycemic or hyperglycemic.

Among drawbacks to this analysis is the gross measurement of insulin use. Unlike tablets that can be counted or recorded electronically when removed from a bottle with a MEMS cap (AARDEX, Zug, Switzerland), insulin may not be measured accurately and is subject to wastage from vials and pens. Mean insulin compliance of 77% for chronic users indicates that most patients are making an effort to take insulin, albeit not as prescribed by their physician. This is an overestimate, because wastage could not be separated from dosing. Wastage in syringe filling, coupled with errors in drawing doses, has been estimated at 12–19% (18,19). If those estimates were extrapolated to this population, overall use of insulin would be reduced from 77 to 58–65%. This type of analysis did not allow determination of how many doses were omitted, taken late, or taken at the prescribed dose. We included only patients who were given a standard prescription defining the number of units and doses to be taken daily, excluding those who were told to

Table 2—*Predictors of compliance with the prescribed insulin regimen among chronic insulin users*

Parameter	Estimate	*t* value	Pr > *t*
Intercept	0.8161	67.74	<0.0001
Age			
≥65 years	0.0077	1.64	0.1014
<65 years	0.0000		
Sex			
Female	0.0019	0.09	0.9251
Male	0.0000		
Race/ethnicity			
African American	−0.0726	−8.29	<0.0001
Hispanic/other	−0.0145	−2.75	0.0060
Mixed/undefined	−0.0068	−1.17	0.2428
Caucasian	0.0000		
Medication regimen			
1 OHA + insulin	−0.0042	−0.83	0.4038
>1 OHA + insulin	0.0058	0.94	0.3474
Insulin only	0.0000		
HbA_{1c} level	−0.0045	−3.32	0.0009
Treatment intensity	0.0285	2.65	0.0080

Table 3—*Regression predicting most recent HbA_{1c} level among chronic insulin users*

Parameter	Estimate	*t* value	Pr > *t*
Intercept	0.8161	67.74	<0.0001
Age			
≥65 years	0.0077	1.64	0.1014
<65 years	0.0000	.	.
Sex			
Female	0.0019	0.09	0.9251
Male	0.0000	.	.
Race/ethnicity			
African American	−0.0726	−8.29	<0.0001
Hispanic/other	−0.0145	−2.75	0.0060
Mixed/undefined	−0.0068	−1.17	0.2428
Caucasian	0.0000		
Medication regimen			
1 OHA + insulin	−0.0042	−0.83	0.4038
>1 OHA + insulin	0.0058	0.94	0.3474
Insulin only	0.0000		
HbA_{1c} level	−0.0045	−3.32	0.0009
Treatment intensity	0.0285	2.65	0.0080

self-adjust doses to limit the difficulty of measuring variable dosing. A more detailed evaluation of individual patient insulin dosing must await the development of a device that electronically monitors insulin delivery (20), such as the AERx Insulin Diabetes Management System (Novo Nordisk, Bagsvaerd, Denmark; Aradigm, Hayward, CA). Nonetheless, observing patients for 2 years provided an overall view of how they used insulin.

Anderson et al. (21) found that most patients with type 1 and 2 diabetes reported numerous missed insulin doses, resulting in a significant association between self-reported compliance and HbA_{1c} level. Reasons for missed doses included forgotten injection time (43%), forgotten supplies (58%), postponement (58%), and purposeful omission (33%). Other surveys have reported that women frequently omitted doses to control weight (22) and adolescents omitted injections before a check-up (23). Morris et al. (7) calculated an adherence index based on insulin dose prescribed and dispensed for 89 children and adolescents. Highest HbA_{1c} levels and more diabetes-related hospitalizations were found in the lowest category of insulin use. Pen users had lower HbA_{1c} levels than syringe users (7.64 and 8.55, respectively). Adolescents used less insulin than children or young adults, suggesting that issues of autonomy were expressed by omitting doses. Another report using an administrative database for a general population showed much lower (63%) insulin use than seen in this population (8). That analysis might not have been limited to patients given specific dosing instructions, which could have biased the results toward fewer refills. Our data concurred with those of Balkrishnan et al. (24), showing that patients taking both types of medication used less insulin than OHAs. These investigators also reported that higher refill rates for diabetes medications (insulin and OHA) was the strongest predictor of health care costs for older type 2 patients, including emergency visits and hospitalization. We found no association between the type of insulin and compliance rates, although this might have been an indicator of the number of daily doses prescribed. A likely reason is that patients needing multiple daily insulin doses were not prescribed a fixed regimen, thereby excluding them from these analyses.

Our data from a large cohort of adult male veterans focuses solely on insulin use in a population for whom a full range of diabetes care is provided (15). These factors remove the potential biases of dealing with type 1 adolescents or adults with inadequate financial or medical resources to be able to manage their diabetes. Nonetheless, we found several characteristics that affected insulin use and HbA_{1c} levels.

Poorer insulin self-management was found for African-American than for Caucasian patients but not Hispanic patients. This was similar to racial differences in insulin self-management in an indigent population reported by Schectman et al. (25). Additional outreach may be needed to African-American veterans to determine how the system can better serve them. Our findings were unlikely to be related to cost of care because veterans with low incomes or service-connected disabilities paid nothing for medical care or prescriptions, whereas others paid $2.00 for a 30-day supply of medication during the study period. Veterans Administration patients receive virtually all of their medications from Veterans Administration pharmacies (26). Piette et al. (14) noted that underuse of diabetes medication related to cost was significantly lower among Veterans Administration patients than patients with private insurance, Medicare, Medicaid, or no health insurance.

An intriguing finding in this study was that patients who had providers that more actively managed their diabetes were more likely to follow their insulin regimen than patients with less active management. Although this finding may result at least in part from clinician awareness of high HbA_{1c} levels, those receiving more intense management had higher insulin use, even when analyses controlled for HbA_{1c} levels. Better insulin self-management among patients with higher treatment intensity scores could suggest that they receive more attention (more visits, better instructions), they perceive themselves as sicker and focus more on their self-care, or they have more ancillary medical assistance, as well as perceived benefits of intensive care. This is paralleled by higher insulin use among older patients (aged ≥65 years), who would be expected to have more medical problems than younger patients. Alternatively, the intensity of diabetes management might have been influenced by provider or patient-level variables or the relationship between provider and patients that were not included in administrative data. These results suggest the need for further research into the effect of clinician management styles.

Better regimen compliance among new insulin users (OR 2.49) probably reflects their willingness to start insulin to lower their HbA_{1c}, as well as attention to newly learned injection methods. In contrast, chronic insulin users may have learned how to manage their dosing suf-

ficiently to avoid problems. If the HbA_{1c} level remains higher than the target, doctors might add an OHA for patients with type 2 diabetes rather than attempt to evaluate the potential for missed insulin doses.

Although their insulin use was similar, patients also taking an OHA had significantly higher HbA_{1c} levels than patients on insulin alone. This could be the result of disease progression or patients' belief that the OHA will cover their insulin lapses. Although Spoelstra et al. (27) hypothesized that poor compliance with OHA dosing might lead to use of insulin, the natural progression of the disease complicates that association. Pugh et al. (1) noted that generalists and specialists differed in their implementation of practice guidelines. When more physicians follow the new, lower target for HbA_{1c}, they might increase insulin doses or move patients to more intensive treatment to reach goals. This should reduce complications and the cost of care (28). Additional analyses of this database will assess the economic impact of poor insulin self-management as well as prescribing practices based on the evolution of guidelines for diabetes treatment. Future analyses should evaluate the influence of duration of diabetes, insulin use, and other patient characteristics, as well as the type of physicians who tended to allow higher HbA_{1c} levels (1).

The significant association between insulin use and HbA_{1c} confirms assumptions that regular dosing is important for glycemic control. The largely elderly, male patients under Veterans Administration care who were receiving chronic treatment with insulin regimens used ~77% of insulin prescribed (unadjusted for wastage), demonstrating good intention to follow the prescription. However, HbA_{1c} higher than the recommended level suggested that the level of injection compliance, the prescribed regimen, or both were inadequate to achieve good glycemic control, particularly with chronic use. This study suggests that insulin refill prescription rates may be used to stimulate a dialog between patient and providers regarding medication use and glycemic control. Improved methods or new devices to monitor the regularity and accuracy of insulin dosing as well as wastage are needed to define where interventions would be useful. Longitudinal insulin dose monitoring would explain whether patients need more instruction about syringe use, how and why to remember when to take doses, or increased dosing intensity to reach target HbA_{1c} levels.

Acknowledgments— The analyses in this study were supported by Novo Nordisk. M.J.P. was supported by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development Service (DII 99–205).

We thank Dan Berlowitz, Graeme Fincke, and Megan Amuan for their helpful comments.

References

1. Pugh MJ, Anderson J, Pogach LM, Berlowitz DR: Differential adoption of pharmacotherapy recommendations for type 2 diabetes by generalists and specialists. *Med Care Res Rev* 60:178–200, 2003
2. Norris SL, Lau J, Smith SJ, Schmid CH, Engelau MM: Self-management education for adults with type 2 diabetes: a meta-analysis of the effect on glycemic control. *Diabetes Care* 25:1159–1171, 2002
3. Glasgow RE: Compliance to diabetes regimens: conceptualization, complexity, and determinants. In *Patient Compliance in Medical Practice and Clinical Trials.* Cramer JA, Spilker B, Eds. New York, Raven Press, 1991, p. 209–224
4. Anderson EA, Usher JA: Understanding and enhancing adherence in adults with diabetes. *Curr Diabetes Reports* 3:141–148, 2003
5. Cramer JA: A systematic review adherence with medications for diabetes. *Diabetes Care* 27:1218–1224, 2004
6. Johnson SB: Methodological issues in diabetes research: measuring adherence. *Diabetes Care* 15:1658–1667, 1992
7. Morris AD, Boyle DIR, McMahon AD, Greene SA, MacDonald TM, Newton RW, the DARTS/MEMO Collaboration: Adherence to insulin treatment, glycemic control, and ketoacidosis in insulin-dependent diabetes mellitus. *Lancet* 350: 1505–1510, 1997
8. Rajagopalan R, Joyce A, Smith D, Ollendorf D, Murray FT: Medication compliance in type 2 diabetes patients: retrospective data analysis (Abstract). *Value Health* 6:328, 2003
9. Maynard C, Chapko MK, Maynard C: Data resources in the Department of Veterans Affairs. *Diabetes Care* 27:B22–B26, 2004
10. U.S. Public Law 104–191, 104th Congress, Health Insurance Portability and Accountability Act of 1996 [article online], 1996. Available from http://privacyruleandresearch.nih.gov. Accessed 11 May 2004
11. Steiner JF, Prochazka AV: The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol* 50:105–116, 1997
12. Berlowitz DR, Ash AS, Hickey EC, Friedman RH, Glickman M, Kader B, Moskowitz MA: Inadequate management of blood pressure in a hypertensive population. *N Engl J Med* 339:1957–1963, 1998
13. Berlowitz DR, Ash AS, Hickey EC, Glickman M, Friedman R, Kader B: Hypertension management in patients with diabetes: the need for more aggressive therapy. *Diabetes Care* 26:355–359, 2003
14. Piette JD, Wagner TH, Potter MB, Schillinger D: Health insurance status, cost-related medication underuse, and outcomes among diabetes patients in three systems of care. *Med Care* 42:102–109, 2004
15. Reiber GE, Koepsell TD, Maynard C, Haas LB, Boyko EJ: Diabetes in nonveterans, veterans, and veterans receiving Department of Veterans Affairs health care. *Diabetes Care* 27:B3–B9, 2004
16. American Diabetes Association: Economic consequences of diabetes in the United States in 1997. *Diabetes Care* 21: 296–309, 1998
17. Pogach LM, Brietzke SA, Cowan CL, Conlin P, Walder D, Sawin CT, Pogach LM: Development of evidence-based clinical practice guidelines for diabetes: the Department of Veterans Affairs/Department of Defense guidelines initiative. *Diabetes Care* 27:B82–B89, 2004
18. Puxty JA, Hunter DH, Burr WA: Accuracy of insulin injection in elderly patients (Abstract). *BMJ (Clin Res Ed)* 287:1762, 1983
19. Kesson CM, Bailie GR: Do diabetic patients inject accurate doses of insulin? (Letter). *Diabetes Care* 4:333, 1981
20. Cramer JA, Okikawa J, Clauson P: Compliance with inhaled insulin using AERx® iDMS Insulin Diabetes Management System (Abstract). *Diabetes* 52(Suppl. 1): A103, 2003
21. Anderson RT, Marrero D, Skovlund SE, Cramer J, Schwartz S: Self-reported compliance with insulin injection therapy in subjects with type 1 and 2 diabetes (Abstract). *Diabetes Metab* 29:A275, 2003
22. Polonsky WH, Anderson BJ, Lohrer PA, Aponte JE, Jacobson AM, Cole CF: Insulin omission in women with IDDM. *Diabetes Care* 17:1178–1185, 1994
23. Weissberg-Benchell J, Glasgow AM, Tynan WD, Wirtz P, Turek J, Ward J: Adolescent diabetes management and mismanagement. *Diabetes Care* 18:77–82, 1995
24. Balkrishnan R, Rajagopalan R, Camacho FT, Hyuston SA, Murray FT, Anderson RT: Predictors of medication adherence

and associated health care costs in an older population with type 2 diabetes mellitus: a longitudinal cohort study. *Clin Ther* 25:2958–2971, 2003
25. Schectman JM, Nadkarni MM, Voss JD: The association between diabetes metabolic control and drug adherence in an indigent population. *Diabetes Care* 25: 1015–1021, 2002
26. Fan VS, Bryson CL, Curtis JR, Fihn SD, Bridevaux PO, McDonell MB, Au DH: Inhaled corticosteroids in chronic obstructive pulmonary disease and risk of death and hospitalization. *Am J Resp Crit Care Med* 168:1488–1494, 2003
27. Spoelstra JA, Stolk RP, Heerdink ER, Klungel OH, Erkens JA, Leufkens HGM, Grobbee DE: Refill compliance in type 2 diabetes mellitus: a predictor of switching to insulin therapy? *Pharmacoepidemiol Drug Safety* 12:121–127, 2003
28. Menzin J, Langley-Hawthorne C, Friedman M, Boulanger L, Cavanaugh R: Potential short-term economic benefits of improved glycemic control: a managed care perspective. *Diabetes Care* 24:51–55, 2001