Comparative Effectiveness of Hypoglycemic Medications Among Veterans

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ABSTRACT

BACKGROUND: The efficacy of diabetic medications among patients with multiple comorbidities is not tested in randomized clinical studies. It is important to monitor the performance of these medications after marketing approvals.

OBJECTIVE: To investigate the risk of all-cause mortality associated with prescription of hypoglycemic agents.

METHODS: We retrospectively examined data from 17,773 type 2 diabetic patients seen from March 2, 1998, to December 13, 2010, in 3 Veterans Administration medical centers. Severity was measured using patients' inpatient and outpatient comorbidities during the last year of visits. Severity-adjusted logistic regression was used to measure the odds ratio for mortality within the study period.

RESULTS: Patients' severity of illness correctly classified mortality for 89.8% of the patients ($P < 0.0001$). Being younger, married, and white decreased severity adjusted risk of mortality. Exposure to the following medications increased severity adjusted risk of mortality: glyburide (odds ratio [OR] = 1.804, 95% CI from 1.518 to 2.145), glipizide (OR = 1.566, 95% CI from 1.333 to 1.839), rosiglitazone (OR = 1.805, 95% CI from 1.378 to 2.365), chlorpropamide (OR = 3.026, 95% CI from 1.096 to 8.351), insulin (OR = 2.382, 95% CI from 2.112 to 2.686). None of the other medications (metformin, acarbose, glimepiride, pioglitazone, repaglinide, troglitazone, or dipeptidyl peptidase-4) were associated with excess mortality beyond what could be expected from the patients' severity of illness or demographic characteristics. The reported excess mortality could not be explained away by use of other concurrent, nondiabetic classes of medications.

CONCLUSION: Our findings suggest chlorpropamide, glipizide, glyburide, insulin, and rosiglitazone increased severity-adjusted mortality in veterans with type 2 diabetes. A decision aid that could optimize selection of hypoglycemic medications based on patients' comorbidities might increase patients' survival.

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What is already known about this subject

- Rosiglitazone and glyburide may increase cardiac events.
- Metformin and acarbose may have a beneficial effect on all-cause mortality.
- Insulin should be initiated when oral medications are not effective.

What this study adds

- Rosiglitazone, glyburide, chlorpropamide, glipizide, and insulin were associated with an increase in severity-adjusted all-cause mortality.
- Metformin and acarbose did not have beneficial severity-adjusted impact on all-cause mortality.

More than 171 million people worldwide have type 2 diabetes, a disease associated with at least doubling of the risk of death.¹ The efficacy of common hypoglycemic medications have been examined in several clinical studies.²⁻⁷ These studies have intentionally excluded patients with multiple comorbidities in order to focus on the effect of medication on the underlying diabetes. The presence of comorbidities is known to affect adherence to diabetes management protocols.⁸ Investigators have examined the effect of pregnancy,⁹ cancer,¹⁰ depression,¹¹ and certain cardiovascular illnesses¹² on management of diabetic patients. The effect of other comorbidities, or combination of these comorbidities, is not well understood. This study fills the gap in knowledge of how hypoglycemic medications affect all-cause risk-adjusted mortality.

Methods

This study is a risk-adjusted retrospective analysis of mortality within 1 cohort of patients. The study examined the period between March 2, 1998, and December 12, 2010. A patient's survival during this period was regressed on (a) severity of illness of the patient in the last year of encounters and (b) the extent of use of the medications in the last year of encounters. The findings can be interpreted as severity-adjusted comparative effectiveness of different hypoglycemic medications. In recent years, different methods of studying comparative effectiveness of medications have led to contradictory findings.¹³ Since the focus of interest is on the relationship between mortality and medication taken by a patient, our method of analysis seems reasonable. Our study results would need to be replicated using other study designs, for example, matched case control, before there is confidence in findings.

The project examined data from the electronic health records of diabetic patients seen in the Veterans Administration (VA) Medical Center Capital Area medical centers, including those in Baltimore, Maryland; Martinsburg, West Virginia; Perry Point, Maryland; and Washington, DC. The analysis was done on 19,223 diabetic patients, 17,773 of whom met the eligibility criteria.

Eligibility Criteria

The eligibility criteria were as follows:

Diabetic: The patient must have had 2 diagnoses of diabetes (*International Classification of Diseases, Ninth Revision, Clinical*

TABLE 1 Logistic Regression of Mortality Associated with Exposure to Hypoglycemic Medications

	Number Exposed	B	SE	Wald Statistic	df	Sig	OR	95% CI for Exp(B)	
								Lower	Upper
Metformin	5,629	-0.125	0.076	2.736	1	0.098	0.883	0.761	1.023
Glyburide ^a	1,732	0.59	0.088	44.706	1	0	1.804	1.518	2.145
Glipizide ^a	2,572	0.448	0.082	29.748	1	0	1.566	1.333	1.839
Rosiglitazone ^a	463	0.591	0.138	18.408	1	0	1.805	1.378	2.365
Acarbose	96	0.369	0.294	1.579	1	0.209	1.446	0.813	2.57
Chlorpropamide ^a	23	1.107	0.518	4.569	1	0.033	3.026	1.096	8.351
Glimepiride	149	0.194	0.299	0.421	1	0.516	1.214	0.676	2.179
Pioglitazone	102	0.416	0.327	1.62	1	0.203	1.516	0.799	2.878
Repaglinide	30	-0.406	0.604	0.453	1	0.501	0.666	0.204	2.174
Insulin ^a	5,236	0.868	0.061	200.722	1	0	2.382	2.112	2.686
DPP4	24	0.294	0.793	0.137	1	0.711	1.342	0.284	6.344
Severity of illness ^a	17,773	13.89	0.326	1,819.207	1	0	1,077,039	568,901.1	2,039,043
Birth year ^a	17,773	-0.031	0.003	147.228	1	0	0.969	0.964	0.974
Male	16,924	0.008	0.183	0.002	1	0.965	1.008	0.705	1.442
White ^a	4,638	-0.4	0.067	35.427	1	0	0.67	0.587	0.765
Hispanic	5,321	-0.082	0.063	1.702	1	0.192	0.921	0.815	1.042
Married ^a	8,164	-0.206	0.058	12.658	1	0	0.814	0.726	0.912
Constant ^a		55.551	5.029	122.033	1	0	1.34E+24		

^aStatistically significant at alpha levels less than 0.05.

B=regression coefficient; CI=confidence interval; df=degree of freedom; DPP4=dipeptidyl peptidase-4; OR=odds ratio; SE=standard error; Sig=significance.

Modification [ICD-9-CM] codes 250.xx, 357.2, 362.0x, 366.41, or 648.0x, where x is any digit).

Minimum data required: Patients with less than 180 days between first and last visits were excluded on suspicion that these patients had too few encounters or may have received care elsewhere.

Inconsistent date of death: Patients with a recorded date of death 30 days prior to their last visit were not included in the analysis. A 30-day interval was allowed because occasionally test results become available after date of death, or visits are coded to have been completed after date of death.

Dependent Variable

The primary end-point variable in this study was all-cause mortality during the study time period. Health system data do not usually reflect death at home or outside the health system. The VA systematically checks with Social Security records to update its files on deaths reported within other systems.

Independent Variables

The independent variables were as follows:

Severity of illness: The composite for severity of illness was calculated from patients' diagnoses during the last year of patients' visits. We used a variant of the Alemi and Walter's severity index, a patented algorithm that assigns severity scores to combinations of diagnoses/procedure codes.¹⁴ Appendix A (available in online article) shows how this measure of severity was constructed; a brief description is provided here:

- The average mortality associated with each diagnosis and

each pair of diagnoses was calculated. One unit of increase in this score is equivalent to a 1-point increase in probability of mortality.

- Pairs of diagnoses that did not repeat at least 5 times across patients were excluded from the analysis.
- A patient's overall severity for each encounter was scored as the average of all of the patient's pairs of diagnoses for hospitalization encounters and single diagnoses for outpatient visits.

The severity scores for each individual diagnosis could theoretically range from 0 to 1, and they actually ranged from .001 to 0.803. The mean severity score was 0.167. The median was 0.140, and the standard deviation was 0.091. The more severe the patients' diagnoses during hospital or outpatient encounters, the higher the average severity score for each patient.

Current medications: This set of independent variables measured exposure to various hypoglycemic medications (metformin, glyburide, glipizide, rosiglitazone, acarbose, chlorpropamide, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, insulin, and dipeptidyl peptidase-4 [DPP4]) and 76 classes of nondiabetic medications (see Appendix B, available in online article). The number of patients who were exposed to each of the hypoglycemic medications is reported in Table 1. The definition of "exposure to medication" was set to any use of the medication independent of dose or days of use. This was done in order to have consistent definitions across classes of medications, where use of different medications within the same class prohibited calculation of cumulative dosage prescribed. Nevertheless, the definition of "exposure" introduced

FIGURE 1 Relationship Between Composite Severity and Mortality

possible errors in the data. To examine the extent of these errors, we repeated our analysis, replacing “exposure to hypoglycemic medications” with the “sum of daily dose prescribed.” The findings of the study did not change; the same medications were found to be associated with increased severity-adjusted mortality. Another problem with our measure of exposure to medications is that it does not reflect actual medication taken but medications prescribed. It is well known that patients do not take medications as prescribed or purchased.¹⁵ We did not have access to data on medication adherence.

Demographics: Year of birth, gender, race, marital status, and ethnicity were used to adjust for differences in mortality. Missing demographic variables were assumed to be the mode of the data. The distribution of the demographic variables is provided in the first column of Table 1.

Statistical Analysis

Data were analyzed using Logistic Regression. The statistical package used was PASW Statistics 18, release version 18.0.0 (SPSS, Inc., 2009, Chicago, IL, www.spss.com). Patients' mortality was regressed on the composite severity measure, demographic measures, concurrent nondiabetic medications, and a set of variables measuring exposure to diabetes medications. This approach controlled for severity of diabetic illness before attributing observed mortality to specific medications.

Results

A key construct, on which much of the remaining analysis rests, was our measure of composite for severity of illness. Figure 1 illustrates the relationship between this index and the observed rates of mortality. To construct this figure, we divided severity scores into uniform intervals and calculated the mortality rate for each interval. On the x-axis are the severity scores, and on the y-axis is the average mortality for patients who received the score. Each point on the graph represented a different number of patients (minimum of 15 and a maximum of 1,316 patients), as some severity intervals were more common. The graph fits our expectations of the relationship between severity of illness

and mortality rates. Low severity scores were associated with low mortality rates, and high scores were associated with high mortality rates. For scores between 20 and 30, there was a rapid increase in mortality rate proportional to the severity score. At the very low and the very high scores, there were occasional errors in the severity score, where an increase in severity was not associated with an increase in mortality. Nevertheless, as a whole, the composite severity score was highly predictive of mortality. It correctly classified 89.6% of observed mortality (chi-square = 142.95, $P < 0.0001$).

Table 1 provides the odds ratio (OR) associated with different hypoglycemic medications and severity-adjusted mortality. An OR larger than 1 indicates medications that increased mortality. An OR less than 1 indicates reduced mortality rate. The regression equation correctly predicted 89.8% of patients examined. The severity index was the best predictor of mortality. Married, younger, and white patients had a lower risk of mortality. After adjustments were made for severity of illness and patient demographics, the remaining variance in mortality was explained by exposure to 5 medications, listed in order of impact on risk-adjusted mortality: glipizide (OR = 1.566), glyburide (OR = 1.804), rosiglitazone (OR = 1.805), insulin (OR = 2.382), and chlorpropamide (OR = 3.026). None of the other medications (metformin, acarbose, glimepiride, pioglitazone, tolazamide, repaglinide, troglitazone, and DPP4) were associated with excess mortality beyond what could be expected from the patients' severity of illness or demographic characteristics.

The data we had were observational data. Therefore, it is not clear that the reported mortality is related to the hypoglycemic medication or a common medication that is prescribed with it. To partially control for possible interactions, we repeated the analysis and included 76 common classes of concurrent medications (Appendix B, available in online article). Insulin, glyburide, glipizide, and rosiglitazone continued to be associated with statistically significant increased mortality. This analysis further confirmed that classes of nondiabetic medications do not explain away the mortality we have attributed to diabetic medications.

Discussion

We presented data on the association between hypoglycemic medications and all-cause severity-adjusted mortality.

This analysis was done on a relatively large sample of diabetic patients. In large samples, even small differences in outcome could be statistically significant. The data were adjusted for patients' severity of illness by examining all patient diagnoses and scoring each pair of diagnoses separately based on the observed mortality within the pair. Analysis of the measure of severity indicated that it performed as expected and that it explained a large percentage of variation in mortality. These data increase confidence that the measure had adequately captured patients' severity of illness.

One finding of our study was the association of insulin with higher severity-adjusted mortality (see Table 1). Traditionally, insulin has been tried after diabetic patients have not been responsive to oral medications. Recent data suggest that earlier use of insulin may be beneficial; replacing oral medications with insulin at onset of treatment of diabetes may lead to better control of hemoglobin A1c and reduced complications.¹⁶ However, despite better glycemic control, all-cause mortality (from hypoglycemia, weight gain, and colorectal cancer) may increase.¹⁷ Our data, while not directly addressing the timing of start of insulin, suggest that exposure to insulin is associated with higher all-cause mortality, even after adjusting for severity of illness. These data fit into the clinical perspective that insulin should be delayed until oral medications fail to maintain glycemic control.

Another finding of our study was that rosiglitazone was associated with increased severity-adjusted all-cause mortality (see Table 1). The original approval of rosiglitazone was based on the ability of the drug to reduce blood glucose and glycated hemoglobin levels.¹⁸ One potential contributing factor may be the adverse effect of the drug on serum lipids. A 2007 study found rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance.¹⁹ The Diabetes Outcome Progression Trial demonstrated 5-year failure rates with rosiglitazone to be lower than metformin or glyburide. Rosiglitazone was associated with more weight gain and edema than either metformin or glyburide but with fewer gastrointestinal events than metformin and with less hypoglycemia than glyburide.²⁰ The current study complements these findings by providing additional data on the impact of rosiglitazone on all-cause mortality.

The published literature suggests that metformin should have reduced severity-adjusted mortality.²¹ Our study did not find a statistically significant relationship between metformin and severity-adjusted mortality. Before severity adjustment, there was a beneficial effect (OR=0.320, 95% confidence interval [CI] from 0.283 to 0.362). After severity adjustment, there was not (OR=0.883, CI from 0.761 to 1.023). This suggests that the beneficial effects attributed to metformin might be due to use of this medication by patients who are younger and less severely ill. Once severity of illness and demographics are taken into account, metformin had no statistically significant impact on mortality (see Table 1).

Post-FDA-release surveillance studies have shown that acarbose may have a beneficial effect on mortality.²² Our data contradict this finding. Prior to severity adjustment, a detrimental effect was associated with acarbose (OR=2.141, 95% CI from 1.335 to 3.435). After severity and demographic adjustment, acarbose had neither detrimental nor beneficial impact on mortality (see Table 1). The study that had shown beneficial effects for acarbose was carried out on Chinese patients. The

differences between our study population and Chinese patients may explain the contradictory findings. Our study was limited to U.S. veterans. The set of comorbidities may be different in different populations.

Limitations

This study was limited because it was an observational study. In observational studies, a number of factors may cause the outcome. Some of these factors are controlled for, but it is not possible to statistically control all possible causes. This study statistically controlled for the patients' severity of illness, concurrent medication classes, and patient demographics. We attributed mortality not explained by these factors to the patients' diabetes medications. Such attributions may be in error. There are other causes of mortality (e.g., obesity, poor diet, substance abuse, lack of exercise) for which we did not statistically control.

Conclusion

These data show that glyburide, glipizide, rosiglitazone, chlorpropamide, and insulin led to severity-adjusted higher mortality rates. It is important to explore under what conditions and for which patients these medications may not be beneficial. Given the large number of hypoglycemic medications and comorbid conditions, it may be important to develop tools that can help selection of optimal medications for diabetic patients that present with comorbidities.

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DISCLOSURES

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Study concept and designed were contributed by Kheirbek and Alemi. Data collection was performed by Alemi and Kheirbek, and data analysis was done by Alemi and Zargoush. Data were interpreted by Kheirbek, Alemi, and Zargoush, who also wrote and revised the manuscript.

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APPENDIX A Method of Scoring Composite Severity Index

The composite severity was scored based on pairs of diagnoses. First, the average mortality associated with each pair of diagnoses that repeated at least 5 times was calculated:

$$p_{j,k} = \frac{\sum_{i,e} D_{i,e,j,k} / n_i}{D_{max}}$$

Where

- $p_{j,k}$ was the estimated probability of mortality in pair of diagnoses “j” and “k,” where “j” is the primary diagnosis, if this information is available, otherwise “j” is the first listed diagnosis.
- D_{max} was the maximum number of days till mortality, for any pair of diagnoses in any encounter of any patient that died.
- n_i was the number of diagnoses pairs for patient “i” across all encounters.
- D_i was the number of days between mortality of patient “i” and diagnoses pair “j” and “k” in encounter “e,” of patient “i.” For patients who did not die, this was set to D_{max} .

Then, the overall severity for an encounter “e” of patient “i” was calculated as the average of the severity of diagnoses within that encounter:

$$O_{i,e} = \frac{\sum p_{j,k}}{r_i}$$

Where

- $p_{j,k}$ was the estimated probability of mortality in pair of diagnoses “j” and “k” within encounter “e.”
- r_i was the number of unique pairs of diagnoses within encounter “e.”

Finally, the overall severity for patient “i” was calculated as:

$$O_i = \frac{\sum_e O_{i,e}}{m_i}$$

Where

- O_i was the overall severity of illness of patient “i.”
- $O_{i,e}$ was the severity of encounter “e” for patient “i.”
- m_i was the number of encounters for patient “i.”

The severity index included diagnoses within the following components: (1) health status diagnoses; (2) endocrine nutrition and metabolic diseases; (3) circulatory diseases; (4) mental diseases and disorders; (5) musculoskeletal and connective tissue; (6) substance use and disorders; (7) eye problems; (8) nervous system; (9) ear, nose, mouth and throat problems; (10) kidney and urinary tract problems; (11) respiratory system problems; (12) digestive system; (13) skin, breast, and subcutaneous tissue problems; (14) male reproductive system problems; (15) hepatobiliary and pancreas diseases; (16) diseases of myeloproliferative neoplasia; (17) injury, poisoning, and drug toxicity; (18) HIV infection, and (19) infectious and parasitic diseases. Each diagnosis was scored independent of its classification in a particular component, and these disease categories are presented as a general guide to the index and not as classes of diagnoses used for scoring. Table A1 shows the top 5 most serious diagnoses within each category.

TABLE A1 Serious Diagnoses Among Diabetic Patients

Component	
Diabetes type	(250.72) Diabetes mellitus with peripheral circulatory disorders type II or unspecified type uncontrolled, (250.12) Diabetes mellitus with ketoacidosis type II or unspecified type uncontrolled, (250.91) Diabetes mellitus with unspecified complication type I not stated as uncontrolled, (250.62) Diabetes mellitus with neurological manifestations type II or unspecified type uncontrolled, (250.71) Diabetes mellitus with peripheral circulatory disorders type I not stated as uncontrolled
Health status	(V64.2) Surgical or other procedure not carried out because of patients decision, (V44.1) Gastrostomy status, (V66.7) Encounter for palliative care, (780.94) Early satiety, (780.94) Other general symptoms
Endocrine nutrition and metabolic diseases	(783.41) Failure to thrive, (269.8) Other nutritional deficiency, (783.7) Adult failure to thrive, (783.4) Lack of expected normal physiological development, (255.4) Carticoadrenal insufficiency
Circulatory diseases	(427.5) Cardiac arrest, (428.22) Chronic systolic heart failure, (250.72) Diabetes with peripheral circulatory disorders, Type II or unspecified type, uncontrolled, (443.89) Other peripheral vascular disease, (798.1) Instantaneous death
Mental diseases and disorders	(310.0) Frontal lobe syndrome, (290.20) Senile dementia with delusional features, (290.10) Pre-senile dementia, uncomplicated, (301.81) Narcissistic personality disorders, (300.09) Other anxiety disorders
Musculoskeletal and connective tissue	(198.5) Secondary malignant neoplasm of bone and bone marrow, (737.10) Kyphosis, acquired postural, (725.) Polymyalgia rheumatic, (730.17) Chronic osteomyelitis involving ankle and foot, (446.5) Giant cell artheritisco
Substance use and disorders	(291.2) Alcohol-induced persisting dementia, (305.03) Alcohol abuse in remission, (304.03) Opioid-type dependence in remission, (304.00) Opioid-type dependence unspecified, (304.71) Combinations of opioid-type drug with any other drug dependence, continuous use

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TABLE A1 Serious Diagnoses Among Diabetic Patients *(continued)*

Component	
Eye problems	(365.63) Glaucoma associated with vascular disorders, (365.60) Glaucoma associated with unspecified ocular disorder, (190.6) Malignant neoplasm of choroid, (376.30) Exophthalmos, unspecified, (371.57) Endothelial corneal dystrophy
Nervous system	(191.8) Malignant neoplasm of other parts of brain, (198.3) Secondary malignant neoplasm of brain and spinal cord, (742.59) Other specified congenital anomalies of spinal cord, (432.1) Subdural hemorrhage, (952.2) Lumbar spinal cord injury without spinal bone injury
Ear, nose, mouth, and throat problems	(389.8) Other specified forms of hearing loss, (142.0) Malignant neoplasm of parotid gland, (195.0) Malignant neoplasm of head, face, and neck, (161.0) Malignant neoplasm of glottis, (382.00) Acute suppurative otitis media without spontaneous rupture of eardrum
Kidney and urinary tract problems	(583.2) Nephritis and nephropathy, not specified as acute or chronic, with lesion of membranoproliferative glomerulonephritis, (188.8) Malignant neoplasm of other specified sites of bladder, (189.0) Malignant neoplasm of kidney, except pelvis, (188.1) Malignant neoplasm of dome of urinary bladder, (593.4) Other ureteric obstruction
Respiratory system problems	(197.0) Secondary malignant neoplasm of lung, (512.1) Iatrogenic pneumothorax, (162.4) Malignant neoplasm of middle lobe, bronchus or lung, (162.9) Malignant neoplasm of bronchus and lung, unspecified, (231.2) Carcinoma in situ of bronchus and lung
Digestive system	(150.5) Malignant neoplasm of lower third of esophagus, (569.81) Fistula of intestine, excluding rectum and anus, (537.3) Other obstruction of duodenum, (008.46) Intestinal infection due to other anaerobes, (787.6) Incontinence of feces
Male reproductive system problems	(185) Malignant neoplasm of prostate, (112.2) Candidiasis of other urogenital sites, (607.81) Balanitis xerotica obliterans, (600) Hyperplasia of prostate, (607.84) Impotence of organic origin
Hepatobiliary and pancreas diseases	(157.0) Malignant neoplasm of head of pancreas, (157.9) Malignant neoplasm of pancreas, part unspecified, (571.6) Biliary cirrhosis, (155.0) Malignant neoplasm of liver, primary, (155.2) Malignant neoplasm of liver, not specified as primary or secondary
Diseases of myeloproliferative neoplasia	(201.42) Hodgkin's disease, lymphocytic predominance involving intrathoracic lymph nodes, (208.00) Acute leukemia of unspecified cell type without remission, (238.6) Neoplasm of uncertain behavior of plasma cells, (199.0) Disseminated malignant neoplasm, (273.8) Other disorders of plasma protein metabolism
Injury, poisoning, and drug toxicity	(886.1) Traumatic amputation of other fingers, complete, partial, complicated, (897.2) Traumatic amputation of legs, complete, partial, unilateral, at or above knee, without mention of complication, (897.6) Traumatic amputation of legs, complete, partial, bilateral, any level, without mention of complication, (897.0) Traumatic amputation of legs, complete, partial, unilateral, below knee, without mention of complication, (964.2) Poisoning by anticoagulants
Human immunodeficiency virus infection	(042) Human immunodeficiency virus, HIV, disease, (478.19) Other disease of nasal cavity and sinuses, (780.96) Generalized pain, (525.61) Open restoration margins, (523.42) Chronic periodontitis, generalized
Infectious and parasitic diseases	(041.89) Bacterial infection due to other specified bacteria, (097.0) Late syphilis, unspecified, (097.1) Latent syphilis, unspecified, (038.9) Unspecified septicemia, (136.9) Unspecified infectious and parasitic diseases
Skin, breast, and subcutaneous tissue problems	(694.5) Pemphigoid, (873.0) Open wound of scalp, without mention of complication, (707.07) Decubitus ulcer, heel, (039.0) Cutaneous actinomycotic infection, (707.03) Decubitus ulcer, lower back

APPENDIX B Seventy-Six Nondiabetic Medications as Independent Variables

This study reports the association between diabetic medications and excess mortality. It is possible that this association might be due to concurrent nondiabetic medications. This appendix lists nondiabetic medications and supplies that were used as an alternative explanation for excess mortality. The analysis was done by the entire class, not by items within the class. The following medication classes were included:

antidotes/deterrents, other	digitalis glycosides	histamine antagonists	bronchodilators, anticholinergic
antihistamines, ethanolamine	alpha blockers/related calcium channel blockers	gastric medications, other	antiasthma, other
antihistamines, piperazine	antianginals	herbs/alternative therapies	non-opioid-containing antitussives/expectorants
antihistamines, butyrophenone	antihypertensive combinations	glucocorticoids	enteral nutrition
antihistamines, other	antihypertensives, other	thyroid supplements	iron
(inactive) penicillin g-related penicillins	thiazides/related diuretics	hormones/synthetics/modifiers, other	calcium
penicillins, amino derivatives	loop diuretics	immune suppressants	potassium
erythromycins/macrolides	potassium sparing/combinations diuretics	investigational agents	cyanocobalamin
antivirals	angiotensin II inhibitor	skeletal muscle relaxants	folic acid/leucovorin
anti-infectives, other	antibacterial, topical	antigout agents	nicotinic acid
parasympatholytics	antifungal, topical	anti-inflammatories, nasal	multivitamins
anticoagulants	anti-inflammatory, topical	nasal and throat, topical, other	multivitamins with minerals
platelet aggregation inhibitors	soaps/shampoos/soap-free cleansers	beta-blockers, topical ophthalmic	pads, gauze, sterile
blood formation products	analgesics, topical	antiglaucoma combinations, topical ophthalmic	pads, gauze with medication added
benzodiazepine derivative sedatives/hypnotics	dermatologicals, topical other	antiglaucoma, other	bandages/dressings, other
sedatives/hypnotics, other	bulk-forming laxatives	anti-inflammatories, topical ophthalmic	diapers
anticonvulsants	hyperosmotic laxatives	eye washes/lubricants	syringes, insulin, injection
tricyclic antidepressants	stimulant laxatives	anti-inflammatories, inhalation	needles, injection
central nervous system medications, other	stool softener	bronchodilators, sympathomimetic, inhalation	supplies, other