EVALUATION OF OUTPATIENT CLINICAL CARE, PATIENT FACTORS, AND MORTALITY ASSOCIATED WITH GLYCEMIC CONTROL IN DIABETES MELLITUS

by

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Evaluation of Outpatient Clinical Care, Patient Factors, and Mortality Associated with Glycemic Control in Diabetes Mellitus.

ABSTRACT

Glycemic control is a commonly used indicator of quality of care in diabetes mellitus, but the relationship between blood sugar measures and other health outcomes has not been well studied in the older diabetic population. While many studies are underway to determine whether better glycemic control improves long term morbidity and mortality in patients with diabetes, not much is known about differences in patients with good and poor glycemic control. This is a retrospective cohort study to examine the relationship between outpatient clinical care and patient factors associated with levels of glycemic control and the relationship between glycemic control and mortality. The study was conducted at a large, urban VA medical center. The cohort consisted of all patients who had a diabetic medication prescribed and had at least two hemoglobin A1c (HgA1c) measurements during 1990 to 1995.

There were 1551 patients identified in the cohort. The VA hospital computer system was used to construct a database for these patients that included demographic, appointment, laboratory, and pharmacy records for the years 1990 through 1995. Patients who had less than four years of follow up were excluded (205 patients). Groups from the cohort were defined based on glycemic control. The 417 patients in the well controlled (WC) group had mean HgA1c measurements of $\leq 7\%$. The 695 patients in the moderately controlled (MC) group had mean HgA1c measurements between 7% and 9%. The 234 patients in the poorly controlled (PC) group had mean HgA1c measurements of $\geq 9\%$. The total number of HgA1c measurements during 1990 to 1995 averaged 8.3 in the WC group, 11.4 in the MC group, and 10.8 in the PC group. The mean age of the WC patients was significantly higher than that of the MC and PC patients (70 years, 67 years, 63 years respectively, $p<0.001$). There were more married patients in the WC and MC

groups compared to the PC group (61%WC, 61%MC, and 53%PC, $p = 0.07$) The PC group utilized more endocrine and ancillary appointments and were shown to be less compliant in clinic attendance. The PC group was prescribed proportionately more of both oral diabetic medication and insulin compared to the other two groups (17% WC, 35% MC, 52% PC, $p<0.001$). Mortality was 38% in the WC group, 25% in the MC group, and 19% in the PC group ($p<0.001$). This remained significant after accounting for the older age in the WC group.

In this population, older married patients with diabetes tended to have better glycemic control. Those with poor control were prescribed more of both insulin and oral diabetic medications, utilized more outpatient services, and had lower outpatient clinic attendance. Good glycemic control was not associated with lower mortality in this population. Hemoglobin A1c measurements appear to be poorly associated with more general health outcomes, mainly mortality, in this population.

Evaluation of Outpatient Clinical Care, Patient Factors, and Mortality Associated with Glycemic Control in Diabetes Mellitus.

INTRODUCTION

Diabetes mellitus is a common chronic illness that accounts for a significant proportion of health care expenditures. In 1992, persons with diabetes were estimated to account for 3.1% of the United States population and 11.9% ($85 billion) of total health care costs. An estimated one in eight health care dollars was spent on diabetes mellitus in 1992 (1). Diabetes is a growing problem. In a 1997 report, 15.7 million people in the United States were estimated to have diabetes mellitus, with about 33% being undiagnosed (2). The importance of treating diabetes is to prevent long term complications caused by hyperglycemia including microvascular (such as retinopathy, neuropathy, nephropathy) and macrovascular (such as cardiovascular events) complications resulting in increased morbidity and mortality and decreased quality of life. Although most health care expenditures among persons with diabetes are for inpatient care (63%), a substantial amount is spent on office visits (10%) as well as drugs and equipment (9%) (1). An HMO based study found that charges for medical care significantly increased for every 1% of HgA1c above 7% (3). Kaiser Permanente of Northern California estimated that per capita expenditures for people with diabetes were nearly $3500 more annually than for nondiabetic matched controls. Most of this cost was for hospitalizations for long term diabetic complications (4). Because the impact of diabetes affects a significant and growing portion of the population, achieving good quality of care in patients with diabetes is essential. Because the majority of costs in care of patients with diabetes is utilized in treating complications, emphasis on prevention of these complications is important and has been shown to be cost-effective (5).

There are several classifications of diabetes, but the majority of persons with diabetes are either Type 1 (also called insulin dependent diabetes mellitus or juvenile-onset diabetes) or Type 2 (also called non-insulin dependent diabetes mellitus or adult-onset diabetes). Type 1 diabetes is based on immune mediated destruction of beta cells in the pancreas and commonly occurs starting in childhood, but can occur at any age, even in the 9th decade of life (6). Type 2 diabetes is generally characterized by insulin resistance and relative insulin deficiency. Type 2 diabetes likely encompasses various forms of diabetes with multiple different pathophysiological mechanisms not yet clearly defined (6, 7). Obesity, lack of physical activity, and aging increases the risk of Type 2 diabetes (6). In general, persons with Type 2 diabetes initially do not need insulin to survive while persons with Type 1 diabetes become dependent on insulin (6).

Until recently, evidence for the efficacy of improving blood sugars in persons with diabetes was mostly based on studies on Type 1 diabetes. The diabetes control and complications trial (DCCT) research group found that intensive therapy, resulting in maintaining glucose concentrations closer to the normal range compared to conventional therapy, significantly delayed the onset and progression of microvascular and neuropathic complications of diabetes in insulin dependent diabetes mellitus (IDDM) (8). Although not statistically significant, analysis of the DCCT data revealed that the number of major macrovascular events (myocardial infarction, coronary artery diseases resulting in bypass surgery) was almost twice as high in the conventional therapy group compared with the intensive therapy group (9). Another study found that long term control of hyperglycemia was associated with a decreased incidence and progression of diabetic retinopathy in both patients with onset of diabetes less than age 30 years and in those over the age of 30 years (10).

Evidence for the efficacy of improving glycemic control in Type 2 diabetes has been evolving. The Kumamoto study from Japan was one of the earlier studies specific to type 2 diabetes (11). Although much smaller than the DCCT study, this study also

suggested that intensive insulin therapy prevents or prolongs the onset of microvascular complications in non-insulin dependent diabetes mellitus (NIDDM) patients (11). Two trials have shown that improved glycemic control can be obtained in NIDDM patients through therapy, the United Kingdom Prospective Diabetes Study (UKPDS) and the Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes (VA CSDM) (12, 13). There has been recent evidence that intensive therapy in Type 2 diabetes produced similar results as the DCCT trial. The UKPDS completed a ten year study comparing intensive glycemic control versus conventional control (14). Intensive control during the ten year study period resulted in a 25% risk reduction for any diabetes-related microvascular endpoint (14). There was no significant reduction in macrovascular endpoints with intensive therapy, although these endpoints occurred less frequently in the intensive therapy group (14). Currently, there is supportive evidence that intensive glycemic control in Type 2 diabetes reduces microvascular complications, but effects on macrovascular complications is still inconclusive (14, 15).

Studies such as the DCCT and UKPDS have required intensive intervention to achieve good control (hemoglobin A1c of about 7% in the intensive groups compared to 8.5-9% and 7.9% in the conventional therapy groups respectively). Goals of therapy for both Type 1 and Type 2 diabetes are the same and based on findings in studies of Type 1 diabetes (16). Although it is important to know that better glycemic control reduces morbidity in patients with Type 1 diabetes, perhaps it is even more important to answer this question in patients with Type 2 diabetes as these patients account for at least 90% of all persons with diabetes (2). The recommended goal of HgA1c for patients with diabetes is less than 7% (normal 4.0 to 6.0%), with action suggested (such as adding therapy, referral to specialist, or further education) when HgA1c is more than 8% (16). Recommendations suggest that good glycemic control in both types of diabetes will be beneficial by preventing diabetic complications. The recent findings of the UKPDS trial show that good glycemic control reduces the risk of microvascular complications in Type

2 diabetes mellitus. However, the effectiveness of good glycemic control on macrovascular complications and mortality is still not fully known.

The underlying pathological differences between Type 1 and Type 2 diabetes are important considerations in trying to achieve good glycemic control. Tight control in Type 2 diabetes may be harder to achieve than in Type 1 diabetes (17). The United Kingdom Prospective Diabetes Study has shown through intensive therapy that lower HgA1c levels were obtainable compared to its conventional therapy group (18). However, over time, HgA1c continued to increase regardless of therapy, leading them to conclude that maintenance of near normal glycemic control over many years may not be feasible (18). This effect was attributed to the underlying deterioration of beta cell function in the progression of disease in Type 2 diabetes (18). The high costs and health care resource utilization to achieve near normal levels of glycemic control emphasize the importance of definitive conclusions in studies specific to Type 2 diabetes before large scale programs to achieve better glycemic control are implemented.

The treatment of diabetes is multifaceted and includes diet, physical activity, and drugs. Successful control of diabetes in individual patients is dependent on these treatments as well as other factors such as patient education, beliefs, and compliance. Health care providers are responsible for providing education and treatments to their patients with diabetes, which is mostly achieved in the outpatient clinical setting. Health care providers are responsible for diabetes and nutritional education, establishing short and long term glycemic goals, necessary medications, self-monitoring of blood glucose (SMBG), referrals to specialized services, and follow up visits (16). Guidelines by the American Diabetes Association (ADA) recommend that regular visits for patients on insulin should be at least quarterly and other patients quarterly or semiannually until treatment goals are achieved. The ADA also recommends glycated hemoglobin monitoring at least one or two times per year in patients with stable glycemic control and quarterly in patients with poor control or who have changes in therapy (16). There is

variation among physician practices in ordering outpatient revisit intervals and laboratory monitoring and the optimal frequency of visits or tests in patients with diabetes is not known (19, 20). These factors influence diabetic control in patients, but the exact interactions are unknown. Although studies have shown that all these factors contribute to glycemic control, it is not clear which factors, if any, have more influence on glycemic control compared to others. Examining characteristics among persons with diabetes who have good or poor control may identify some of these factors to allow more focused, effective, and efficient treatment.

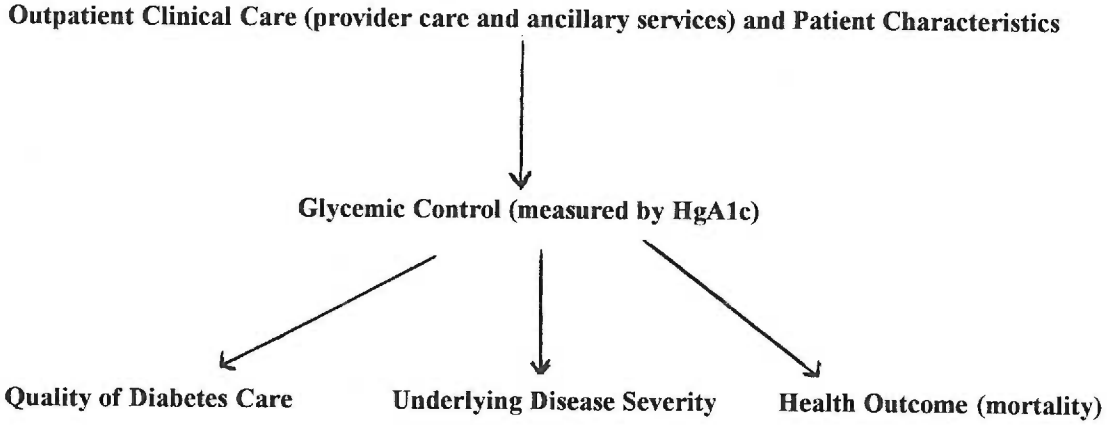
In the era of health care cost constraints, health outcomes of prevalent diseases such as diabetes are important to explore. Glycemic control is often used as a marker for good medical care of patients with diabetes mellitus. Achieving near-normal hemoglobin A1c values implies effective medical care with the expectation of good health outcomes. Trials such as the DCCT and UKPDS have shown that this is true for diabetes specific microvascular disease; but not much is know about more general health outcomes. The focus on blood glucose control in many studies has been criticized as being too narrow and that assessment of diabetes care needs to consider other variables such as the overall health and quality of life in patients as well as long term health outcomes, such as mortality (21, 22, 23). The association between glycemic control and other health outcomes has not been well explored in previous studies. Glycated hemoglobin, such as HgA1c, is often used as a measure of clinical health care outcomes in diabetes care (24). In implementation of diabetic care guidelines, such as the American Diabetes Association guidelines (16), glycated hemoglobin has been used as a measure of success of these guidelines, inferring this will result in lower diabetic complications.

Good quality of care in patients with diabetes is often interpreted through achieving HgA1c values near normal levels. Hemoglobin A1c is clearly a good physiologic outcome measure (25). But the relationship of glycated hemoglobin values to other outcomes may differ in specific populations. It can be an indicator of treatment

effectiveness, but can also be an indicator of underlying disease severity. How glycated hemoglobin is associated with more general health outcomes, such as mortality must also be explored. Because diabetes is a prevalent chronic disease with significant health and economic costs, guidelines, such as from the ADA (16) and the Oregon Diabetes Project (26), become increasingly important to maintain high standards of care and manage costs efficiently. If hemoglobin A1c is used as a tool for measuring the impact of these guidelines on effectiveness of diabetes care, the relationship of HgA1c and more broader health outcomes must be better defined.

This project explores factors associated with glycemic control, as measured by HgA1c, and other health outcomes through a perspective that has not been well studied in the current literature. The conceptual framework of this project explores the relationship of three components: 1) outpatient clinical care and patient characteristics, 2) glycemic control and 3), the relationship of glycemic control to quality of diabetes care, disease severity, and mortality.

Conceptual Framework:



The model represents some of the major components in the outpatient treatment of diabetes. Outpatient clinical care includes provider follow up and ancillary services. Provider follow up includes clinic visits, laboratory monitoring of glycemic control, such as with hemoglobin A1c measurements, and prescribing drugs. Ancillary services include referrals for diabetic education, diabetes specific nursing services such as teaching how to monitor capillary blood glucose, or follow up of therapy. Patient characteristics include demographics, compliance, comorbid conditions, concurrent medications, and diabetic medications. All these factors interact and influence glycemic control. The third component of the model emphasizes the importance of understanding the relationship of glycemic control (HgA1c), a physiologic outcome, to more global outcomes. There are many variables that interact in a patient's ability to achieve good glycemic control; incorporating all of them in a meaningful study is difficult.

By studying a more homogeneous population of persons with diabetes, such as veterans, some of the most outstanding differences between patients with good and poor glycemic control can be identified. The VA population provides a specific population of older patients with poorer health and lower socioeconomic status (27). In 1996, the prevalence of diabetes mellitus in persons using the VA was 19% (27).

This project is based on the hypothesis that there are identifiable differences between persons with diabetes who have good glycemic control and poor glycemic control. Identifying these differences enables providers to better understand the interactions of outpatient care and patient characteristics and predict which persons with diabetes are more likely to be difficult to control. This can guide the health care provider to focus resources more efficiently to improve glycemic control and delay or prevent costly complications that impact quality of life. Additionally, identifying differences will help determine the relationship of glycemic control to quality of diabetes care, disease severity, and mortality.

The project objectives are: 1) To describe provider practice patterns, utilization of ancillary services, and patient characteristics among patients with good, moderate, and poor glycemic control. 2) To examine the relationship of mortality in persons with diabetes with different levels of glycemic control.

METHODS: STUDY DESIGN

This study was conducted at the Portland Veterans Affairs Medical Center (PVAMC) in a retrospective cohort design. This setting has the following advantages: 1) There is a substantial number of patients who have diabetes, allowing adequate sample size for this study. 2) Most veterans receive care and medications exclusively in the VA medical center, making patient records, laboratory tests, and prescription data complete. 3) The PVAMC core computer system provides a complete, easily obtainable data base for many measures of this study and thus provides an efficient and accurate source for gathering data within a reasonable amount of time.

The VA computer system was used to identify all patients in this study. Selection of study patients through the VA database was done in a stepwise process to assure accuracy in the identification of all patients with diabetes in the VA system receiving care in the year 1990. First, all patients in 1990 with either a HgA1c value and/ or a diabetic medication on formulary during 1990 were identified. All HgA1c values and diabetic medications for these patients were extracted for a six year period beginning in 1990 through 1995. Patients who had only one HgA1c value and patients who did not have any diabetic medications prescribed during this six year period were excluded. This eliminated patients who do not have diabetes as well as patients with diet controlled diabetes. A diabetic medication was either a medication containing insulin or one of the oral agents on the VA formulary. Through this process a total of 1551 patients were identified. The VA computer system was used to construct a database for these patients that included demographic, appointment, laboratory, and pharmacy records during the study period. Patients who had less than four years of follow up were excluded from the study, unless they had died (205 patients excluded). All patients who died were included in the study. Follow up was defined as having at least one outpatient clinic appointment in any VA

clinic in each year of the study. The remaining1346 patients were classified into three groups based on their average HgA1c during the study period. The well controlled group (WC) had average HgA1c measurements of $\leq 7\%$. The poorly controlled group (PC) had average HgA1c of $\geq 9\%$. The patients with HgA1c averages between these two groups were in the moderately controlled group (MC). The six year period allowed adequate time for follow up with the patient's primary care provider as well as ancillary services and accumulation of laboratory data.

METHODS: MEASURES

The database obtained from the VA computer system contained demographic information including age, employment status, marital status, and whether the patient had died. Laboratory data included the values and number of HgA1c measurements and cholesterol values. Clinical data included all patient appointments during the study period and whether they attended those appointments. Pharmacy data included all types of diabetic medication on the VA formulary as well as nitrates, antihypertensive drugs, and cholesterol lowering medications. In addition, the PVAMC also has a detailed Cancer Registry that contains all cancer data on any patient treated at the PVAMC diagnosed with cancer. This database was started in 1974 and includes all pathological data as well as cancer treatments and follow up. The Cancer Registry estimates the database to be over 98% accurate in data collection, based on physician review of a random sample of patients in the database annually (28). This registry was used to identify any patients in the cohort who had cancer, what type of cancer, and if the patient died during the study period. The Birls Benefit Delivery Information database was also used to identify patients who died during the study period. This is a national VA database for the Unites States and obtains information of deaths through three separate sources: the social security administration, self report from someone who knew the decedent, and from any deaths in a VA hospital or nursing home facility (29).

Frequency of follow up of patients by providers and utilization of ancillary services was determined using the clinical data in the database. All provider appointments were classified into General Medicine (GM) appointments and Endocrinology (Endo) appointments. The utilization of ancillary services was determined in a similar manner. Ancillary services were defined as patient appointments with the dietitian, diabetic nursing related appointments such as "CBG" (capillary blood glucose) clinic or diabetic nurse appointment, or enrollment in diabetes education classes. Only appointments that were

attended by the patient were included in analyses. Appointments other than General Medicine or Endocrine clinic appointments were excluded. Podiatry, optometry, and ophthalmology appointments were not included under ancillary services because it could not be determined whether the purpose of these visits was for diabetes specific problems.

The clinic database also provided information on whether the patients attended their appointments, did not show up ("no showed"), or if the appointments were cancelled. Cancelled appointments consisted of cancellation by the clinic or if the patient notified the clinic to cancel the appointment. Cancelled appointments were judged not to be good indicators of compliance and were not used in estimating it. Through this information, attendance of clinic appointments (appts.) was estimated using a compliance index:

Compliance Index = Number of appts. attended / (Number of appts attended + Number of appts. no showed)

All diabetic medications on each patient were available, and patients were classified as either using insulin, an oral diabetic medication, or both agents during the study period. Commonly prescribed drugs used for coronary artery disease and hypertension were also extracted as indicators of comorbidity. Cholesterol values and cholesterol medications during the study period were also used as comorbidity measures.

The demographic database also indicated whether a patient had died during the study period. Additionally, the Cancer Registry at the PVAMC was used to determine if cancer was related to the cause of death. Determining whether cancer contributed to death was done by looking at each case individually by the author. The author was blinded to the patient's level of glycemic control. Cancer related death was determined if it was so stated on the Cancer Registry summary, if the cancer was extensive (e.g.. metastatic cancer), and through review of hospital discharge summaries when available.

To confirm the accuracy of deaths, all study subjects were checked through the Birls national VA database.

Comorbidity was estimated using several variables. The pharmacy data was used to compare use of cardiac drugs and cholesterol lowering medications among groups. Cardiac drugs included nitrates and two classes of antihypertensive medications on the VA formulary (beta blockers and calcium channel blockers) that were most likely to be prescribed in patients with cardiac disease. All lipid lowering medications available on the VA formulary were included in the pharmacy database search. The average of all cholesterol values on each individual was also used as a measure of comorbidity. Additionally all patients in the study who were registered in the Cancer Registry were identified. Patients were classified as having a cancer comorbidity if they were listed in the Cancer Registry, unless it was a non-melanoma skin cancer (See Appendix A).

METHODS: DATA ANALYSES

The information from the VA computer system was organized using the relational database program, Visual DBase 5.5. After organizing and coding the data, statistical analyses were done using SPSS version 9.0. Descriptive statistics were used to characterize most data. Comparison of continuous data between groups was done using independent samples T - tests for two groups, or One-way ANOVA for more than two groups. Discrete data comparison between groups was done using Chi - square. Logistic regression was used to examine the relationship of multiple variables with mortality. HgA1c values were analyzed as both a continuous variable and also in groups (WC, MC, PC) in order to make the results more clinically meaningful.

RESULTS

A total of 1551 patients were identified through the above criteria. Patients with less than four years of follow up were excluded. Of the remaining patients, 417 patients were in the well controlled (WC) group, with average HgA1c $\leq$ 7%, 234 patients were in the poorly controlled (PC) group, with average HgA1c $\geq$ 9%, and 695 patients were in the moderately controlled (MC) group, with average HgA1c between 7% and 9%. The normal range for HgA1c at the PVAMC laboratory is 3.4 - 6.1%. All patients who died during the study period were included in the analyses, regardless of length of follow up. (Table 1)

Table 1: Cohort

Total patients identified:	1551	
205 patients excluded for follow up less than 4 years		
Patients in Cohort	1346	HgA1c average (%)
	417 (WC)	$\leq$ 7%
	695 (MC)	7% < MC < 9%
	234 (PC)	$\geq$ 9%

The average age in the WC group was 70 years, 67 years in the MC group, and 63 years in the PC group ($p<0.001$). Patients were more likely to be married in the WC group (61%) and MC group (61%) compared to the PC (53%) group, but this difference was not statistically significant, ($p>0.05$). Patients were more likely to be retired in the WC group compared to the MC group and PC group, but this was mostly attributable to the WC group's older age.

The average HgA1c was 6.1% in the WC group, 7.9% in the MC group, and 9.7% in the PC group ($p<0.001$). The HgA1c test was ordered more frequently in the MC group and PC group compared to WC group during the six year study period, (11.4 MC, 10.8 PC, 8.3 WC, $p<0.001$). (Table 2)

Table 2:

HgA1c	**WC** (≤ 7%)	**MC** (7%<MC<9%)	**PC** (≥ 9%)
Age (years)	70.0	66.8	62.7*
Married (%)	61.1%	61.0%	52.8%
Retired (%)	77.3%	67.6%	54.9%**
HgA1c (no. tests)	8.3±5.9	11.4±6.7	10.8±6.5 *
Avg. years of follow up	5.02	5.43	5.45 *
HgA1c (no. tests/year)	1.7	2.1	2.0
HgA1c average	6.11%	7.94%	9.66% *

*statistically significant ($p<0.05$, One way ANOVA)

**statistically significant ($p<0.05$, Chi square)

The average duration of follow up for the well controlled group was 5.02 years, 5.43 years for the moderately controlled group, and 5.45 years for the poorly controlled group, ($p<0.001$). There was no difference in the average number of General Medicine appointments between groups (WC 2.5/year, MC 2.6/year, PC 2.7/year, $p=0.49$). The poorly controlled and moderately controlled groups utilized slightly more endocrine appointments compared to the well controlled group (PC 0.7/yr, MC 0.7/yr, WC 0.4/yr,

p<0.001). The trend was similar in utilization of ancillary appointments (PC 0.9/yr, MC 0.8/yr, WC 0.5/yr, p<0.001). (Table 3) The total number of all outpatient clinic appointments (including cancellations and no shows) did not differ among the three groups during the six year study period (WC 126, MC 137, PC 131, p>0.05).

As described earlier, the following equation was used as a measure of compliance: **[Compliance = Number of clinics attended / (Number attended + Number no showed)]**

The closer the value to one, the more compliant the patient. No shows indicated the patient did not cancel in advance. Clinic appointments that were cancelled consisted of those cancelled by the VA clinic or if the patient cancelled or rescheduled. Neither of these were used in the equation. Using this estimate, compliance with appointments was slightly better among the well controlled and moderately controlled patients compared with poorly controlled patients (WC 0.90, MC 0.90, PC 0.85, p=0.002). (Table 3)

Table 3: Clinic Data

HgA1c	**WC** (≤ 7%)	**MC** (7%<MC<9%)	**PC** (≥ 9%)
N	417	695	234
Years of follow up	5.02	5.43	5.45 *
GM/year	2.50 (± 1.70)	2.59 (±1.80)	2.67 (± 1.67)
Endo/year	0.37(± 0.88)	0.69(±1.24)	0.69(± 1.20)*
Ancillary/year	0.48(±0.67)	0.82(±0.93)	0.93(±0.98)*
Compliance	0.90	0.90	0.85 *

*statistically significant (p<0.05, one-way ANOVA)

Prescribing of diabetic medications was also studied between groups. The database identified patients who were prescribed only insulin, patients who were prescribed only oral diabetic agents, and patients who were prescribed both types of drugs during the entire six year period. In those patients who were only prescribed insulin, the percentages were approximately the same in each group (WC 26%, MC 33%, PC 28%). Most patients in the WC group were prescribed only an oral diabetic medication while most patients in the PC group were prescribed both an oral diabetic medication and insulin during the study period. (Table 4)

Table 4: Diabetic Medications

HgA1c	**WC** (≤ 7 %)	**MC** (7%<MC<9%)	**PC** (≥ 9%)
N *	413	693	234
Only Oral med.	238(58%)	221(32%)	47(20%)
Only Insulin	107(26%)	230(33%)	65(28%)
Both meds	68(16%)	242(35%)	122(52%)

Chi-square, $p<0.001$

Total patients in analysis = 1340.
* Six patients with missing data.

The VA computer system also identified whether a patient had died. The Cancer Registry identified nine additional patients who died during the study period. These nine patients were not listed as dead in the VA computer demographic information but were included in the mortality analyses because the Cancer Registry was judged to be more accurate. All study patients were checked through Birls national database. Birls

identified 22 additional patients who died during the study period. However, there were 15 patients not identified by Birls who were identified as dead in the VA database. These additional patients from the Cancer Registry and the Birls database, as well as the 15 patients from the VA database, were rechecked in the VA database. If they were not entered as a death in the VA database, they had been lost to follow up earlier than the date of death identified by the Birls database or Cancer Registry. All patients identified as having died in any of these three data sources were included in the mortality analyses. Mortality was significantly higher in the well controlled group compared to the moderately controlled group and the poorly controlled group (WC 38%, MC 25%, PC 19%, Chi square $p<0.001$). Deaths from cancer were not significantly different between groups. Independent samples T tests between average age of death and average age of alive patients were done within each group and were significant in WC group (age 72 vs. 69, $p=0.005$) and the MC group (age 70 vs. 66, $p<0.001$), but not in the PC group (age 65 vs. 62, $p=0.134$). (Table 5)

Table 5: Mortality

HgA1c	WC (≤ 7%)	MC (7%<MC<9%)	PC (≥ 9%)
N	417	695	234
Patients Died	157(38%)	173(25%)	45(19%) *
Patients Alive	260(62%)	522(75%)	189(81%)
Avg. Age in years (At time of death)	72	70	65 **
Avg. Age in years (Alive)	69	66	62 **
Cancer related death	24(15.3%)	20(11.6%)	5(11.1%)***

* $p < 0.001$, Chi square
** $p < 0.001$, One way ANOVA
*** Chi square, $p = 0.461$

Indicators of comorbid conditions in this study included medications that were associated with coronary artery disease, cholesterol values and medications, and also patients with cancers identified through the Cancer Registry database. Cardiac medications studied were nitrates (oral, sublingual, and topical), calcium channel blockers and beta blockers. There were no differences between groups in the proportion of patients prescribed nitrates or beta blockers. There were proportionately more patients prescribed calcium channel blockers in the well controlled and moderately controlled groups compared to the poorly controlled group (WC 47%, MC 52%, PC 38%, Chi-square, p=0.001). (Table 6)

Table 6: Cardiac Medications

HgA1c	WC (≤ 7%)	MC (7%<MC<9%)	PC (≥ 9%)
N **	413	693	234
SL NTG	188(46%)	357(52%)	124(53%)
Nitro Patch/Pill	145(35%)	274(40%)	85(36%)
Beta Blocker	116(28%)	189(27%)	51(22%)
Ca Channel Blocker	194(47%)	358(52%)	89(38%)*

*Chi square, p = 0.001
**6 patients not included in analysis, data missing.

Total cholesterol values were obtained to determine the average total cholesterol in the six year study period for each patient. Additionally, whether the patient had a prescription filled for any cholesterol medication during the study period was also identified. All cholesterol lowering medications available on the VA formulary during the six year study period were included in the analyses. These were niacin, gemfibrozil, any "statin" drug, and colestipol. Cholesterol values and medication data were available on 1068 patients. Table 7 reveals the cholesterol medication prescriptions between each group. There was no significant difference of any cholesterol medications prescribed between the three groups, except for gemfibrozil, which was prescribed more often in the poorly controlled group. The proportion of study patients with any type of cholesterol medication prescribed during the study period was not significantly different between the three groups. (Table 7)

Table 7: Cholesterol Medications

HgA1c	WC (≤ 7%)	MC (7%<MC<9%)	PC (≥ 9%)
N *	334	554	180
Niacin	13(3.9%)	20(3.6%)	8(4.4%)
Statin	6(1.8%)	7(1.3%)	3(1.3%)
Colestipol	14(4.2%)	17(3.1%)	6(3.3%)
Gemfibrozil	28(8.4%)	67(12.1%)	33(18.3%)**
Any Chol. Med	51(15.3%)	93(16.8%)	39(21.7%)***

*278 patients not included in analysis, data missing.
**Chi square, p = 0.004
***Chi square, p = 0.18, not significant.

Total Cholesterol values were averaged and compared between groups. Triglyceride values were also obtained, but fewer patients had these values during the study period. The poorly controlled group had significantly higher cholesterol values and triglyceride values. (Table 8a)

Table 8a: Cholesterol Values
Total Cholesterol:

HgA1c	WC (≤ 7%)	MC (7%<MC<9%)	PC (≥ 9%)
N	334	554	180
Avg. No. of Chol.*	8.6	9.2	8.8
Avg. Cholesterol (mg/dl)	195	205	214**

* Average number of cholesterol tests ordered in the study period.
** One way ANOVA, p<0.001

Table 8a: (continued)
Triglycerides:

HgA1c	**WC** (≤ 7%)	**MC** (7%<MC<9%)	**PC** (≥ 9%)
N	134	253	86
Avg. Triglycerides (mg/dl)	316	315	444*

*One way ANOVA, p=0.017

Cholesterol values and cholesterol medications, if prescribed, during the six year study period was not obtained on 278 patients in the study during the original data collection by the programmer. Prescription data during 1990 through 1995 on these patients were not obtainable by the author. However, archived cholesterol values during this period were accessible. The proportionate number of patients from each group with data missing was not significantly different between each of the three groups. (Table 8b)

Table 8b: Patients without cholesterol data

HgA1c	**WC** (≤ 7%)	**MC** (7%<MC<9%)	**PC** (≥ 9%)
N	83(20%)	141(20%)	54(23%)*

*Chi square, p = 0.595, Not Significant.

In order to be certain that these 278 patients did not have different average total cholesterol values within each group compared to the other 1068 patients, a sample of 20

patients from each group was taken. All 60 of these patients had at least one cholesterol value during the study period. All total cholesterol values during the study period on each of these 60 patients were obtained by the author and the average total cholesterols were calculated. The average total cholesterol values were higher in the poorly controlled group, similar to table 8a. (Table 8c)

Table 8c: Cholesterol data

HgA1c	**WC** (≤ 7%)	**MC** (7%<MC<9%)	**PC** (≥ 9%)
N	20	20	20
Avg. No. of Chol.	6.9	7.7	8.0*
Avg. Cholesterol (mg/dl)	182	185	218**

* Average number of cholesterol tests ordered in the study period. One way ANOVA, $p = 0.783$.
**One way ANOVA, $p = 0.003$

Table 9 compares average hemoglobin A1c, age, total cholesterol, triglycerides, and having a diagnosis of cancer between live patients in the study and those who died. Those who died had a significantly lower average hemoglobin A1c, average total cholesterol, and average triglycerides compared to those who did not die. Those who died were also older and had more diagnoses of cancers compared to the study patients who did not die.

Table 9:

	Alive	Dead	
N	971	375	
Mean Hemoglobin A1c (%)	7.8%	7.2%	t test, $p<0.001$
Mean Age (years)	66	70	t test, $p<0.001$
Mean Total Cholesterol (mg/dl)	207	195	t test, $p<0.001$
Mean Triglycerides (mg/dl)	361	264	t test, $p=0.018$
Cancer Diagnosis (%)	129(13%)	86(23%)	chi square, $p<0.001$

It is possible that persons who are terminally ill may have lower hemoglobin A1c values near the date of death, and thus account for the lower hemoglobin A1c average in the patients who died compared to the remainder of the study patients. In order to evaluate this, the average hemoglobin A1c values were recalculated on the study patients who died, excluding values near the time of death . The average was calculated omitting values the last year before death (HgA1c minus 1 year), and also omitting values the last two years before death (HgA1c minus 2 years). These recalculations did not show a clinically significant change in hemoglobin A1c averages. (Table 10).

Table 10: Hemoglobin A1c averages in patients who died during the study period.

Group	HgA1c Average Total length of follow up	HgA1c Average Minus 1 year	HgA1c Average Minus 2 years
WC	5.9%	5.9%	5.8%
MC	7.9%	7.8%	7.7%
PC	9.6%	9.6%	9.1%

See **Appendix B** for detailed description of this table.

Logistic regression analysis was performed to determine the associations with variables measured in this study and death. All possible variables that might have a clinically meaningful relationship with whether or not a person in the study died were included in the analysis. Nine variables in the regression analysis explained 11.5% of the variance of death (R-square = 0.115). Death was associated with lower average hemoglobin A1c values, which accounted for 3.8% of the variance. Nitrate prescriptions were positively associated with death while beta blockers and oral diabetic medications were negatively associated. Having a cancer and older age was associated with death. Being seen in endocrine or ancillary clinics was negatively associated with death. Finally, having a lower average total cholesterol was associated with death. (Table 11)

Table 11: Forward Stepwise Logistic Regression

Variable	B*	R-square	Change in R-square	p
HgA1c	--	0.038	----	<0.0001
Nitrate**	+	0.057	0.019	<0.0001
Betablocker	--	0.070	0.013	0.0002
Cancer	+	0.081	0.011	0.0004
Endocrine Clinic	--	0.092	0.011	0.0012
Ancillary Clinics	--	0.100	0.008	0.0031
Avg. Cholesterol	--	0.108	0.008	0.0039
Age	+	0.111	0.003	0.0417
Oral DM Med.	--	0.115	0.004	0.0333

* Standardized regression coefficient (**B**), sign associated with coefficient.
** Nitrate was defined as nitroglycerin either in patch form or pill form, excluding sublingual nitroglycerin.

DISCUSSION AND CONCLUSIONS

This study found several interesting associations when comparing patients with good, moderate, and poor glycemic control. In this cohort, persons who have diabetes with good glycemic control were more likely to be married and older in age compared to those with poor glycemic control. This suggests that social support, or spousal support may play an important role in helping with glycemic control.

The study does not differentiate between Type 1 and Type 2 diabetes. But based on disease prevalence, it is clear that the majority of patients in this study have Type 2 diabetes. There is a possibility that the well controlled group may have some patients who do not actually have diabetes, but the requirement that a diabetic medication was prescribed during the six year study period minimized this possibility. The duration of each patient's diabetes was not identified in this study. However, it is known that the proportion of patients with Type 2 diabetes who use insulin increases with duration of diabetes and the use of oral agents declines (5). More well controlled patients were prescribed solely oral diabetic agents in the six year period compared to the poorly controlled patients. In addition, the poorly controlled patients were prescribed more of both insulin and an oral agent during the six year period. This pattern suggests that patients in the poorly controlled group had the disease for a longer duration. This does not explain why the mortality is higher in the well controlled group.

Glycemic control was evaluated as three separate groups and as a continuous variable in order to make the results more clinically interpretable. The HgA1c values defining each group were chosen to be able to compare groups with a substantial difference in control, mainly between the WC and PC group. HgA1c of 7% was chosen as the upper boundary for the WC group because it is consistent with the ADA recommended treatment goal for HgA1c in diabetes mellitus. Also, the well controlled group in this study had average HgA1c values that are similar to the intensive therapy

groups in the Diabetes Control and Complications Trial, the United Kingdom Prospective Diabetes Study, and the Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes (8, 12, 14).

Data on clinic appointments suggest that endocrine and ancillary clinics are utilized more frequently in patients with poor glycemic control, although this difference is small. It also suggests that these patients are less compliant with their appointments compared to those with good glycemic control. Proportionately more patients with poor control are being referred to diabetic specialty clinics, which have been shown to give better quality of care compared to general medicine clinics at another VA hospital (30). The average frequency of clinic follow up in the general medicine and endocrine clinics and the frequency of HgA1c monitoring were below the recommendations of the ADA guidelines, especially in the poorly controlled group. Despite the increased medical follow up, persons with poorly controlled diabetes maintained hemoglobin A1c averages above 9%. Perhaps this is because more intensive medical care is needed. On the other hand, perhaps even closer follow up in certain poorly controlled patients is not enough to achieve improvement in glycemic control. This suggests that there are other factors, not identified in the scope of this study that affect glycemic control. A study on patients with Type 1 diabetes found that patient attitudes towards the provider-patient interaction influenced clinic attendance and that lower attendance rates of clinical services were associated with poorer glycemic control (31). Another reason could be that HgA1c is more of an indicator of disease severity rather than response to treatment in this population. A study that identified clinical characteristics related to poor glycemic control in persons with Type 2 diabetes supports these results. They found that poor control could reflect progression of failure in islet functioning, consistent with UKPDS findings (7, 18). Additionally, patients' psychosocial characteristics and attitudes were also associated with poor glycemic control (7).

Comorbidity influences glycemic control and mortality. The VA patient population as a whole represents an older, predominantly male population with poorer health compared to all persons with diabetes. The overall comorbidity of these patients should be above those of the general population in the United States. Factors, such as smoking, hypertension, and obesity were not measured in this study. However, no major differences in cardiac medications or prevalence of cancers were found between groups. The study did find that cholesterol values and triglyceride values were significantly higher in those patients with poor glycemic control, but this is the group with proportionately lower mortality.

Surprisingly, mortality was associated with lower HgA1c levels even after accounting for the older age in patients with good glycemic control in the logistic regression analysis. Of the variables used in the analysis, average HgA1c explained most of the variance in mortality. The indicators of comorbidity used in this study suggest that there is not a substantial difference between the groups that could account for the difference in mortality. The higher total cholesterol values in the poorly controlled group make it unlikely that treatment of cholesterol confounded the differences in mortality. It is possible that patients who are terminally ill may have lower HgA1c values near the time of death because of serious illness. However, calculations of HgA1c averages, excluding values from the last one or two years before year of death, did not change the averages dramatically (See Appendix B).

Glycemic control may indicate better outcomes specific to diabetic complications in well controlled, randomized trials, but this cannot be generalized to represent overall health in this VA population. One study on veterans with diabetes found that glycated hemoglobin levels did not correlate with measures of functional status scores using the SF 20 general health survey (32). In a prospective feasibility trial to study the risks and benefits of intensive treatment in Type 2 diabetes by the VA CSDM, mortality in the two groups were similar although there were more cardiovascular events in patients with a

lower HgA1c (33). Measurement of hemoglobin A1c is insufficient alone to assess medical care in diabetes. More study needs to be done to explore the relationship of glycemic control and overall health of a patient.

In conclusion, this study reveals there are identifiable differences between persons with well controlled and poorly controlled diabetes in this VA population. This is a beginning to better define the interactions of outpatient diabetes care and patient characteristics on glycemic control. More detailed study needs to be done to explore these differences. Glycemic control is commonly used as an indicator of quality of care in persons with diabetes. However, this study suggests that glycated hemoglobin values in this population may not reflect quality of care in patients with diabetes, but may indicate underlying disease severity. The higher mortality in the well controlled group also suggests that glycemic control may not be a good indicator of more general long term health outcomes, such as mortality, in this specific population. Caution should be used in interpreting glycemic control as a predictor of overall health outcome. These findings emphasize the need to broaden the narrow focus on evaluation of diabetes care, not just to better glycemic control, but more general health outcomes.

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Appendix A: List of Cancers in Study Patients in Cancer Registry.

Total Patients in Study: 1346
Total Patients in Cancer Registry: 224 (112 alive, 88 dead, 24 cases excluded because cancer diagnosed and entered in register after study period, 12/31/95)

Cancers: Alive patients in Study
112 patients (10 patients with 2 cancers, 1 patient with 3 cancers)

Prostate Cancer (Adenocarcinoma)	total	34
Colon Cancer (Adenocarcinoma, Ampulla of Vater, Lymphoma)	total	21
Bladder Cancer (Transitional Cell Carcinoma)	total	12
Head and Neck	total	13
Skin (Merkel, Basal Cell, Squamous Cell, Hutchinson's Freckle)	total	6 *
Skin (Melanoma)	total	6
Kidney (Renal Cell, Transitional Cell, Papillary Adenocarcinoma)	total	6
Lung (Squamous Cell, Large Cell, Carcinoid, Pleura)	total	4
Brain (Meningioma)	total	4
Penis (Squamous Cell Carcinoma In Situ)	total	3 *
Thyroid (Papillary, Adenocarcinoma)	total	3
Esophagus (Sarcoma, Squamous Cell Carcinoma)	total	2
Stomach (Adenocarcinoma, Leiomyosarcoma)	total	2
Pancreas (Adenocarcinoma)	total	2

Breast (Infiltrating Ductal)		
	total	2
Lymphoma/ Leukemia		
	total	2
Thymus		
	total	1
Liver (Hepatocellular Carcinoma)		
	total	1
Total Cancers		**124**
Total Patients		**112**

Cancers: Dead Patients in Cancer Registry, Cancer contributing to death
49 patients (4 patients with 2 cancers, 1 patient with 3 cancers)

Lung (Squamous Cell, Adenocarcinoma, Large Cell, Mesothelioma)		
	total	20
Prostate (Adenocarcinoma)		
	total	6
Colon (Adenocarcinoma, Mucinous adenocarcinoma)		
	total	4
Stomach (Adenocarcinoma, Lymphoma)		
	total	4
Bladder (Transitional Cell Carcinoma)		
	total	3
Pancreas (Adenocarcinoma)		
	total	3
Head and Neck (Squamous Cell)		
	total	3
Unknown Primary (Squamous Cell, Adenocarcinoma)		
	total	3
Multiple Myeloma		
	total	2
Kidney (Renal Cell Carcinoma)		
	total	2
Liver (Hepatocellular Carcinoma)		
	total	1

Peritoneum (Mesothelioma)		
	total	1
Leukemia (Acute Myeloid)		
	total	1
Bile Duct (Cholangiocarcinoma)		
	total	1
Breast (Infiltrating Ductal)		
	total	1
Total Cancers		**55**
Total Patients		**49**

Cancers: Dead Patients in Cancer Registry, Cancer not contributing to death
38 patients (5 patients with 2 cancers, 1 patient with 7 cancers)

Prostate (Adenocarcinoma)		
	total	10
Colon		
	total	9
Head and Neck		
	total	7 (all same patient)
Lung (Bronchio-alveolar, Adenocarcinoma, Squamous Cell)		
	total	7
Skin (Melanoma)		
	total	2
Liver (Hepatocellular, incidental on autopsy)		
	total	2
Bladder/Ureter (Transitional Cell)		
	total	3
Skin (Hutchinson's Freckle)		
	total	1 *
Soft Tissue Unknown Site (Chondrosarcoma)		
	total	1
Mediastinum (Neurilemmoma)		
	total	1
Pituitary		
	total	1

Brain (Astrocytoma)		
	total	1
Myeloproliferative Disease		
	total	1
Kidney		
	total	1
Multiple Myeloma		
	total	1
Skin (Basal Cell)		
	total	1

Total Cancers	**49**
Total Patients	**38**

Missing Data on One patient in registry but cancer type incomplete.

Total Missing Data	**1**

* Cancers excluded as a comorbidity. 10 cancers excluded, but only 8 patients excluded. Two patients had second cancers counted as comorbidities.

Appendix B: HgA1c Averages Omitting Values One and Two Years Before Year of Death.

The tables below contain patients who died in the study.

If a patient died in 1995:

HgA1c average (Total length of follow up) equals the average of all HgA1c values on patient.
HgA1c average (Minus 1 year) equals the average of all HgA1c values excluding values in 1995. (1990 through 1994 values)
HgA1c average (Minus 2 years) equals the average of all HgA1c values excluding values in 1995 and 1994. (1990 through 1993 values)

Paired T test was done within each group with the total HgA1c average and the adjusted average.

Many patients were not included because the adjusted averages were not able to be done for multiple reasons, as patients did not consistently have HgA1c values for every year or they died early in the study.

Group	N	HgA1c Average Total length of follow up	HgA1c Average Minus 1 year
WC	126	5.91%	5.86% p = 0.01
MC	153	7.85%	7.83% p=0.50
PC	38	9.61%	9.57% p=0.81

Group	N	HgA1c Average Total length of follow up	HgA1c Average Minus 2 years
WC	113	5.93%	5.85% p = 0.16
MC	138	7.87%	7.69% p=0.001
PC	35	9.61%	9.05% p=0.006