Technology Assessment

Technology Assessment Program

Applicability of the Evidence Regarding Intensive Glycemic Control and Self-Monitored Blood Glucose to Medicare Patients with Type 2 Diabetes

DRAFT REPORT

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Agency for Healthcare Research and Quality
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Applicability of the Evidence Regarding Intensive Glycemic Control and Self-Monitored Blood Glucose to Medicare Patients with Type 2 Diabetes

Technology Assessment Draft Report

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Tufts-NEMC EPC

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Chapter 1. Introduction

This technology assessment report on intensive glycemic control and self-monitoring of blood glucose (SMBG) in patients with type 2 diabetes mellitus is prepared by the Tufts-New England Medical Center Evidence-based Practice Center (Tufts-NEMC EPC) for a Medicare Coverage Advisory Committee (MCAC) meeting. The primary goal of the report is to describe the applicability of the larger, long-duration studies to the nondialysis Medicare population (i.e., people at least 65 years old).

The specific questions addressed are described in the Methods chapter (Chapter 2). Below is a narrative review of diabetes (focusing on type 1), its epidemiology in the US, complications due the disease and its treatment, intensive glycemic control, and patient monitoring of glycemia.

Definition of diabetes

Diabetes mellitus is a group of metabolic disorders characterized by abnormal fuel metabolism, which results most notably in hyperglycemia and dyslipidemia, due to defects in insulin secretion, insulin action, or both. Diabetes is a serious chronic disease without a definitive cure, which is associated with significant morbidity and mortality, both acute and chronic.

Types of diabetes

Type 2 diabetes, previously called non-insulin-dependent diabetes mellitus (NIDDM) is the most prevalent type, accounting for up to 95 percent of all cases of diagnosed diabetes.[1] Approximately 5 percent of cases are due to type 1 diabetes, previously called insulin-dependent diabetes mellitus (IDDM).

Type 1 diabetes refers to cell-mediated autoimmune destruction of pancreatic beta islet cells, which leads to absolute insulin deficiency. All patients with type 1 diabetes require insulin for survival. Peak incidence occurs during puberty although disease onset can occur at any age. The incidence of type 1 diabetes is rising in almost all populations and the age at onset is declining. There are an estimated 500,000 to one million people with type 1 diabetes in the United States or 0.16 – 0.32 percent of the population; there are approximately 20,000 new cases per year. There is no known way to prevent type 1 diabetes.

Type 2 diabetes is characterized by varying degrees of insulin resistance and insulin deficiency. Resistance to the action of insulin results in impaired insulin mediated glucose uptake in the periphery (by muscle and fat) and incomplete suppression of hepatic glucose output. To overcome the insulin resistance (and therefore prevent abnormal fuel metabolism and maintain normal glucose and lipid levels), beta cells will increase the amount of insulin secreted. Higher circulating insulin levels will overcome the impedance to the action of insulin. This state of high insulin levels with euglycemia persists for many years. As the need for insulin rises, the pancreas gradually loses its ability to produce it. The abnormal fuel metabolism characteristic of diabetes (hyperglycemia and dyslipidemia) occurs when there is a mismatch between insulin requirements, as dictated by insulin resistance, and insulin supply, as determined by beta cell function. The nature of the disease and its polygenic causes result in a wide range of insulin sensitivity and insulin secretion, thus in a wide range of clinical manifestations. Type 2 diabetes

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is associated with older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity (non-White). Type 2 diabetes will continue to be a major health problem in the United States and the developed world, as sedentary lifestyle and obesity, become more prevalent.

Diabetes in the Medicare population

In general, type 1 diabetes is more prevalent in children and adolescents and the majority of type 2 diabetes cases occur in adults; however, the exact distribution of these two major types of diabetes by age is difficult to ascertain for a variety of reasons: (1) a great degree of clinical overlap exists between type 1 and type 2 diabetes, therefore, one cannot exclude either type of diabetes on the basis of the patient's age alone. For example, a patient with type 2 diabetes but with severe insulin deficiency will require insulin and may be misclassified as type 1 diabetes; (2) specific testing is often required to identify the type of diabetes. Such testing is done infrequently in clinical practice; (3) once a patient is treated exclusively with insulin, clinicians frequently fail to identify the specific etiology of diabetes and refer to all insulin-requiring patients (whether they have type 1 or type 2) as IDDM; and (4) patients with type 1 diabetes are now expected to survive long enough to reach the Medicare age (65 years) and to suffer from other conditions associated with type 2 diabetes (hypertension, dyslipidemia etc) further complicating the clinical distinction between the types of diabetes.

Epidemiology of diabetes

General population

Diabetes is one of the most common chronic diseases in the US. It is estimated that in 1999-2002, 19.3 million US adults or about 9.3 percent of the total adult US population had diabetes (6.5 percent diagnosed and 2.8 percent undiagnosed).[2] In 2005, approximately 1.5 million new cases of diabetes were diagnosed in US adults.[1] At this rate, it is estimated that more than 25 million people in the US alone will have been diagnosed with diabetes by the year 2025.

The increase in the incidence and prevalence of diabetes over the last few decades and the rise anticipated over the next few decades can be attributed to many factors including, change in diagnostic criteria, increase in diagnosis due to increased awareness, aging of the population, decreasing mortality, increase in the prevalence of obesity and growth in minority populations.

Medicare-specific

From 1980 through 2004, the prevalence of diagnosed diabetes increased in all age groups.[1,2] However, diabetes, similar to other chronic conditions, disproportionately affects the older population. In general, throughout the time period 1980-2004, people aged ≥65 years had the highest prevalence among any age group. Furthermore, the prevalence of diabetes (diagnosed and undiagnosed) in people aged ≥65 years increased from 18.6 percent to 21.8 percent between 1988-1994 and 1999-2002, paralleling the increase in the total US adult population.[1,2] It is estimated that currently over 22 percent of the population over 65 years old (eligible for Medicare) or 7.9 million individuals in the US have diabetes (15.8 percent diagnosed and 5.8 percent undiagnosed, Table 1).[2] People aged ≥65 years make up almost 40 percent of all those with diagnosed diabetes, and the prevalence in this age group is more than 10 times that in people younger than 45 years of age.[1] There are 575,000 new cases of diabetes among people aged ≥60 years.[1]

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Recently published lifetime risk and estimates of length and quality of life with diabetes are shown in Table 2 adapted from Narayan et al.[3] As an example, the lifetime risk for diagnosis of diabetes in a cohort of individuals who reached the Medicare age (65 years) in 2005 was estimated at 19 percent for men and 22 percent for women.

Life expectancy of people with diabetes is estimated to be 4-19 years less than that for people without diabetes.[3,4] Life shortening due to diabetes is negatively correlated with the age at diagnosis. In the older population with lower life expectancy because of other illnesses, diabetes contributes less to a shortened life expectancy. For example, a man diagnosed with diabetes at age 60 is estimated to live with diabetes for another 15 years, which represents a 7-year shortened life expectancy (11 years in quality-adjusted life years) compared to a 60-year old without diabetes.[3] The primary cause of premature death is macrovascular disease, including heart disease and stroke.[1] Also among those patients who develop kidney failure (microvascular disease), the primary cause of death is cardiovascular disease.[5]

Economic burden

The direct medical and indirect expenditures attributable to diabetes in 2002 were estimated at $132 billion.[6] Of that amount, $92 billion was direct medical costs, 52 percent of which were incurred by people >65 years old. Approximately 57 percent of direct medical costs were due to inpatient care (hospitalization or nursing home).

Complications of diabetes

Acute complications

Hyperglycemia

Acute complications directly due to diabetes are related to severe hyperglycemia and include polyuria, polydipsia, polyphagia, weight loss and blurred vision. Patients may exhibit impaired growth and increased susceptibility to infections. Acute marked hyperglycemia may lead to diabetic ketoacidosis (DKA) in type 1 diabetes or to the hyperglycemic hyperosmolar nonketotic syndrome (HHNS) in type 2 diabetes.

Hypoglycemia

Patients with diabetes who are treated with oral medications (especially insulin-secretagogues) or insulin are also at risk for hypoglycemia. The latter is recognized as a major limitation in achieving good glycemic control. The frequency, severity and sequelae of hypoglycemia varies. Mild hypoglycemia is generally defined by the ability to self-treat while severe is defined by the need for external help (Grade 3 hypoglycemia requires oral carbohydrates with help of others; Grade 4 is hypoglycemic coma). With aging, symptoms of hypoglycemia become less intense because of an attenuation of the autonomic response to low blood sugar.[7] The diminished symptomatic response limits the time available to treat and places the elderly at high risk for developing the neuroglycopenic symptoms of hypoglycemia. Furthermore, hypoglycemia in the elderly may precipitate serious morbidity, such as vascular events, osteoporotic fracture or intracranial bleeding from a fall. The occurrence and severity of hypoglycemia can also be affected by interactions between antidiabetes medications and other medications and (diabetes-related) autonomic neuropathy. Target levels of glycemic control can also impact on hypoglycemia, such that it is likely that patients attempting to achieve lower target levels are more likely to overshoot into hypoglycemia.

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In type 1 diabetes, mild hypoglycemia occurs approximately twice a week while the frequency of severe hypoglycemia ranges from 0.2 to 1.7 episodes per patient per year.[7,8] The annual prevalence (number of patients reporting at least one episode) of severe hypoglycemia is 30-40 percent. Estimates on the frequency of hypoglycemia in patients with type 2 diabetes are less accurate for a variety of reasons. In the largest trial in type 2 diabetes patients aged 25-65 years (UKPDS), the reported mean proportion of patients with at least one episode of severe hypoglycemia was 0.6 and 2.3 percent for those on sulfonylurea and insulin respectively.[9] In other smaller studies (age range 40-87 years), the prevalence of severe hypoglycemia was 0.6-0.8 percent on sulfonylurea and 0-15 percent on insulin. The frequency of severe hypoglycemia in type 2 diabetes patients (age range 27-87 years) is 0.02 to 0.35 episodes per patient per year, 10-fold lower than in type 1 diabetes. Age is a risk factor for severe hypoglycemia but specific data on the population over 65 are not available. Additional data on the risk of severe hypoglycemia with type 2 diabetes is presented below.

Chronic complications

Chronic complications are due to chronic persistent hyperglycemia which leads to vascular damage and, in turn, end-organ damage of various organs, especially the eyes, kidneys, nerves, heart, and brain. Unfortunately, many patients with diabetes remain asymptomatic and undiagnosed for long periods, so that the first presentation of the disease is frequently a chronic complication. Indeed, about 50 percent of newly diagnosed type 2 diabetes have already developed a vascular complication. Complications associated with diabetes are classified as microvascular and macrovascular.

Microvascular complications include retinopathy with potential loss of vision, nephropathy leading to kidney failure, peripheral neuropathy leading to pain, foot ulcers, and limb amputation and autonomic neuropathy causing gastrointestinal, genitourinary, cardiovascular symptoms and sexual dysfunction. Microvascular complications are a significant cause of morbidity. Diabetes is the leading cause of blindness (12,000 – 14,000 new cases/year), chronic kidney disease (44,400 new cases of end-stage kidney disease) and nontraumatic limb amputation (82,000 per year) in the US. Persistent chronic hyperglycemia is the major contributor to the microvascular complications, which are highly specific for diabetes. The microvascular complications occur more commonly in patients with type 1 diabetes.[10] In the UKPDS trial of people 65 years and younger with newly diagnosed type 2 diabetes, over about a decade approximately 11 microvascular events (retinopathy and kidney failure) occurred per 1000 patient-years (in the conventional treatment arm).[11]

Macrovascular complications include coronary heart disease, peripheral vascular disease and cerebrovascular disease (stroke). Compared to people without diabetes, persons with diabetes are 2 to 4 times more likely to develop heart disease or suffer a stroke. People with diabetes, but without previous myocardial infarction, have as high a risk of myocardial infarction as people without diabetes who have had a previous myocardial infarction.[12] Macrovascular complications are the main cause of mortality, specifically heart disease and stroke account for about 65 percent of deaths in people with diabetes.[1] Although persistent chronic hyperglycemia is recognized to contribute to macrovascular complications, associated conditions (hypertension, dyslipidemia, smoking) appear to be the primary contributing factors to the macrovascular complications. Therefore, macrovascular complications are more common in patients with type 2 diabetes who frequently exhibit a dysmetabolic syndrome.[11,13] The UKPDS trial found that approximately 24

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macrovascular events (myocardial infarction, stroke, or peripheral vascular events) occurred per 1000 patient-year in the conventional treatment arm.[11]

Mortality

In 2002, diabetes was the sixth leading cause of death based on the 73,249 US death certificates in which diabetes was listed as the underlying cause of death. According to death certificate reports, diabetes contributed to a total of 224,092 deaths, though diabetes is likely to be underreported as a cause of death. Overall, the risk for death among people with diabetes is about twice that of people without diabetes of similar age. All-cause mortality occurred approximately 19 times per 1000 patient years in the conventional treatment arm of UKPDS.[11]

Technologies for monitoring blood glucose

Monitoring glycemic status is paramount importance in the management of diabetes, because it provides the means to evaluate efficacy of treatment and guide further therapeutic interventions. Glucose monitoring has been traditionally achieved by a combination of testing during office visits and self-monitoring of blood glucose by patients on a daily basis.

Hemoglobin A1c (HbA1c)

Hyperglycemia causes glycosylation of hemoglobin to an extent dependent on the ambient glucose level. Glycosylated hemoglobin (its major form being HbA1c) provides an excellent measure of the degree of glycemia over the proceeding 2-3 months, and its levels are correlated with microvascular and macrovascular complications in observational and interventional studies. As a result, HbA1c is considered the "gold standard" for monitoring glycemic status and guiding therapy.

Self-monitoring of blood glucose (SMBG)

HbA1c provides a quantitative and reliable way of monitoring long-term glycemic control and guiding therapy; however, it is of little value in helping patients manage their glycemia on a daily basis. SMBG allows patients to monitor their glycemic status and make adjustments to their regimen on a day-to-day basis. Specifically, SMBG can allow patients to more finely adjust their insulin and other antidiabetes medication doses, diets, and exercise levels and patterns. SMBG may also allow patients to identify problem foods or activities that cause spikes in their blood glucoses. Thus, SMBG can result in positive feedback of better management techniques for patients. Until recently, the only clinically available method for SMBG was the use of capillary blood glucose monitors but newer glucose monitoring technologies are emerging, as described below.

It should be noted that home monitoring is a multibillion-dollar industry with sales forecast to reach $3 billion in 2008.

Capillary Blood Glucose Monitors (Glucometers)

Capillary blood glucose monitoring involves finger pricking to get a small amount of whole blood that is applied to a test strip. The strip is then placed in a small hand-held device that quantifies the glucose concentration. Results from glucose meters are generally less accurate than measures using laboratory methods. In addition, operator-related errors are common.[14,15]

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Continuous glucose monitoring (CGM)

CGM utilizes a minimally invasive device that provides glucose measurements from the subcutaneous tissue every 1-5 minutes. Medical personnel or the patients themselves place a catheter in the patient's abdominal subcutaneous tissue. The catheter contains a small electrode (sensor, probe) which is attached to a small plastic disk about the size of a dime. The disk is taped to the skin to hold the sensor in place. The sensor continuously measures glucose in the patient's subcutaneous tissue. The glucose values are stored in a separate monitor, which collects 288 readings a day or 864 readings over 72 hours.

In its original form, the patient did not have access to real time glucose values, but more recently, devices that provide real time data to patient have become available. All measurement information can be imported to a computer for storage and analysis. Currently, CGM devices are used to provide glucose trends over a 3-7 day period and they are approved for use in conjunction with traditional glucometers. In fact, obtaining blood glucose values 2-4 times a day using a blood glucometer is required to calibrate the CGM device. Although CGM does not replace traditional glucometers, it does provide much more information compared to SMBG alone. Future development in this technology should allow CGM devices to work together with insulin pumps and function as an external beta islet cell ("artificial pancreas") with ability to detect glucose levels and adjust insulin delivery to maintain euglycemia with avoidance of symptomatic glycemic excursions. However, currently, CGM has been studied primarily in children with type 1 diabetes. It is unclear whether CGM provides added value to traditional SMBG.[16-18]

Glucowatch®

Another noninvasive device, Glucowatch®, uses reverse iontophoresis to measure glucose levels through the skin. The device is worn on the wrist and can painlessly take it is capable of providing up to six painless glucose measurements per hour for 13 hours. However, the device requires calibration with a fingerstick blood glucose measurement.[19,20]

Evidence on monitoring of glycemia for type 1 diabetes

Based on the DCCT results[10] and other smaller experimental or observations studies,[21-26] SMBG is recognized to be fundamental in patients with type 1 diabetes for achieving and maintaining the near normal glycemia required to prevent or delay the microvascular complications of the disease. There is no evidence, however, to suggest that SMBG results in reversal of microvascular disease. SMBG provides real-time feedback including information on the effect of daily activities (eating, activity etc) on glycemia and the presence of transient glycemic excursions, thereby allowing patients with type 1 diabetes to modify their lifestyle and apply short-term adjustments in insulin therapy to avoid symptomatic hyper- or hypoglycemia. Frequent SMBG testing is therefore a well-established management plan for patients with type 1 diabetes especially among those aiming for tight glycemic control who are at highest risk for severe hypoglycemia. Professional organizations[27-30] recommend frequent (three times or more) daily SMBG for type 1 diabetics.

In addition to its potential benefits outlined above, SMBG may also have adverse effects on quality of life by increasing patient's anxiety and worry, which may, at least in part, be due to inadequate understanding by patients and health care providers of the importance of SMBG. Often SMBG becomes the goal by itself as opposed to the means of achieving the goal, which is improved glycemia. Frequently in practice, patients are given a glucometer with few instructions

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on proper interpretation of the data. In addition, when tightened glycemic control is achieved via SMBG, there may be an increased risk of severe hypoglycemia episodes. Finally, SMBG can be prohibitively expensive for many patients[31] as strips cost about $0.70 each.

Evidence for intensive glycemic control for type 1 diabetes

Based on results from DCCT[10], it is currently accepted that patients with type 1 diabetes need to achieve blood glucose levels as close to normal as possible to prevent the incidence of diabetes-specific microvascular complications. In the DCCT trial, intensive treatment (HbA1c 7.3% vs. 9.1%) reduced the development of retinopathy by 76 percent (89 percent among those with duration of diabetes of less than 2.5 years), nephropathy by 56 percent and neuropathy by 69 percent.[32] In type 1 diabetes, for every percentage point drop in HbA1c blood test results (e.g., from 8% to 7%) there is a 40 and 25 percent reduction in the risk of retinopathy and nephropathy respectively.[33,34] However, there is no evidence to suggest that microvascular disease improves with intensive glycemic control.

Although there is epidemiologic evidence linking chronic hyperglycemia to increased risk for macrovascular complications, there is limited evidence that tight glycemic control reduces the development or progression of cardiovascular disease in patients with type 1 diabetes. Recently, in the observational followup study to the DCCT, it was shown that participants originally assigned to tight glycemic control had a reduction in cardiovascular disease by 42 percent over an 11-year followup period.[35]

The following systematic review summarizes and assesses the applicability of the larger published studies related to both intensive glycemic control and SMBG in patients with type 2 diabetes mellitus to the nondialysis-dependent Medicare population.

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Table 1. Crude prevalence (percent population) of diabetes in men and women 65 years of age or older in the US in 1999-2002 (adapted from Cowie et al.[2])

	Diagnosed Diabetes	Undiagnosed Diabetes	Impaired Fasting Glucose
Total Population	15.8 (14.0–17.8)	5.8 (4.1–8.0)	39.1 (35.5–42.9)
Men	15.8 (13.1–18.8)	7.9 (5.5–11.2)	43.2 (37.2–49.4)
Women	15.9 (13.8–18.2)	4.2 (2.5–6.9)	36.0 (32.0–40.2)
Non-Hispanic Whites	14.3 (12.3–16.5)	6.0 (4.1–8.6)	40.0 (36.2–43.9)
Men	14.3 (11.5–17.7)	8.3 (5.6–12.0)	45.0 (38.5–51.7)
Women	14.3 (12.0–16.9)	4.2 (2.3–7.7)	36.2 (31.8–40.9)
Non-Hispanic Blacks	28.5 (22.8–34.9)	7.2 (3.6–13.9)	24.5 (17.9–32.5)
Men	29.2 (21.5–38.2)	7.6 (2.6–20.3)	23.0 (13.6–36.2)
Women	28.0 (21.6–35.5)	6.9 (2.8–16.3)	25.6 (18.8–33.8)
Mexican-Americans	24.9 (22.0–28.0)	7.8 (3.8–15.2)	34.3 (27.8–41.6)
Men	25.6 (20.3–31.8)	8.0 (3.4–17.9)	31.9 (24.4–40.6)
Women	24.3 (19.0–30.6)	7.6 (2.5–20.4)	36.1 (25.3–48.5)

Data are % (95% CI). Data are based on NHANES standardized to the 2000 U.S. Census population by age and sex for the total population and race/ethnic groups and by age for sex-groups.

Table 2. Residual lifetime risk for diabetes(adapted from Narayan et al.[3])

Baseline Age (years)	Lifetime risk (%)	
	Men	Women
Birth	33	39
10	32	38
20	32	37
30	31	36
40	30	33
50	26	28
60	19	22
70	11	15
80	5	7

Values obtained through a probabilistic sensitivity analysis.

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Chapter 2. Methods

Key questions addressed in this report

The key questions in this report sought to identify the existing scientific evidence regarding the frequency of glucose testing and glycemic control and its applicability to the majority of Medicare diabetes patients (patients with type 2 diabetes who are age 65 years and older). Specifically:

1. Provide background information on type 1 and type 2 diabetes and their complications, and information on the prevalence of the types of diabetes in the Medicare population. Briefly compare and contrast types 1 and 2 diabetes and their complications. Provide a brief narrative review of the evidence on glucose monitoring in type 1 diabetes patients.
2. Through the systematic review process, describe the applicability of the literature to the non-dialysis-dependent Medicare population in regards to the following three (3) questions:
    A. The relationship between tighter glycemic control and clinical outcomes (both benefits and harms) in patients with type 2 diabetes.
    B. The effect of frequency of glucose monitoring on clinical outcomes in patients with type 2 diabetes.
    C. The effect of frequency of glucose monitoring on glycemic control (HbA1c) in patients with type 2 diabetes.

Furthermore it was requested that:
For questions 2.A-C, there should be a specific focus on generalizability of studies to Medicare patients, outcomes measured, study design and time scale of studies. Inclusion criteria for studies in questions 2.A-C: prospective, including observational; comparative only; minimum duration 1 year for clinical outcomes (macrovascular [cardiovascular], microvascular [retinopathy, nephropathy], and neuropathy using hard clinical outcomes such as myocardial infarction, stroke, amputation, dialysis, legal blindness, 3 step change in retinopathy score), 3 months for hypoglycemia outcomes (hyperosmolar coma, and blood/serum glucose < 50 mg/dL and requiring third party intervention or blood/serum glucose < 30 mg/dL), and 3 months for glycemic control outcomes (HbA1c, glycated hemoglobin);.

Literature search strategy

We conducted a comprehensive literature search for publications on frequency of monitoring and glycemic control in MEDLINE. An iterative process was used where the search strategy was successively revised based on articles that were found to be missing from the original search, and based on changes to the key questions during the development process. The final search was performed April 18, 2006. The search included English language articles on diabetes (types 1 and 2) in adults with relevant study designs. These studies were crossed with articles on blood glucose self monitoring; drug administration schedules; insulin infusion systems; insulin; blood glucose analysis; physiologic monitoring; patient education; and glucose monitoring, testing, screening, control, and related terms. Systematic reviews and guidelines pertinent to the key questions that were found from this search were retrieved. The reference lists of these articles

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were used to find additional articles. As noted above, the missing articles were also used to revise the original literature search.

Study selection

All abstracts identified through the literature search were screened manually by two people. At this stage all studies, regardless of study design or sample size, that evaluated any form of glycemic control or of self-monitoring were tentatively accepted. Upon finalization of the key questions, these abstracts were rescreened to select those articles for retrieval.

The following eligibility criteria were used.

Population

Adult (age ≥18 years), type 2 diabetes of any duration, outpatient population; excluding studies of predominantly patients with end-stage renal disease or who are pregnant. Studies where more than half the subjects had type 1 diabetes were excluded.

Interventions

Intensive glycemic control where the goal of treatment was to reduce HbA1c or other measures of glycemic control to near normal, regardless of method used; self-monitoring of blood glucose, regardless of method, including continuous glucose monitoring.

Comparators

None required, but comparators of interest were usual care glycemic control, glycemic control with a goal above normal, or no self-monitoring of blood glucose; self-monitoring of urine glucose was ignored.

Outcomes

Abstracts were not relied on to determine study eligibility based on reported outcomes. Articles with the following outcomes were included, if otherwise eligible. When outcomes were deemed to be sufficiently similar to the outcomes of interest, we favored inclusion of the outcomes.

Clinical outcomes. Mortality, all-cause, or event-related; cardiac events (e.g., myocardial infarction, heart failure); cerebrovascular events; peripheral vascular events (e.g., intermittent claudication); peripheral neuropathy events (i.e., lower extremity ulceration or amputation); kidney events (e.g., dialysis); and retinopathy events (e.g., blindness, 3-step change in retinopathy score).

Hypoglycemia outcomes. Severe hypoglycemia events such as Stage 3 or 4 hypoglycemia, where patients require assistance from someone else. However, we allowed various definitions of severe hypoglycemia. When the definitions provided by the studies were unclear, we favored including the studies. We also reviewed studies for reporting of other adverse events related to the interventions.

Glycemia outcomes. For studies of SMBG, we included studies with any measure of glycohemoglobin, favoring HbA1c. We did not include fasting blood glucose or other measures

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of glycemia as outcomes. We also did not review success at achieving lower HbA1c with intensive glycemic control.

Study design

We included only prospective studies of any design, including randomized controlled trials; nonrandomized, prospective comparative studies (intervention vs. control, but not randomized); and prospective cohort studies (i.e., pre-post studies without a control group).

Clinical outcomes. For clinical outcomes, we included only those studies that evaluated at least 100 subjects in the intervention arm. The minimum duration of follow-up was 12 months.

Adverse events or glycemia outcomes. For nonclinical outcomes, we included only those studies that evaluated at least 50 subjects in the intervention arm. The minimum duration of follow-up was 3 months.

Data extraction

"Evidence Tables" were created to capture all the data of interest for this report. Data were extracted directly into these tables. Each eligible study was extracted by a single reviewer. All data entries were reviewed by at least one other reviewer. Any data extraction issues were reviewed at weekly meetings and resolved through consensus. Occasional sections were re-extracted to ensure that uniform definitions were applied across all extracted studies. Any problems or corrections were noted through spot checks of extracted data and during the creation of summary and evidence tables. Items extracted included: factors related to study design (including type of study, intervention year, and study duration), population characteristics (including sample size, age, HbA1c, body mass index, percent using insulin, and comorbidities), interventions and control groups (glycemic control, frequency of glucose monitoring), outcomes of interest (number of patients in the treatment and control groups, clinical outcomes, hypoglycemia, HbA1c, and results, including within treatment change and/or between treatment differences).

All articles were also extracted by a single reviewer for reported analyses of "linearity." I.e., intensive glycemic control studies that analyzed whether achieved HbA1c was correlated to any of the outcomes of interest, or SMBG studies that analyzed whether frequency of self-monitoring was correlated to any of the outcomes of interest (including HbA1c).

As agreed upon with AHRQ and CMS Staff, for this report study quality was not assessed.

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Chapter 3. Results

Results of Literature Search (Figure 1)

Through our MEDLINE searches, we identified and screened 7,551 abstracts; an additional 10 articles were found from other sources. Of these, 292 apparently pertained to patients with diabetes being managed with tightened glycemic control and/or self-monitoring of blood glucose (SMBG). Of these, 153 articles of primary studies and 36 review articles were retrieved, from which, 30 articles representing 22 studies met eligibility criteria. Reasons for exclusion of the remaining retrieved articles (See Appendix A) included: sample size too small or study duration too short (34 articles), wrong population (32 articles), retrospective or cross-sectional design (21 articles), no intervention or outcome of interest (22 articles), being a letter or having no primary data (8 articles), or being a duplicate publication with no additional data of interest for this report (6 articles). Of the remaining (unretrieved) 103 abstracts, 38 were rejected for being either retrospective, cross-sectional, or of the wrong population (e.g., type 1 diabetes, children, or dialysis-dependent); 65 were rejected for including fewer than 50 participants. Of note, the screening process occurred in parallel with the key question formulation process, such that many articles were retrieved that did not meet final eligibility criteria.

Among the 22 eligible articles, nine evaluated intensive glycemic control. Three of these studies met criteria and included clinical outcomes of interest; eight met criteria for hypoglycemia outcomes; and three evaluated correlations between achieved glycemic control and outcomes of interest. Thirteen studies evaluated SMBG. None of these studies included clinical outcomes of interest; three met criteria for hypoglycemia outcomes; 11 met criteria for glycemia outcomes; and two evaluated correlations between frequency of self-monitoring and outcomes of interest. Of note, no study that met eligibility criteria evaluated continuous glucose monitoring.

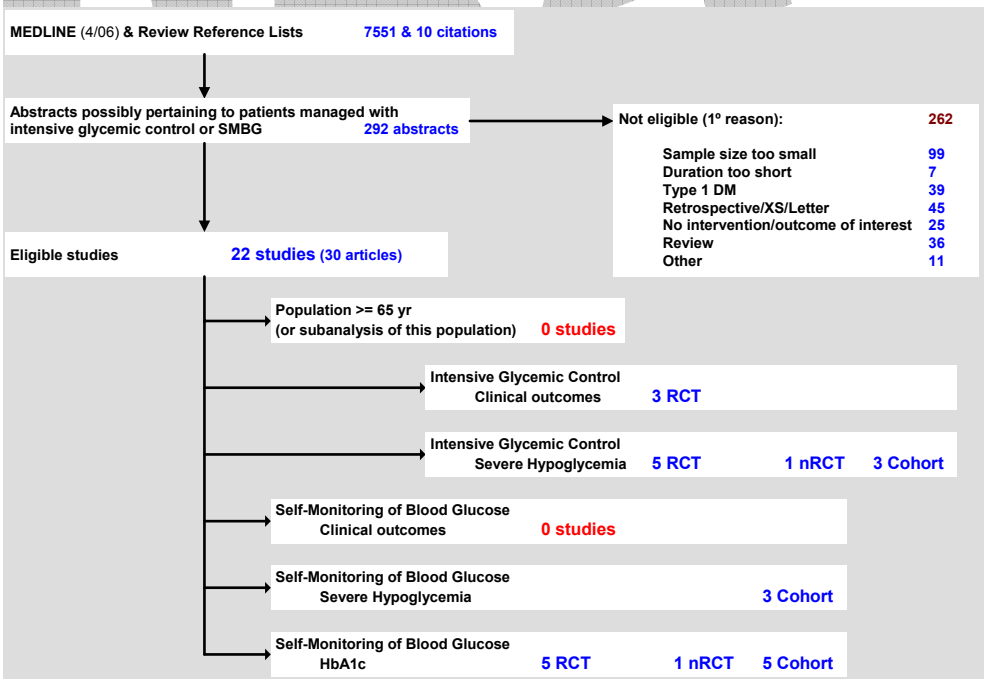

Figure 1. Flowchart of articles screened and evaluated.

Intensive glycemic control and clinical events in patients with type 2 diabetes (Table 3)

Study descriptions

Three studies met eligibility criteria evaluating the effect of intensive glycemic control on clinical events in at least 100 patients with type 2 diabetes, with 1 year followup. All three studies were randomized controlled trials of only patients with type 2 diabetes. The UKPDS trial was a very large trial (3,867 participants) with a long follow-up period (approximately 10-11 years), from 1977 to 1991.[11,13] The other two trials were much smaller and followed patients mostly during the 1990s. The VA CSDM trial followed 153 patients for up to 27 months[36-42] and Shichiri 2000[43] followed 110 patients for 8 years. The three trials varied in how many subjects used insulin, from 0 to 100 percent. The UKPDS trial included only patients with newly diagnosed diabetes; their mean HbA1c was substantially lower (mean 7.1%) than the other two trials (approximately 9%).

The three trials used different regimens to achieve intensive glycemic control. The UKPDS and VA CSDM trials set goals of essentially normal glycemia (fasting blood glucose [FBG] < 108 mg/dL and HbA1c between 4.1 and 6.0%, respectively). The Shichiri 2000 study had somewhat looser goals for glycemic control, using a variety of measures.

Applicability to the Medicare population

The mean age of the trials ranged from 50 to 60, but a minority of subjects were aged 65 years or older at the beginning of each trial. The maximum ages, per eligibility criteria, at enrollment were 65, 69, and 70 years old. No study performed separate analyses for older patients. As noted, the UKDPDS trials included only patients with newly diagnosed diabetes. The other trials included patients who had had diabetes for approximately a decade. The three trials varied in the prevalence of albuminuria and retinopathy at baseline. The Shichiri 2000 trial also may have reduced applicability to the (American) Medicare population in that it included insulin-using patients with type 2 diabetes who were much more typical of the disease in Japan than in the US. As such, these patients were relatively thin with a mean body mass indices (BMI) of 19.5 to 21.6 kg/m^2 (depending on the subgroup, overweight is defined as BMI > 25 kg/m^2).

Study results

Mortality (Table 3.d)

All three trials reported mortality data; although only the UKPDS trial included sufficient numbers of patients for meaningful statistical analyses. The UKPDS trial found nonsignificant trends for decreased all-cause and diabetes-related mortality rates with intensive glycemic control at about 10 years follow-up (relative risk [RR] = 0.54 and 0.50, respectively, in a patient population with underlying death rates of 19 and 11.5 deaths per 1000 patient-years, respectively). The other two trials found similar numbers of patients who died, regardless of treatment.

Cardiovascular events (Table 3.e)

All three trials reported results regarding cardiovascular events. The UKPDS trial had sufficient participants to allow analysis of specific events, including cardiac, stroke, and peripheral vascular disease events. The greatest beneficial effects (net reductions) found with

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intensive glycemic control were for nonfatal (RR = 0.79) and total myocardial infarctions (RR = 0.84); although these effects were of marginal statistical significance (P = 0.06 and 0.05, respectively). A marginally significant reduction in fatal sudden death events was also found (RR = 0.54, P = 0.05); although this event was relatively rare (1.6 events per 1000 patient-years in the conventional treatment arm). No differences were found between intensive and usual glycemic control for other cardiovascular outcomes. The other two trials found no significant differences for all cardiovascular events, although the VA CSDM trial found that more patients using intensive glycemic control had cardiovascular events.

Retinopathy (Table 3.f)

All three trials reported retinopathy-related outcomes. Shichiri 2000, though, was the only trial that was designed primarily to evaluate retinopathy. They found that among both patients receiving the intervention for primary prevention (no retinopathy at baseline) and for secondary prevention (simple retinopathy at baseline) intensive glycemic control resulted in substantial reductions in progression of retinopathy after 8 years (risk reduction = 68 and 57 percent, respectively; P = 0.02, both). However, no significant differences were found in development of preproliferative or proliferative retinopathy in either group. No patient without retinopathy at baseline developed preproliferative or proliferative retinopathy. However, development of nonproliferative retinopathy, though rare, was less common in the intensive control arm (1.5 vs. 3.0 percent).

The UKPDS trial found a significant net reduction in the need for retinal photocoagulation after about 10 years with intensive glycemic control (RR = 0.71, P = 0.003), but no significant differences in vitreous hemorrhage or blindness events. However, combining all microvascular events (due to retinopathy and kidney failure), a substantial and statistically significant reduction was found (RR = 0.75, P = 0.01) The VA CSDM trial found an interesting pattern in retinopathy progression during the first two years of follow-up. Patients receiving intensive glycemic control were more likely to have retinopathy progression during the first 12 months, but then less likely to have continued progression during the next 12 months, such that at 24 months, the rates of progression were nearly identical. However, none of these trends were statistically significant.

None of the studies reported on improvement in levels of retinopathy among patients on intensive glycemic control.

Kidney events (Table 3.g)

UKPDS found no statistically significant difference in rates of kidney failure after about 10 years between interventions (although, as noted above, a significant reduction in all microvascular events was found). No study reported on kidney function (e.g., serum creatinine or glomerular filtration rate).The VA CSDM trial found significantly slower progression of microalbuminuria at 2 years, and Shichiri 2000 found risk reductions of 74 and 60 percent in progression of nephropathy at 8 years in patients with either no retinopathy or simple retinopathy, respectively, at baseline. None of the studies reported on improvement in levels of kidney function among patients on intensive glycemic control.

Neuropathy events (Table3.h)

No statistically significant differences were reported in a wide range of neuropathy events either in the UKPDS or the VA CSDM trial.

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Conclusions

Three randomized controlled trials met inclusion criteria for this report. All included only a minority of patients age 65 years or older at study baseline and the largest trial, UKPDS, included very few patients age 65 years at baseline. The applicability of the UKPDS trial to the Medicare population is further hampered by their eligibility criteria, such that only those with newly diagnosed diabetes were enrolled; probably for this reason, the patients' level of glycemia at baseline was relatively low. Shichiri 2000 may also be of limited applicability to the US Medicare population as this Japanese study included relatively thin, insulin-using patients. This population of patients may have a sufficiently different etiology of their diabetes that progression of clinical disease in these patients may differ greatly from more typical, overweight, Americans with type 2 diabetes.

Overall, these three trials do not support clinical benefits from intensive glycemic control for mortality, cardiovascular events, kidney failure, or severe neuropathy-related events; although trends were found for benefits for several outcomes. Regarding retinopathy, the UKPDS trial found a significant reduction in need for photocoagulation, but not vitreous hemorrhage or blindness; the VA CSDM trial found no significant effect on retinopathy progression; but Shichiri 2000, which was specifically designed to address retinopathy outcomes and included a different population of patients, found large, statistically significant reductions in progression of retinopathy, but not of development of preproliferative or proliferative retinopathy. The studies do not provide evidence for any improvements in retinopathy or kidney function with intensive glycemic control.

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Table 3. Studies of intensive glycemic control and clinical outcomes.

3.a. Applicability of "large" prospective studies to non-dialysis-dependent Medicare population (baseline data)

Author, Year UI	N	Mean Age (Range)	~%≥65 yr	Mean Duration DM	% DM 2	% Using Insulin
UKPDS trial 1 9742976 [11] 9742977 [13]	3867	53 (25-65) [a]	~0%	"Newly diagnosed"	100%	0%
VA CSDM trial (7 publications) [36-42]	153	60 (40-69) [a]	<50%	7.9 yr (all<15 yr)	100%	59%
Shichiri, 2000 10860187 [43]	110	50 (<70) [a]	<<50%	1° Pr: 6.5 yr 2° Pr: 10.5 yr	100%	100%

1° Pr, primary prevention of retinopathy substudy; 2° Pr, secondary prevention substudy

[a] Eligibility criteria

3.b. Baseline "severity of disease" in studies

Author, Year UI	Mean A_{1c} (Range)	% CVD (Details)	Mean GFR [SCr] (Range)	Albuminuria	% Retinopathy	Other Comorbidies	Mean BMI (Range)
UKPDS trial 1 9742976 9742977	7.1% (nd)	nd	[0.92] (0.76-1.1)	Proteinuria 1.9%	36%	nd	27.5 (nd)
VA CSDM trial (7 publications)	9.4% (6.6, nd) [b]	38% (13% AMI, 18% angina/CAD, 2% CHF, 7% CVA, 5% TIA, 14% claudication, 5% CABG)	nd	Albuminuria (24 hr): 46%: <30 mg/d 47%: 30-299 mg/d 6%: >299 mg/d Albuminuria (single void): 38%: ACR >0.30)	NPDR: 45% mild 9% moderate PDR 3% mild / moderate	nd	31.0 (nd)
Shichiri, 2000 10860187	9.2% (nd)	nd	nd [<1.5 mg/dL]	All <300 mg/24 hr	1°Pr: 0% 2°Pr: 100% (simple)	No neuropathy	20.5 (nd)

1° Pr, primary prevention of retinopathy substudy; 2° Pr, secondary prevention substudy; ACR, albumin/creatinine ratio; NPDR: Non-productive diabetic retinopathy; PDR: Productive diabetic retinopathy

[b] Eligibility criteria

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538 **3.c. Study designs**

Author, Year UI	Design	Intervention Year(s)	Study Duration	Intervention Goal	Control Goal	Other DM Treatments / Cointerventions
UKPDS trial 1 9742976 9742977	RCT	1977-1991	Mean 10-11.1 yr	**Tx:** Sulfonylureas or insulin **Goal:** FBG < 108 mg/dL	**Tx:** Diet alone, sulfonylureas or insulin if symptomatic **Goal:** FBG <270 mg/dL	Dietary counseling
VA CSDM trial (7 publications)	RCT	1990-1993	Up to 27 mo	**Tx:** Insulin (≥1x/d) +/- glipizide **Goal:** HbA1c 4.1-6.0%	**Tx:** Insulin (1x/d) **Goal:** HbA1c <13%	No
Shichiri, 2000 10860187	RCT	<1992-1999	8 yr	**Tx:** Insulin (4x/d) **Goals:** FBG<140 mg/dL 2h pPr<200 mg/dL HbA1c<7.0% MAGE<100 mg/dL	**Tx:** Insulin (1-2x/d) **Goal:** FBG<140 mg/mL	nd

539 BW, body weight; RCT, randomized controlled trial; nRCT, nonrandomized controlled trial; Cohort (uncontrolled)
540 Tx, drug treatments; FBG, fasting blood glucose; 2h pPr, 2 hour post-prandial; MAGE, mean amplitude of glycemic excursions
541
542
543 **3.d. Mortality Results** (All randomized controlled trials)

Author, Year UI	Outcome	N (Tx)	N (Cx)	Effect Magnitude (Control Rate)	P value
UKPDS trial 1 9742976 9742977	All-cause mortality	2729	1138	RR=0.54 (0.80-1.10) (Cx: 18.9 events/1000 pt-yr)	NS
	DM-related death			RR=0.50 (0.73-1.11) (Cx: 11.5 events/1000 pt-yr)	NS
VA CSDM trial (7 publications)	All-cause mortality	75	78	5 vs 5	NS
Shichiri, 2000 10860187	Reported deaths	55	55	5 vs 7	nd

544 Cx:, event rate in control arm; RR, relative risk.

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545 **3.e. Cardiovascular Events** (All randomized controlled trials)

Author, Year UI	Outcome	N (Tx)	N (Cx)	Effect Magnitude (Control Rate)	P value
UKPDS trial 1 9742976 9742977	Fatal myocardial infarction	2729	1138	RR=0.94 (0.68-1.30) (Cx: 8.0 events/1000 pt-yr)	NS
	Non-fatal myocardial infarction			RR=0.79 (0.58-1.09) (Cx: 9.5 events/1000 pt-yr)	0.06
	Myocardial infarction (Total)			RR=0.84 (0.71-1.00) (Cx: 17.4 events/1000 pt-yr)	0.05
	Fatal sudden death			RR=0.54 (0.24-1.21) (Cx: 1.6 events/1000 pt-yr)	0.05
	Heart failure			RR=0.91 (0.54-1.52) (Cx: 3.3 events/1000 pt-yr)	NS
	Angina			RR=1.02 (0.71-1.46) (Cx: 17.4 events/1000 pt-yr)	NS
	Fatal stroke			RR=1.17 (0.54-2.54) (Cx: 1.8 events/1000 pt-yr)	NS
	Non-fatal stroke			RR=1.07. (0.68 -1.69) (Cx: 4.0 events/1000 pt-yr)	NS
	Total stroke			RR=1.11 (0.81 -1.51) (Cx: 5.0 events/1000 pt-yr)	NS
	Death from peripheral vascular disease			RR=0.26 (0.03 -2.77) (Cx: 0.3 events/1000 pt-yr)	NS
VA CSDM trial (7 publications)	All cardiovascular events	75	78	35 events (24 pts, Tx) vs 26 events (16 pts, Cx)	NS (Total and for each specific outcome)
Shichiri, 2000 10860187	All cardiovascular events	55	55	RD = –0.7 events/100 pt-yr (Cx: 1.3)	nd (implied NS)

546 Cx:, event rate or change from baseline in control arm; Cx, control arm (usual care); Tx, treatment arm (intensive glycemic control); RD, risk
547 difference; RR, relative risk.
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549 **3.f. Retinopathy Results** (All randomized controlled trials)

Author, Year UI	Outcome	N (Tx)	N (Cx)	Effect Magnitude (Control Rate)	P value
UKPDS trial 1 9742976 9742977	Retinal photocoagulation	2729	1138	RR= 0.71 (0.53 –0.96) (Cx: 11.0 events/1000 pt-yr)	0.003
	Vitreous hemorrhage			RR= 0.77 (0.28 –2.11) (Cx: 0.9 events/1000 pt-yr)	NS
	Blind in one eye			RR= 0.84 (0.51 –1.40) (Cx: 3.5 events/1000 pt-yr)	NS
	Microvascular (includes kidney disease, also in section 3.g) [d]			RR= 0.75 (0.60 –0.98) (Cx: 11.4 events/1000 pt-yr)	0.01
VA CSDM trial (7 publications)	Retinopathy progression, baseline to 12 mo	75	78	RD = +12.1% (Cx: 19.7%)	NS
				Δ Retinopathy Levels: Net Δ = +0.30 (Cx: 0.64)	NS
	Retinopathy progression, 12 to 24 mo	75	78	RD = –8.2% (Cx: 18.0%)	NS
	Retinopathy progression, baseline to 24 mo	75	78	RD = +0.5% (Cx: 32.8%)	NS
Shichiri, 2000 10860187	Retinopathy progression (1° Pr)	27	28	Risk Reduction: 68% (Cx: 48%, 6.0 events/100 pt-yr)	0.02
	Retinopathy progression (2° Pr)	28	27	Risk Reduction: 57% (Cx: 56%, 7.0 events/100 pt-yr)	0.02
	Development of preproliferative or proliferative retinopathy (1° Pr)	27	28	None	nd
	Development of preproliferative or proliferative retinopathy (2° Pr)	28	27	RD = –1.5 events/100 pt-yr (Cx: 3.0)	NS

550 Cx:, event rate or change from baseline in control arm; C RD, risk difference.
551 1° Pr, primary prevention of retinopathy substudy; 2° Pr, secondary prevention substudy.
552 **VA CSDM trial:** Also, no effect of intensive treatment among the subcohort with some retinopathy at baseline
553
554 [d] retinopathy requiring photocoagulation, vitreous hemorrhage, and/or fatal or nonfatal kidney failure.

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555 **3.g. Kidney Results** (All randomized controlled trials)

Author, Year UI	Outcome	N (Tx)	N (Cx)	Effect Magnitude (Control Rate)	P value
UKPDS trial 1 9742976 9742977	Kidney failure	2729	1138	RR= 0.73 (0.25 –2.14) (Cx: 0.8 events/1000 pt-yr)	NS
	Death from kidney failure			RR= 1.63 (0.21 –12.49) (Cx: 0.2 events/1000 pt-yr)	NS
	Microvascular (includes kidney disease, also in section 3.f) [d]			RR= 0.75 (0.60 –0.98) (Cx: 11.4 events/1000 pt-yr)	0.01
VA CSDM trial (7 publications)	Progression of microalbuminuria (ACR)	75	78	Net Δ = –0.095 (Cx: 0.141)	0.04
Shichiri, 2000 10860187	Nephropathy progression (1°Pr)	27	28	Risk Reduction: 74% (Cx: 43.5%, 5.4 events/100 pt-yr)	0.03
	Nephropathy progression (2°Pr)	28	27	Risk Reduction: 60% (Cx: 40.0%, 5.0 events/100 pt-yr)	0.04

556 Cx:, event rate or change from baseline in control arm; RD, risk difference.
557 ACR, albumin:creatinine ratio from AM urine sample
558 **Shichiri:** Progression to albuminuria was seen only in the CIT groups (both primary and secondary prevention)
559
560 [d] retinopathy requiring photocoagulation, vitreous hemorrhage, and/or fatal or nonfatal kidney failure.
561
562
563 **3.h. Neuropathy Results** (All randomized controlled trials)

Author, Year UI	Outcome	N (Tx)	N (Cx)	Effect Magnitude (Control Rate)	P value
UKPDS trial 1 9742976 9742977	Amputation	2729	1138	RR=0.61 (0.28-1.33) (Cx: 1.6 events/1000 pt-yr)	NS
	Amputation or death from PVD			RR=0.65 (0.38-1.18) (Cx: 1.6 events/1000 pt-yr)	NS
VA CSDM trial (7 publications)	Cranial neuropathy signs & symptoms	75	78	RD = –69% (Cx: +30%)	NS
	Erectile dysfunction	75	78	RD = +2% (Cx: +20%)	NS
	Autonomic neuropathy GI or sweating symptoms	75	78	No change	NS

564 Cx:, event rate or change from baseline in control arm; RD, risk difference; RR, relative risk.
565 LE, lower extremity; UE, upper extremity; GI, gastrointestinal; PVD, peripheral vascular disease

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Intensive glycemic control and risk of severe hypoglycemia in patients with type 2 diabetes (Table 4)

Study descriptions

There were nine studies identified that met our inclusion criteria including any prospective study design, type 2 diabetes, sample size of at least 50 patients, and study duration of 3 months follow-up or more. We examined the effects of intensive glycemic control on major or severe hypoglycemia events. The nine studies included five randomized controlled trials (in 13 included articles),[11,13,36-46] one non-randomized comparison,[47] and three prospective cohort studies.[48-50] The sample sizes ranged from 62 to 3,867 subjects. UKPDS trial 1, the largest trial, followed newly diagnosed patients for mean of 10-11.2 years. The 3 prospective cohort studies and one of the randomized trials followed the patients for 1 year each. Studies varied widely in the percentage of patients using insulin, and thus possibly in levels of native insulin and glucose disposal. Interventions included step-up insulin regimens or multidose insulin alone, or in combination with other interventions such as diet, exercise, education, computer-assisted care, self-monitoring, or monitoring by healthcare providers. FBG goals for intensive glycemic control ranged from <108 to <140 mg/dL.

Applicability to the Medicare population

The mean age of the subjects ranged from 52 to 66 years. Three studies had over 50 percent of the patients older than 65 years (van der Does 1998, Albisser 2001, and de Sonnnaville 1997), and in Goddijn 1999, the patient population ranged from 31 to 83 years. Two of the larger studies (UDPDS trials 1 and 2) had no patients over the age of 65. No study performed separate analyses for older patients. All of the studies reported populations to have type 2 diabetes except Albisser 2001, which probably also included patients with type 1 diabetes. Most of the subjects were overweight with the studies reporting mean body mass index ranging from 27 to 31.3, except for the Japanese study Shichiri 2000, which had a mean body mass index of 20.5 kg/m^2. The mean HbA1c reported ranged from 6.9% to 10.4%. Prevalence of cardiovascular disease, kidney disease, and retinopathy were rarely reported.

Study results

The largest trial, UKPDS trial 1, reported that significantly more patients being treated with intensive glycemic control had at least one major (or any) hypoglycemic episodes a year than patients on conventional treatment; although the exact numbers for this comparison were not reported. However, data regarding what treatments patients were receiving (regardless of glycemic goal of treatment) indicate that between approximately 1 and 2 percent of patients have major hypoglycemic events during the first 10 years of treatment. In the follow-up trial (UKPDS trial 2), between 1.4 and 3.4 percent of patients annually receiving different antidiabetic treatments for intensive glycemic control reported major hypoglycemic episodes, compared to no such episodes for patients receiving conventional treatment; however, no statistical analysis was reported comparing the two groups. These studies did not analyze the frequency of events, per se, but only the percentage of patients suffering events. The remaining three, relatively small trials, reported no or very few severe hypoglycemic events, with no difference between the two interventions. Similarly, the nonrandomized comparative study (de Sonnaville 1997) reported grade 3 and 4 hypoglycemia only among patients receiving intensive glycemic control.

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Among the three studies without usual care arms, two reported no severe hypoglycemic events. These two studies (Albisser 2001 and Goddijn 1999) may have been the most recently conducted studies (prior to 2001 and 1999, respectively, although the exact study dates were not reported). The third uncontrolled study, Saudek 1996, was a randomized trial comparing traditional multidose insulin and implanted insulin pumps. In both arms, patients received intensive glycemic control. With multidose insulin, severe hypoglycemia occurred at a similar rate as in the UKPDS trials; however, substantially more patient with an implanted insulin pump had severe hypoglycemia episodes.

Conclusions

Nine studies met the inclusion criteria for this report. Eight studies explicitly included only patients with type 2 diabetes and three studies had mean ages above 65 years old. The two UKPDS trials and the nonrandomized controlled study, all relatively large, provide evidence that severe hypoglycemic episodes are significantly (or at least substantially) more common among patients being treated with intensive glycemic control. It is unclear whether the lack of difference in effect of the other comparative trials was due to differences in the studies or to an insufficient number of subjects to detect possible differences. However, it is notable, that the two studies (possibly) conducted most recently both report no episodes of severe hypoglycemic episodes among a large number of subjects. This raises the possibility that with more recent treatment protocols or training methods, that the risk of severe hypoglycemic episodes is very low.

In contrast with the relatively small percentage of patients with type 2 diabetes with severe hypoglycemic episodes (less than 2 percent, or fewer than 1 episode per 100 patient-years), in DCCT (among patients with type 1 diabetes), with intensive therapy, there were 62 severe hypoglycemic episodes per 100 patient-years compared with 19 such episodes per 100 patient-years in the conventional-therapy group.[51]

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Table 4. Studies of intensive glycemic control and hypoglycemia.
4.a. Applicability of "large" prospective studies to non-dialysis-dependent Medicare population (baseline data)

Author, Year UI	N	Mean Age (Range)	~%≥65 yr	Mean Duration DM	% DM 2	% Using Insulin
Randomized controlled trials						
UKPDS trial 1 9742976 [11] 9742977 [13]	3867	53 (25-65) [a]	~0%	"Newly diagnosed"	100%	0%
UKPDS trial 2 [b] 10388978 [44] 11815505 [45]	826	52 (25-65) [a]	~0%	"Newly diagnosed"	100%	0%
Van der Does, 1988 9839098 [46]	176	64 (40-75) [a]	~50%	4.0 yr	100%	26%
VA CSDM trial (7 publications) [36-42]	153	60 (40-69) [a]	<50%	7.9 yr (all<15 yr)	100%	59%
Shichiri, 2000 10860187 [43]	110	50 (<70) [a]	<50%	1°Pr: 6.5 yr 2°Pr: 10.5 yr	100%	100%
Nonrandomized controlled study						
de Sonnaville, 1997 9389427 [47]	350	66 (nd)	~50%	6.4 yr	100%	4%
Prospective cohort						
Albisser, 2001 11911169 [50]	978	58 (19-81)	<50%	nd	nd	nd
Goddijn, 1999 10229289 [48]	94	nd (31-83)	nd	8.5 yr	100%	0%
Saudek, 1996 8861991 [49]	62	56 (40-69)	<50%	8.8 yr	100%	100%

[a] Eligibility criteria
[b] With the realization that progressive hyperglycemia was occurring in all randomized groups in UKPDS Study 1 and that additional therapy might be desirable at the stage of sulfonylurea inadequacy rather than sulfonylurea failure, a modified protocol (Glucose Study 2) was introduced in the last 8 UKPDS centers. This protocol, the aim of which was to determine whether a more aggressive glucose control policy could minimize hyperglycemic progression, differed only in that insulin therapy was added immediately inpatients allocated to sulfonylurea therapy if maximal doses did not maintain FPG level <108 mg/dl (6 mmol/L).

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4.b. Baseline "severity of disease" in studies

Author, Year UI	Mean A_{1c} (Range)	% CVD (Details)	Mean GFR [SCr] (Range)	Albuminuria	% Retinopathy	Other Comorbidies	Mean BMI (Range)
Randomized controlled trials							
UKPDS trial 1 9742976 9742977	7.1 (nd)	nd	[0.92] (0.76-1.1)	Proteinuria 1.9%	36%	nd	27.5 (nd)
UKPDS trial 2 10388978 11815505	6.9 (6.1-8.0)	nd	nd [≤2.0] [c]	nd	nd	nd	28.8 (nd)
Van der Does, 1988 9839098	7.5	21%	nd	nd	nd	8% hypoglycemia (grade 2)	28
VA CSDM trial (7 publications)	9.4 (6.6, nd)[1]	38% (13% AMI, 18% angina/CAD, 2% CHF, 7% CVA, 5% TIA, 14% claudication, 5% CABG)	nd	Albuminuria (24 hr): 46%: <30 mg/d 47%: 30-299 mg/d 6%: >299 mg/d Albuminuria (single void): 38%: ACR >0.30)	NPDR: 45% mild 9% moderate PDR 3% mild / moderate	nd	31.0 (nd)
Shichiri, 2000 10860187	9.2 (nd)	nd	nd [<1.5]	All <300 mg/24 hr	1°Pr: 0% 2°Pr: 100% (simple)	No neuropathy	20.5 (nd)
Nonrandomized controlled study							
de Sonnaville, 1997 9389427	7.5 (nd)	nd	nd	nd	nd	nd	Men ~27 Women ~28.5 (nd)
Prospective cohort studies							
Albisser, 2001 11911169	8.8	nd	nd	nd	nd	nd	nd
Goddijn, 1999 10229289	10.4 (nd)	nd	nd	nd	nd	ND	27.6 (nd)
Saudek, 1996 8861991	8.9	nd	nd	nd	nd	nd	31.3

1° Pr, primary prevention of retinopathy substudy; 2° Pr, secondary prevention substudy; ACR, albumin/creatinine ratio; NPDR: Non-productive diabetic retinopathy; PDR: Productive diabetic retinopathy

[c] Eligibility criteria

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649 **4.c. Study designs**

Author, Year UI	Design	Intervention Year(s)	Study Duration	Intervention Goal	Control Goal	Other DM Treatments / Cointerventions
Randomized controlled trials						
UKPDS trial 1 9742976 9742977	RCT	1977-1991	Mean 10-11.1 yr	**Tx:** Sulfonylureas or insulin **Goal:** FBG < 108 mg/dL	**Tx:** Diet alone, sulfonylureas or insulin if symptomatic **Goal:** FBG <270 mg/dL	Dietary counseling
UKPDS trial 2 10388978 11815505	RCT	1987-1991	6 yr	**Tx:** Sulfonylureas or insulin **Goal:** FBG < 108 mg/dL	**Tx:** Diet alone, sulfonylureas or insulin if symptomatic **Goal:** FBG <270 mg/dL	Dietary counseling
Van der Does, 1988 9839098	RCT	1992-1994	1 yr	**Tx:** Metformin, sulfonylureas or insulin **Goal:** FBG < 117.1 mg/dL	**Tx:** Metformin, sulfonylureas or insulin **Goal:** FBG < 153.1 mg/dL	nd
VA CSDM trial (7 publications)	RCT	1990-1993	Up to 27 mo	**Tx:** Insulin (≥1x/d) +/- glipizide **Goal:** HbA1c 4.1-6.0%	**Tx:** Insulin (1x/d) **Goal:** HbA1c <13%	No
Shichiri, 2000 10860187	RCT	<1992-1999	8 yr	**Tx:** Insulin (4x/d) **Goals:** FBG<140 mg/dL 2hPG<200 mg/dL HbA1c<7.0% MAGE<100 mg/dL	**Tx:** Insulin (1-2x/d) **Goal:** FBG<140 mg/mL	nd
Nonrandomized controlled study						
de Sonnaville, 1997 9389427	nRCT	1992	2 yr	**Tx:** Sulphonylureas, metformin, insulin **Goal:** FBG<117.1 mg/dL	**Tx:** Sulphonylureas, metformin, insulin **Goal:** FBG<153.1 mg/dL	nd

650 **Continued.**

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4.c. Study Designs. Continued.

Author, Year UI	Design	Intervention Year(s)	Study Duration	Intervention Goal	Control Goal	Other DM Treatments / Cointerventions
Prospective cohort studies						
Albisser, 2001 11911169	Prospective cohort	<2001	1 yr	**Tx:** Training (nd drugs) **Goal:** pPG=140 mg/dL (implied)		nd
				Tx: Computer (nd drugs) **Goal:** pPG=140 mg/dL		
				Tx: Education (nd drugs) **Goal:** pPG="as close to normal as possible"		
Goddijn, 1999 10229289	Prospective cohort	<1999	1 yr	**Tx:** Insulin and oral drugs **Goal:** HbA1c<8%		nd
Saudek, 1996 8861991	Prospective cohort	<1996	1 yr	**Tx:** Multidose insulin **Goal:** FBG<130 mg/dL; RBG 80-115		Diet Exercise
				Tx: Implantable insulin pump **Goal:** FBG<130 mg/dL; RBG 80-115		

pPG, preprandial glucose; Tx, drug treatments; FBG, fasting blood glucose; RBG, random blood glucose; 2hPG, 2-hour post-prandial glucose; MAGE, mean amplitude of glycemic excursions

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654 **4.d. Study Results**

Author, Year UI	Outcome (Definition)	N (Tx)	N (Cx)	Effect Magnitude	P Value
Randomized controlled trials					
UKPDS trial 1 9742976 9742977	Major hypoglycemic episodes, per year (if 3rd-party help or medical intervention necessary)	2729	1138	Proportion of patients with ≥1 major, or any, hypoglycemic episode in a year was significantly higher for intensive treatment group than for conventional treatment group [d] (Rates per 100 pt-yr were not reported)	<0.05
				Diet or conventional treatment 0.7%	nd
				Chlorpropamide 1.0%	
				Glibenclamide 1.4%	
				Insulin 1.8%	
UKPDS trial 2 10388978 11815505	Major hypoglycemic episodes, per year (if 3rd-party help or medical intervention necessary)	584 [e]	242	Conventional Rx: 0 (Rates per 100 pt-yr were not reported)	
				Intensive Rx Insulin alone: 3.4% (95% CI 2.2-4.5)	nd
				Sulfonylurea (±insulin): 1.6% (95% CI 0.9-2.2)	nd
				Chlorpropamide (±insulin): 1.8% (95% CI 0.8-2.7)	nd
				Glipizide (±insulin): 1.4% (95% CI 0.6-2.2)	nd
Van der Does, 1988 9839098	Hypoglycemic events Grade 3 (help from others necessary)	174		0 events	
VA CSDM trial (7 publications)	Severe hypoglycemia (help from others necessary)	75	78	5 events (in 5 pts) vs 2 events (in 2 pts) or 0.03/pt/yr vs 0.01/pt/yr	NS
Shichiri, 2000 10860187	Severe hypoglycemia (help from others necessary, BG <50 mg/dL, prompt recovery after glucose loading)	55	55	0 events	
Nonrandomized controlled study					
de Sonnaville, 1997 9389427	Hypoglycemia Grade 3 (required oral carbohydrates with help of others)	350	68	4 times in 2 yr for those on sulphonylureas vs No episodes reported	nd
	Hypoglycemia Grade 4 (hypoglycemic coma)	350	68	13 episodes of suspected coma (3 events of cardiac arrhythmia, 1 event of transient ischemic attack, and 9 events by 7 insulin-treated patients) vs. No episodes reported	

655 **Continued.**

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656 **4.d. Study Results. Continued.**

Author, Year UI	Outcome	N (Tx)	N (Cx)	Effect Magnitude (Tx vs. Cx)	P Value
Prospective cohort studies					
Albisser, 2001 11911169	Severe hypoglycemic events (not defined)				
	Training	589		0 events	
	Computer	238		0 events	
	Education	151		0 events	
Goddijn, 1999 10229289	Hypoglycemia (needing assistance)	94		0 events	
Saudek, 1996 8861991	Definite severe hypoglycemia (not defined)	59 (MDI)		0.98 events/100 pt-yr	
		62 (IIP)		7.85 events/100 pt-yr	

657 BG, blood glucose; MDI, multidose insulin; IIP, implantable insulin pump;
658
659 [d] Annual data also graphically reported. During first 10 years, the rates of "major episodes" remains stable. Beyond 10 years, the rates appear to
660 rise, but the numbers of subjects analyzed diminish rapidly (Figure 9 [11] and Figure 4 [13] in original articles).
661 [e] Of the 826 patients whose fasting plasma glucose was between 108 to 270 mg/dL were randomized, 242 were assigned conventional glucose
662 control policy, and 584 were assigned intensive glucose control policy (in which 245 with insulin alone, 339 with sulfonylurea and insulin).
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Correlation of intensive glycemic control with outcomes in patients with type 2 diabetes

Study descriptions

Five of the studies on intensive glycemic control in patients with type 2 diabetes reported on analyses correlating level of glycemic control with clinical outcomes of interest (in six articles).[38,40,43,44,46,48] All three studies reporting clinical outcomes (UKPDS, VA CSDM, and Shichiri 2000) also evaluated the correlation. Two of these and two other studies also evaluated the correlation of achieved HbA1c with frequency of hypoglycemia episodes (UKPDS, VA CSDM, van der Does 1998, and Goddijn 1999). Overall, these studies had fair applicability to the Medicare population (details have been given in the previous sections).

Clinical events (Table 5)

Study results

The authors of the UKPDS trial combined all patients from all trial arms for their analyses. They found that patients with microvascular complications (retinal photocoagulation, vitreous hemorrhage, or kidney failure) achieved significantly higher HbA1c than those without complications; however, no difference in HbA1c was found among those with and without macrovascular complications (nonfatal myocardial infarction, angina, heart failure, stroke). Notably, though, in this trial of newly diagnosed patients with diabetes, only about 2 percent of patients developed either micro- or macrovascular complications over about 10 years of treatment.

Similarly Shichiri 2000 found continuously increasing rates of both retinopathy and nephropathy with higher levels of achieved HbA1c, fasting blood glucose (FBG), or 2-hour post-prandial glucose (See original article's Figure 5[43]). This Japanese study of normal-weight patients was relatively small; though patients were followed for 8 years and had high rates of both clinical outcomes.

In contrast, one publication of the VA CSDM trial found that by both univariate and multivariate Cox regression, after about 2 years of treatment, there was a borderline trend (P = 0.10 and 0.06, respectively) toward more cardiovascular events in patients with lower HbA1c. They reported that the trend was almost entirely attributable to patients assigned to the intensive glycemic control arm.

Conclusions

Two long-term studies, one of newly diagnosed patients with type 2 diabetes, one of patients with long-standing disease, found that lower achieved HbA1c, primarily via intensive glycemic control, correlated with lower rates of microvascular complications (retinopathy and nephropathy, both studies) and macrovascular complications (cardiovascular events, one study). One of these studies provided evidence of a continuous increase in microvascular complications with increasingly poor glycemic control over a wide range of glycemia.

While the VA CSDM study found a trend toward a correlation between better glycemic control and increased rate of cardiovascular events in the first 2 years of intervention, the authors suggest caution in interpreting these results and compare them to the transiently worsened retinopathy found with intensive glycemic control in studies of insulin-dependent diabetes (and also found after 12 months within the same study).

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Overall, there is evidence to suggest a long-term reduction in micro- and macrovascular events with improved glycemic control within these studies; however, it may be the case that a transient increase in cardiovascular events may occur with the introduction of intensive glycemic control.

Hypoglycemia (Table 6)

Study results

Across the four studies that reported a correlation between either achieved HbA1c or change in HbA1c and hypoglycemia outcomes, each used a different definition of hypoglycemia were used and performed a unique analysis. No study evaluated only the rate of grade 3 or greater hypoglycemia. Only van der Does 1998 was unambiguous about what level of severity of hypoglycemia was being analyzed.

The largest study with the longest duration of follow-up, UKPDS, found no difference in mean HbA1c among patients who reported hypoglycemia events and those that did not. Two smaller, 1 year studies (van der Does 1998 and Goddijn 1999) both found that higher percentages of patients whose glycemia was more tightly controlled had hypoglycemia episodes, but neither finding was statistically significant. The VA CSDM trial reported that "After the initial mean HbA1c fell in phase I to 7.8% with relatively few hypoglycemic events, each additional 0.5% fall of HbA1c caused a doubling of the reported number of reactions." However, no further details or statistical analysis was reported.

Conclusions

While one study suggests an exponential increase in hypoglycemia episodes with continually decreasing HbA1c below approximately 8%, overall the evidence weakly suggests only a possible correlation between tightness of glycemic control and frequency of hypoglycemia episodes. Importantly, none of the reviewed studies that analyzed correlations evaluated the outcome of interest, grade 3 or higher episodes of hypoglycemia.

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731 **Table 5.** Correlation of glycemic control and clinical outcomes.

Author, Year UI	N (% events) Tx	Cx	Study Duration	Predictor	Statistical Method	Outcome		Effect	P-value
UKPDS trial 1 10388978 [44]	3104 (1.7% micro) (2.0% macro)		Mean 10-11.1 yr	HbA1c (%)	t test			HbA1c	
						Microvascular complications [a]	+	9.6%	0.0007
							–	8.3%	
						Macrovascular complications [b]	+	8.3%	NS
							–	8.3%	
VA CSDM trial 9009975 [40]	75 (32%)	78 (21%)	Up to 27 mo	HbA1c (1% increase)	Univariate Cox	Clinical CVD events		RR=0.84 (95% CI 0.68, 1.03)	0.10
					Multivariate Cox			RR=0.81 (95% CI 0.55, 1.01)	0.06
Shichiri, 2000 10860187 [43]	55 (20% retinop)	55 (52% retinop)	8 yr	HbA1c (%)	Regression	Rate of worsening of Retinopathy		Continuously increasing risk	nd
				FBG (mg/dL)					nd
				2hPG (mg/dL)					nd
(See study Figure 5)	(14% neph)	(42% neph)		HbA1c (%)		Rate of worsening of Nephropathy		Continuously increasing risk	nd
				FBG (mg/dL)					nd
				2hPG (mg/dL)					nd

732 CI, confidence interval; 2hPG, 2 hour post-prandial glucose; retinop, retinopathy progression; neph, nephropathy progression.
733
734 [a] Retinal photocoagulation, vitreous hemorrhage, or renal failure
735 [b] Nonfatal myocardial infarction, angina, heart failure, stroke
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737 **Table 6.** Correlation of glycemic control and hypoglycemia.

Author, Year UI	N (% events) Tx	Cx	Study Duration	Predictor	Statistical Method	Outcome		Effect	P-value
UKPDS trial 1 10388978 [44]	1121, on insulin (50%)		Mean 10-11.1 yr	HbA1c (%)	t test	Report of hypoglycemia (?severity) at office visits (# reports)		HbA1c	NS
							0	8.6%	
							1	8.4%	
							2+	8.6%	
Van der Does, 1988 9839098 [46]	174 (7.5%)		1 yr	HbA1c decrease ≥1.0% vs. <1.0%	?t test	Grade 2 hypoglycemia		9.5% (≥1%) vs. 6.8% (<1%) had events	NS (implied)
VA CSDM trial 9571345 [38]	75 (mean ~6.5 episodes in 3 months)	78	Up to 27 mo	HbA1c (0.5% decrease)	Qualitative	Non-severe or severe hypoglycemia events		"After the initial mean HbA1c fell in phase I to 7.8% with relatively few hypoglycemic events, each additional 0.5% fall of HbA1c caused a doubling of the reported number of reactions"	
Goddijn, 1999 10229289 [48]	94 (19%)	--	1 yr	Achieved HbA1c≤8% vs. >8%	t test	Change in "hypoglycemia complaints"		+14% (≤8%) vs. +10.8% (>8%)	NS

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Self-monitored blood glucose and glycemic control (HbA1c) in patients with type 2 diabetes

Randomized trials (Table 7)

Study descriptions

We identified five randomized trials meeting our inclusion criteria (Guerci 2003, Schwedes 2002, Fontbonne 1989, Davidson 2005, Kibriya 1999).[52-56] We included all prospective studies with a minimum sample size of 50 subjects and a minimum duration of follow-up of 6 months. Their sample size ranged from 64 to 689 patients; four included more than 100 patients. The trials were published between 1989 and 2005.

The frequency of glucose monitoring in the experimental arms was highly variable, ranging from 2-3 daily measurements every two weeks to six measurements per day (on average). Similarly, the duration of the intervention was 6 months in four trials and more than a year in two trials (approximately 15 and 18 months). Only Kibriya 1999 reports advising the patients how to act based on SMBG measurements, whereas the other studies do not mention any relevant information. The comparator management plan was absence of self-monitoring in all trials. One trial (Fontbonne 1989) was completed before the 1990s, whereas all other studies were estimated to have been completed later than 1997, when the latest amendments to the diagnostic criteria for diabetes were made. In all trials, patients in both arms received concomitant treatment. In one trial, patients were on insulin or oral agents (Kibriya 1999) during the intervention. Schwedes 2002 and Fontbonne 1989 reported that a dietary intervention was used with or without oral antidiabetic drugs. In the remaining two trials, patients received oral antidiabetic drugs (Guerci 2003 and Davidson 2005).

Applicability to the Medicare population

The mean age of the participants ranged from 50 years to 62 years. Thus, in all studies the estimated proportion of patients who were older than 65 years is less than half; in two studies it was probably less than a quarter of the assessed patients (Kibriya 1999 and Davidson 2005). No study performed separate analyses for older patients. The average duration of diabetes was more than 5 years in the four trials that reported the pertinent information, and was over 10 years only in Fontbonne 1989. All trials included patients with type 2 diabetes only. In the remaining trials, none of the participants was on insulin before entering the trial (with the possible exception of Kibriya 1999, where the pertinent information was not mentioned).

The included trials did not report information about the presence of cardiovascular disease, kidney disease, retinopathy, or other comorbidities in the enrolled patients. The average BMI of the studied populations was over 25 kg/m^2 (the boundary for overweight) in all but Kibriya 1999; thus, in five trials more than half (all in Schwedes 2002) of the subjects were overweight. In three trials (Guerci 2003, Schwedes 2002, Davidson 2005), it is estimated that half or more were obese (mean BMI was at least 30 kg/m^2). On average, HbA1c levels implied suboptimal control of blood glucose in the included patients (mean level was approximately 8% or greater in all trials). An elevated HbA1c level was a prerequisite (based on the inclusion criteria) in at least two trials (Guerci 2003 and Schwedes 2002).

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Study results (Figure 2, Panel B)

The studies are inconclusive about whether use of SMBG results in clinically significant reductions in HbA1c in patients with type 2 diabetes. The two largest trials (Guerci 2003 and Schwedes 2002) found that the net differences between SMBG and no SMBG were small (<0.5%), but highly statistically significant (both P = 0.009). Only one small study (Kibriya 1999) found a relatively large net difference in HbA1c (-1%), though it was unclear whether this effect was statistically significant. The remaining two trials found no clinically or statistically significant benefit on HbA1c of SMBG.

Conclusion

Overall, we identified five RCTs that met our inclusion criteria. These RCTs have fair applicability to people with type 2 diabetes in the Medicare population, although they typically enrolled younger patients and perhaps patients with a shorter duration of diabetes. The frequency of glucose monitoring was variable, as was the length of the intervention, the proportion of patients who needed insulin at baseline and the type of concomitant treatments. Importantly, only one of the studies reported that they advised patients to alter their diabetes treatment based on the SMBG readings. The studies may suggest a small, though possibly clinically nonsignificant, reduction in HbA1c with SMBG; though overall the studies are inconclusive. There was no clear pattern across studies regarding how the intensity of the SMBG protocols (frequency of monitoring) or baseline HbA1c related to net changes in HbA1c. The studies were each very different in how frequently (and on which days) SMBG was performed. In addition, given that most of the studies did not report how patients or clinicians changed their behavior or treatments, these analyses do not explain how the use of SMBG resulted in improved HbA1c. No eligible study evaluated continuous glucose monitoring or other home blood glucose measurement techniques.

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Table 7. Randomized controlled trials of self monitoring of blood glucose levels and glycemic control

7.a Applicability of "large" randomized controlled trials to non-dialysis-dependent Medicare population (baseline data)

Author, Year UI	N	Mean Age (Range)	~%≥65 yr	Mean Duration DM	% DM 2	% Using Insulin
Guerci, 2003 14707887 [52]	689	62 (40-75) [a]	<50%	8.0 yr	100%	0%
Schwedes, 2002 12401734 [55]	223	60 (45-70) [a]	<50%	5.3 yr	100%	0%
Fontbonne, 1989 2630378 [53]	110	55 (nd)	<50%	12.5 yr (≥3 yr) [a]	100%	0%
Davidson, 2005 15808142 [54]	88	50 (nd)	<<50%	5.6 yr	100%	0%
Kibriya, 1999 10624792 [56]	64	50 (35-65)	~0%	nd	100%	nd

[a] Eligibility criteria

7.b Baseline "severity of disease" in studies

Author, Year UI	Mean A_{1c} (Range)	% CVD (Details)	Mean GFR [SCr] (Range)	Albuminuria	Retinopathy (Details)	Other Comorbidies	Mean BMI (Range)
Guerci, 2003 14707887	9.0 (7.5-11.0)[a]	nd	nd	nd	nd	nd	30.0 (nd)
Schwedes, 2002 12401734	8.4 (7.5-10.0)[a]	nd	nd	nd	nd	nd	31.4 (>25) [a]
Fontbonne, 1989 2630378	8.2 (nd)	nd	nd	nd	nd	nd	27.1 (nd)
Davidson, 2005 15808142	8.4 (nd)	nd	nd	nd	nd	nd	32.2 (nd)
Kibriya, 1999 10624792	7.9 (nd)	nd	nd	nd	0	nd	23.9 (nd)

[a] Eligibility criteria

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7.c Study designs

Author, Year UI	Design	Intervention Year(s)	Study Duration	Intervention (Frequency)	Control	Other DM Treatments / Cointerventions
Guerci, 2003 14707887	RCT	<2003	24 wk	SMBG (≥6x/wk) Did not report training on how to respond to readings	No SMBG	99.5% on oral antidiabetics ~80% on fibrates, ACEI, or HMG-CoA reductase inhibitors
Schwedes, 2002 12401734	RCT	<2002	24 wk	SMBG (6x/d on 2 d/wk) Did not report training on how to respond to readings	No SMBG	Diet alone +/- sulfonylurea or metformin
Fontbonne, 1989 2630378	RCT	<1989	6 mo	SBGM (2x/d every other day; 3x/d on Saturdays) Did not report training on how to respond to readings	No SMBG	Dietary intervention and/or oral antidiabetic agents
Davidson, 2005 15808142	RCT	<2005	6 mo	SMBG (6x/d; 6 d/wk) Did not report training on how to respond to readings	No SMBG	Metformin, sulfonylurea, and/or thiazolidinedione
Kibriya, 1999 10624792	RCT	<1999	18 mo	SMBG (2-3x/d every 2 wk) Medications adjusted based on SMBG readings, as necessary	No SMBG	Oral hypoglycemic agents or insulin

ACEI: Angiotensinogen converting enzyme inhibitors; d: day(s); mo: month(s); RCT: Randomized controlled trial; SMBG: Self monitoring of blood glucose; wk: week(s)

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7.d Glycemic Control Results

Author, Year UI	Outcome	N (Tx)	N (Cx)	Effect Magnitude (Change in Control Group)	P value
Guerci, 2003 14707887	Δ HbA1c	345	344	Net Δ = –0.28% (Cx: –0.60%)	0.009
Schwedes, 2002 12401734	Δ HbA1c	113	110	Net Δ = –0.46% (95% CI –0.77, –0.11) (Cx: –0.54%)	0.009
Fontbonne, 1989 2630378	Δ HbA1c	56	54	Net Δ = +0.14% (Cx: –0.50)	nd
Davidson, 2005 15808142	Δ HbA1c	43	45	Net Δ = –0.2% (95% CI: –1.1, 0.6%) (Cx: –0.6%)	NS
Kibriya, 1999 10624792	Δ HbA1c	32	32	Net Δ = –0.99% (Cx: -0.38%)	nd (Tx: P=0.02 Cx: NS compared to baseline)

95% CI, 95% confidence interval; Cx, control arm (usual care); Tx, treatment arm (intensive glycemic control).

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Cohort studies (Table 8)

Study descriptions

We identified one nonrandomized controlled study[57] and five single-arm, uncontrolled cohort studies meeting eligibility criteria.[58-62] We included all prospective studies with a minimum sample size of 50 subjects and a minimum 3-month duration of follow-up. The sample size of these six studies ranged from 70 to 1,896 patients.

The frequency of glucose monitoring in the five cohort studies ranged widely, from two to three times a week to four times daily. In the Rutten 1990 study, SMBG was performed when desired by the patients in the intervention arm but the frequency of SMBG was not reported; the patients in the control arm were not instructed in SMBG. Both Rutten 1990 and Ozmen 2003 reported that antidiabetes treatments were adjusted based on SMBG readings. How SMGB readings were acted on by the other studies was not reported. The intervention years were before 1990 in one study (Rutten 1990), 1993 to 1994 in another study (Miles 1997), and after 1997 for the other four studies.

Applicability to the Medicare population

The mean age of the study participants ranged from 40 to 65 years old at baseline. Only the nonrandomized controlled study, Rutten 1990 and the cohort study Miles 1997 had patient samples about half of whom were 65 years or older. No study performed separate analyses for older patients. All patients had type 2 diabetes, with the exception of patients in Halimi 2001, which did not report diabetes type, but probably included at least some patients with type 1 diabetes. The mean duration of diabetes ranged from newly diagnosed to 9 years. Only Halimi 2001 reported that all patients used insulin. A minority of patients used insulin in three studies; two studies did not report insulin use. Two studies reported that sulphonylureas and/or metformin were also used (Franciosi 2005 and Ozmen 2003). The mean baseline HbA1c levels ranged from 7% to 10%.

Study results (Figure 2, Panel A)

Statistically significant improvements in glycemic control as measured by HbA1c were found in the nonrandomized comparative study (SMBG vs. no SMBG) and four of five of the uncontrolled cohort studies (final vs. baseline). The nonrandomized controlled study (Rutten 1990) and Halimi 2001 (which probably included many patients with type 1 diabetes) found improvements in HbA1c that were similar to the effects found in the randomized controlled trials. However, three of the cohort studies (Ozmen 2003, Miles 1997, and Banister 2004) found considerably larger changes from baseline, approximately –1.5% to –2.5%.

In contrast, in a 3 year prospective cohort study where patients continued using SMBG as they (and presumably their clinicians) saw fit, no effect of SMBG practice on metabolic control was found.

Conclusion

Overall, the nonrandomized study and the uncontrolled cohort studies were in general agreement with the findings of the randomized controlled trials, which indicate that use of SMBG is associated with a small reduction in HbA1c. Interpretation of these results, without equivalent control arms, though is difficult. Also similar to the randomized controlled trials, though, the majority of subjects were younger than 65 years old. Along with poor reporting

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858 regarding comorbidities and antidiabetic medication use, calling into question the applicability of
859 these studies to the Medicare population.

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860 **Table 8. Nonrandomized controlled and cohort studies of self monitoring of blood glucose levels and glycemic control**
861 **8.a Applicability of "large" prospective studies to non-dialysis-dependent Medicare population (baseline data)**

Author, Year UI	N	Mean Age (Range)	~%≥65 yr	Mean Duration DM	% DM 2	% Using Insulin
Nonrandomized controlled study						
Rutten, 1990 2289639	127	63 (40-75) [a]	~50%	8.8 yr	100%	nd
Cohort studies						
Franciosi, 2005 15975106	1896	62 (nd)	<50%	9.1 yr	100%	0%
Ozmen, 2003 12738396	267	58 (nd)	<50%	8.6 yr	100%	34%
Miles, 1997 9270457	150	65 (31-91)	~50	0 (newly diagnosed cases)	100%	nd (probably 0% but not explicitly stated)
Halimi, 2001 11852377	143	40 (≥18) [a]	<<50%	14.2 yr	nd	100%
Banister, 2004 15127069	70	49 (nd)	<<50%	nd	100%	nd

862 [a] Eligibility criteria
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8.b Baseline "severity of disease" in studies

Author, Year UI	Mean A_{1c} (Range)	% CVD (Details)	Mean GFR [SCr] (Range)	Mean Albuminuria (Category)	% Retinopathy (Details)	Other Comorbidies	Mean BMI (Range)
Nonrandomized controlled study							
Rutten, 1990 2289639	9.3 (nd)	nd	nd	nd	nd	nd	QI: 51% <27, 21% 27-30; 27% >30
Cohort studies							
Franciosi, 2005 15975106	7.2 (nd)	nd	nd	nd	nd	Mean total illness burden index = 12.7	28 (nd)
Ozmen, 2003 12738396	9.1 (4% <6, 17% 6.1-6.9, 20% 7.0-7.9, 16% 8-8.9; 44% >9)	nd	nd	nd	28% background diabetic retinopathy (DR) 20% had proliferative DR	nd	29.1 (nd)
Miles, 1997 9270457	10.3 (nd)	nd	nd	nd	nd	nd	27.3 (nd)
Halimi, 2001 11852377	Monitor A: 9.8 Monitor B: 9.5 Monitor C: 9.3 (nd)	nd	nd	nd	nd	nd	24.1 (nd)
Banister, 2004 15127069	9.7 (5.2-16.2)	nd	nd	nd	nd	nd	34 (90% >25)

QI, Quetelet index (<27 = acceptable, 27-30 = over weight, >30 = obesity)

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867 **8.c Study designs**

Author, Year UI	Design	Intervention Year(s)	Study Duration	Intervention (Frequency)	Control	Other DM Treatments / Cointerventions
Nonrandomized controlled study						
Rutten, 1990 2289639	Prospective, nRCT	<1990	1 yr	SMBG when desired by the patient Medications adjusted based on SMBG readings, as necessary	No SMBG	
Cohort studies						
Franciosi, 2005 15975106	Cohort	<2005	3 yr	Self-reported SMBG frequency (≥1/d, ≥1/wk, <1/wk or never) No active interventions		Diet only, Sulphonylureas, Metformin, or Sulphonylureas + metformin
Ozmen, 2003 12738396	Cohort	1997-2001	1 yr	SMBG (Month 1: 2-3x/wk. During the next 11 mo: as necessary to maintain normoglycemia). Clinicians evaluated SMBG readings to adjust treatment		Diet alone, insulin +/- sulphonylureas, acarbose or metformin
Miles, 1997 9270457	Cohort	1993-1994	3 & 6 mo.	SMBG (1/d) Did not report training on how to respond to readings		
Halimi, 2001 11852377	Cohort	<2001	6 mo.	SMBG (4x/d, 3 different monitors) Did not report training on how to respond to readings		All patients were insulin-treated.
Banister, 2004 15127069	Cohort	2001	2-12 mo	SMBG (1x/d) Did not report training on how to respond to readings		

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868 **8.d Study Results**

Author, Year UI	Outcome	N (Tx)	N (Cx)	Effect Magnitude (Change in Control Group)	Significant?
Nonrandomized controlled study					
Rutten, 1990 2289639	Mean changes in HbA1c	55	72	Net Δ = –0.94% (Cx: +0.46%) [b]	<0.01
Cohort studies					
Franciosi, 2005 15975106	HbA1c	1896		No effect of SMBG practice on metabolic control	NS
Ozmen, 2003 12738396	HbA1c	267		6 mo Δ = –1.3%	0.001
				12 mo Δ = –1.9%	0.001 (6 mo vs 12 mo NS)
	HbA1c, stratified by optic fundi findings			Mean HbA1c Baseline / 6 mo / 12 mo No DR: 7.9 / 6.7 / 5.8 Background DR: 9.6 / 7.8 / 8.3 Proliferative DR: 11.7 / 8.9 / 8.0	
Miles, 1997 9270457	HbA1c	58		3 mo Δ = –1.5% (-1.9, -1.06)	<0.05
				6 mo Δ = –2.5% (-3.9, -1.3)	<0.05
Halimi, 2001 11852377	HbA1c	143		3 mo Δ = –0.3% (monitor A) –0.7% (monitor B) –0.64% (monitor C)	<0.05 (NS between monitors)
				6 mo Δ = –0.6% (monitor A) –0.9% (monitor B) –1.0% (monitor C)	<0.05 (NS between monitors)
Banister, 2004 15127069	HbA1c	70		–1.5%	<0.001

869 DR, diabetic retinopathy; Cx, change from baseline in control group
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871 [b] Adjusted for baseline HbA1c
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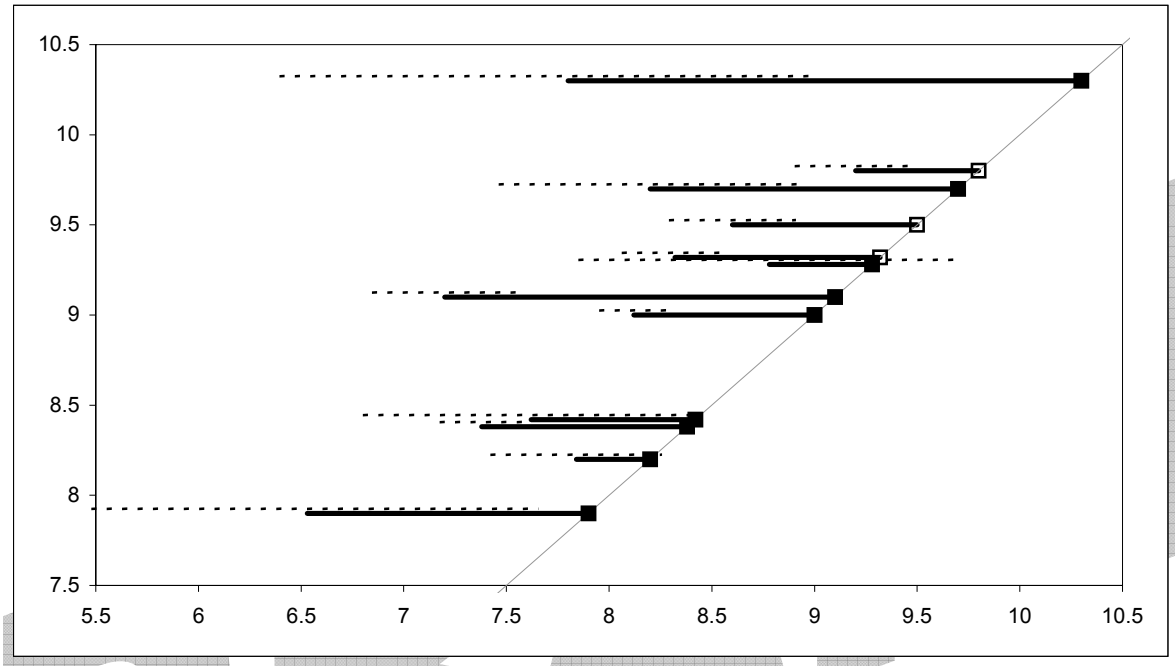
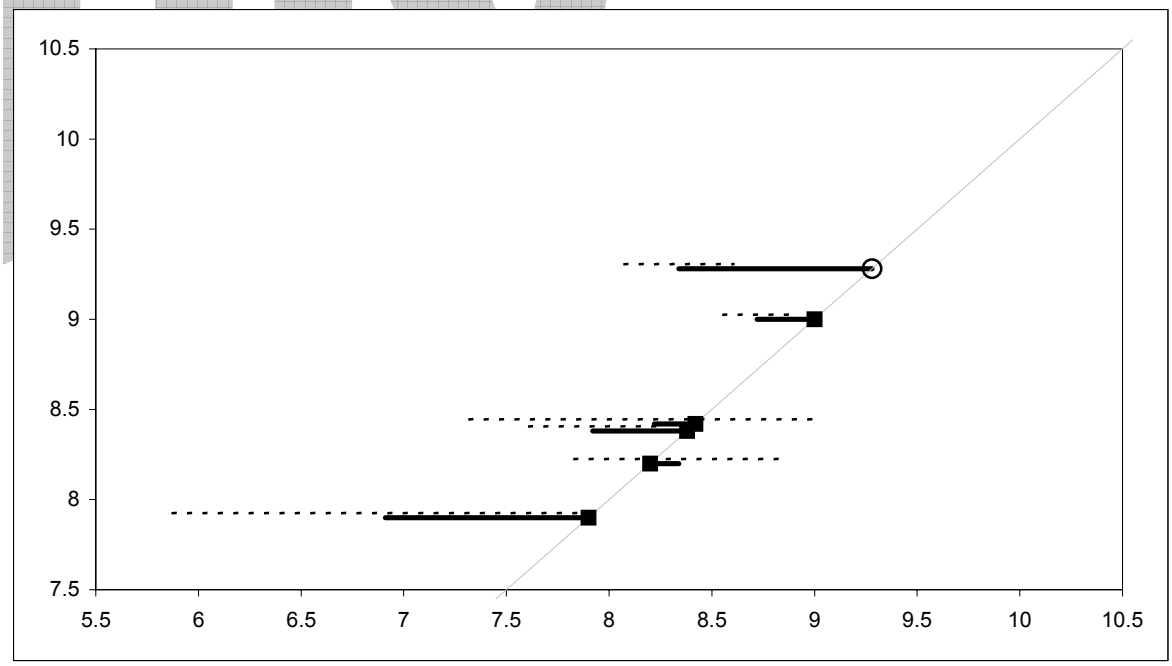
Figure 2. The effect of SMBG on HbA1c (%) in cohorts of patients using SMBG (**Panel A**, final vs baseline, all studies that reported data, cohorts indicated by open squares are all from the same study) and in comparative studies (**Panel B**, baseline of SMBG cohort and net change [change in SMBG cohort minus change in No SMBG cohort] applied, study indicated by open circle was not randomized). Studies/cohorts are distributed along y-axis only to allow visualization of distribution of baseline values. Only final followup timepoint data from each study are included. Dotted lines are 95% confidence intervals of changes or net changes in HbA1c (generally not reported, therefore estimated from available data). Light gray diagonal line is line of identity.

Panel A. SMBG cohorts (baseline and final HbA1c (%))



Panel B. SMBG vs No SMBG (baseline in SMBG cohort and net change HbA1c (%))



Self monitored blood glucose and risk of severe hypoglycemia in patients with type 2 diabetes (Table 9)

Study descriptions

We identified three cohort studies meeting our inclusion criteria (Murata 2004, Halimi 2001, and Cox 1994).[60,63,64] We included all prospective studies with a minimum sample size of 50 subjects and a minimum duration of follow-up of 6 months. No comparative studies (randomized or nonrandomized) reported on severe hypoglycemia outcomes. The sample sizes of these studies were 344, 143, and 78 patients, respectively. Halimi 2001 and Cox 1994 are similar with respect to their interventions and study duration. In these two studies, the frequency of glucose monitoring ranged from two to four measurements daily and the duration of the intervention was 6 months. In Murata 2004, it is indicated that patients monitored their blood glucose at an average of 15.3 measurements per week and that the duration of the intervention was 1 year. It appears as if the number of measurements only regards those patients who developed hypoglycemia throughout the study duration; however, this is not made clear. In addition, it was reported that 159 of the 344 patients intensified their monitoring to four measurements daily for 8 weeks and then resumed the original intervention. Patients in all studies were insulin-treated. In addition, diabetes treatments were determined by the patients and their primary care physicians in Murata 2004; however, the particular treatments are not mentioned. Patients in the Cox 1994 study underwent Blood Glucose Awareness Training in order to learn greater awareness of blood glucose fluctuations.

Applicability to the Medicare population

The mean age of the participants ranged from 38 to 65 years. In all the studies, no more than 50 percent of the patients were older than 65 years; in Cox 1994, none of the patients was older than 65 years. No study performed separate analyses for older patients. The mean duration of diabetes in patients was about 14 to 15 years in two of the studies (Murata 2004 and Halimi 2001) and 19 years in the other study (Cox 1994). All patients in Murata 2004 had insulin-treated type 2 diabetes; however, it is not specified how many patients had type 2 diabetes in Halimi 2001 and Cox 1994. It is possible that a sizeable number of subjects in these two studies had type 1 diabetes as the mean ages and the mean durations of diabetes diagnosis data imply that many patients were diagnosed in their 20s.

Halimi 2001 and Cox 1994 did not report any information regarding the presence of cardiovascular disease, kidney disease, retinopathy and other comorbidities in their patients. Some patients in the Murata study presented with vascular disease, stroke, micro- and macrovascular complications, myocardial infarction, retinopathy, “self-disability”, neuropathy and lower extremity amputations and/or ulcers. Mean HbA1c in all studies was greater than 8%, indicating suboptimal control of blood glucose. Patients in Murata 2004 and Halimi 2001 had a mean BMI of 32.0 and 24.1 kg/m^2, respectively. Information on the mean BMI of patients in the Cox study was not provided.

Study results

The largest study, Murata 2004, measured symptomatic hypoglycemic episodes, defined as hypoglycemia with autonomic symptoms: palpitations, sweating, tremor, or neuroglycopenic symptoms: dizziness, loss of coordination and trouble concentrating. It is unclear how many of

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929 the episodes were of grade 3 or 4 severity. During 1 year of SMBG, 52 percent of patients had at
930 least one episode of symptomatic hypoglycemia. Symptoms were scored as '0' if a patient did
931 not experience any symptoms, as '1' if a patient had mild-to-moderate symptoms and as '2' if a
932 patient had a depressed level of consciousness or required the assistance of others. For each
933 subject, a representative symptom score, on a scale of 0-2, was calculated for each hypoglycemic
934 episode. The mean symptom score was 0.85.
935 Halimi 2001 reported that the number of weekly hypoglycemic episodes during the 6 months
936 increased from an average of 1.9 episodes to an average of 6.2 episodes. Halimi 2001 also
937 reported no hospitalizations or severe adverse events. Statistical significance was not provided
938 for any of these results.
939 In the Cox 1994 study, subjects reported a mean of 8.6 episodes of hypoglycemic stupor and
940 0.81 episodes of hypoglycemic unconsciousness over 6 months of SMBG; 25 percent of subjects
941 reported no severe hypoglycemia episodes.

942 **Conclusions**

943 Three cohort studies met the inclusion criteria for this report. Only one study (Murata 2004)
944 definitely included only patients with type 2 diabetes; approximately half of the subjects were
945 age 65 years or older. The other two studies were of much younger populations and may include
946 a large number of patients with type 1 diabetes. In two of the studies (Cox 1994 and Murata
947 2004), over half of the patients suffered from severe hypoglycemia and in the third study (Halimi
948 2001), the number of weekly hypoglycemic episodes increased by an average of four episodes.
949 Hypoglycemia occurred among a sizeable number of patients performing self-monitoring of
950 blood glucose levels; however, as these patients were not compared to patients who were not
951 self-monitoring, it is difficult to determine to what degree SMBG played a role in the
952 hypoglycemia events, as opposed to other changes that occurred in the patients' diabetes
953 management during the course of the studies.

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954 **Table 9. Studies of self monitoring of blood glucose levels and hypoglycemia**
955 **9.a. Applicability of "large" prospective studies to non-dialysis-dependent Medicare population (baseline data)**

Author, Year UI	N	Mean Age (Range)	~%≥65 yr	Mean Duration DM	% DM 2	% Using Insulin
Murata, 2004 15163479	344	65 (35, upper nd) [a]	~50%	14.5 yr	100%	100%
Halimi, 2001 11852377	143	40 (≥18)	<<50%	14.2 yr	nd	100%
Cox, 1994 7989471	78	38 (nd)	<<50%	19.3 yr	nd	100%

956 [a] Based on inclusion criteria.
957
958
959 **9.b. Baseline "severity of disease" in studies**

Author, Year UI	Mean A_{1c} (Range)	% CVD (Details)	Mean GFR [SCr] (Range)	Mean Albuminuria (Category [A])	% Retinopathy (Details)	Other Comorbidies	Mean BMI (Range)
Murata, 2004 15163479	8.0 (nd)	35% PVD 5% LE amputation 14% LE ulcers 30% MI 13% stroke	<2.8 mg/dL	nd	32% retinopathy (No details)	70% described themselves as self-disabled 58% neuropathy	32.0 (nd)
Halimi, 2001 11852377	9.6	nd	nd	nd	nd	nd	24.1
Cox, 1994 7989471	10.3 (nd)	nd	nd	nd	nd	nd	nd

960 PVD, peripheral vascular disease; MI, myocardial infarction; LE, lower extremity
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9.c. Study Designs

Author, Year UI	Design	Intervention Year(s)	Study Duration	Intervention (Frequency)	Control	Other DM Treatments / Cointerventions
Murata, 2004 15163479	Cohort	2001-2002	Up to 52 wk	SMBG (15.3x/wk) [b] Patients instructed in diabetes management based on SMBG readings		Per patients' primary care physicians
Halimi, 2001 11852377	Cohort	<2001	6 mo	SMBG (4x/day) Did not report training on how to respond to readings		Insulin
Cox, 1994 7989471	Cohort	<1994	6 mo	SMBG (≥2x/day) No training on how to respond to readings (implied)		Insulin

[b] It appears as if the 15.3x/wk only regards those patients who developed hypoglycemia throughout the study duration; however, this is not made clear. A subset (n = 159) intensified SMBG – 4x daily – for 8 weeks and then resumed their 'usual' frequency.

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967 **9.d. Study Results** (all uncontrolled cohort studies)

Author, Year UI	Outcome (Definition)	N (Tx)	N (Cx)	Effect Magnitude	Significant?
Murata, 2004 15163479	Symptomatic hypoglycemia (See footnote c)	344		52% of total had at least one symptomatic hypoglycemic episode	
				The average symptom score was 0.85 [d]	
Halimi, 2001 11852377	Weekly hypoglycemic episodes (not defined)	143		Increased from an average of 1.9 episodes to an average of 6.2 episodes	
	Hospitalizations/severe adverse events (not defined)	143		No patients were hospitalized or suffered any severe adverse events	
Cox, 1994 7989471	Severe hypoglycemia (unconsciousness or stupor, assistance is required)	78		Mean 8.6 episodes of hypoglycemic stupor and 0.81 episodes of hypoglycemic unconsciousness during the 6 mo period	
				20 (26%) subjects reported no severe hypoglycemic episodes during the 6 mo	

968 [c] Hypoglycemia was defined as a recorded glucose level ≤60 mg/dL. An episode was considered symptomatic if the subject had relevant
969 autonomic symptoms (palpitations, sweating, tremor) or neuroglycopenic symptoms (dizziness, loss of coordination, trouble concentrating).
970 [d] Symptoms were scored as '0' if there were no symptoms, as '1' if patient had mild-to-moderate symptoms and as '2' if patient had a depressed
971 level of consciousness or required the assistance of others. For each subject, a representative symptom score (on a scale of 0-2, based on the
972 scoring of symptoms) was calculated for each hypoglycemic episode.

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Correlation of self-monitoring frequency with outcomes in patients with type 2 diabetes (Table 10)

Study descriptions

Two of the studies on SMBG reported analyses correlating SMBG frequency with achieved HbA1c; no study attempted to correlate SMBG frequency with hypoglycemia episodes or clinical events.[53,59] Fontbonne 1989 was a 6 month randomized controlled trial comparing SMBG to usual care in patients with type 2 diabetes who were not using insulin treatment. The study did not report how patients' management of their diabetes was altered based on the SMBG readings. Franciosi 2005 was a large prospective, observational uncontrolled, 3 year cohort study, also of patients with type 2 diabetes who were not using insulin treatment. As an observational study, there was no protocol regarding how patients or clinicians responded to SMBG readings. Overall, these studies had fair applicability to the Medicare population (details have been given in the previous sections).

Study results

Franciosi 2005 evaluated 1896 patients with type 2 diabetes using SMBG for 3 years. The study reported that "changes in SMBG frequency during the study period failed to show any statistically significant impact on metabolic control." Overall, there was a trend that increasing the frequency of SMBG was associated with a slight decrease in mean HbA1c ($\beta = -0.13$; $P = 0.08$). However, among patients who changed frequency of monitoring, but did not change treatment of their diabetes, there was no correlation between frequency and HbA1c.

Among the subjects randomized to the SMBG arm, Fontbonne 1989 correlated the number of blood glucose strips used with the change in HbA1c over a 6 month period. Linear regression yielded a statistically significant correlation ($P<0.02$) such that, by regression, using no strips predicts an increase in HbA1c of approximately 1%, while using 500 strips in 6 months predicts a decrease in HbA1c of approximately 3% (See Figure 3 in study article). In addition, those patients who obtained a decrease in HbA1c of ≥1% used significantly more strips than those with smaller changes (229 vs. 153 strips, $P<0.01$).

Conclusions

Although the evidence is limited, the two studies suggest that increased frequency of SMBG is associated with better HbA1c levels. Any such correlation would clearly be a proxy for the effect of modifications in diet, diabetes treatment, or other factors on glycemic control. The lack of a correlation in the large cohort study between SMBG frequency and change in HbA1c among patients remaining on the same treatment may suggest that frequent SMBG is allowing clinicians and patients to better gauge the need for changes in treatment. Similarly in the smaller trial, the correlation between number of strips used and change in HbA1c may be a proxy for how compulsive patients are about their glycemia. Possibly, those patients who chose to monitor frequently were more likely to alter their diet, have more intensive treatment, and be more adherent to the diabetes management plan.

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1011 **Table 10.** Correlation of SMBG frequency and achieved HbA1c.

Author, Year UI	N Tx	 Cx	Study Duration	Predictor	Statistical Method	Outcome	Effect	P-value
HbA1c outcome								
Franciosi, 2005 15975106	1896	--	3 yr	Increase in monitoring frequency [a]	Regression	ΔHbA1c	β=−0.13	0.08
				Among patients who changed frequency without changing treatment [a]			β=−0.015	0.6
Fontbonne, 1989 2630378 (See study Figure 3)	56	(54) [b]	6 mo	No. BG strips used [c]	Regression	ΔHbA1c	▲Strips → ▼A1c r=0.36	<0.02
					t test		ΔHbA1c≥1% (229 strips) vs. <1% (153 strips)	<0.01

1012 BG strips, blood glucose reactive strips
1013
1014 [a] Observational study. No protocol was reported regarding what changes were made based on SMBG readings.
1015 [2] Not included in analysis.
1016 [c] Study did not report on any training on how to respond to SMBG readings.

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Chapter 4. Summary and Discussion

Summary of findings

Question A

Through the systematic review process, describe the applicability of the literature to the non-dialysis-dependent Medicare population in regards to

The relationship between tighter glycemic control and clinical outcomes (both benefits and harms) in patients with type 2 diabetes.

Clinical events

Study descriptions and applicability to Medicare population

For the purposes of this report, we included all prospective studies of intensive glycemic control in predominantly patients with type 2 diabetes with a minimum sample size of 100 patients followed for at least 1 year.

Three randomized controlled trials met eligibility criteria, including the large UKPDS trial. Although all trials included at least some patients age 65 or older, these patients represented a small minority overall. Furthermore, no study performed separate analyses for older patients. Notably, the UKPDS trial included only patients with newly diagnosed diabetes, with a mean baseline HbA1c of 7%. The baseline HbA1c in the other two trials was approximately 9%; however one study was performed among relative thin Japanese patients, a population that may be of only limited applicability to the large majority of American patients with type 2 diabetes. The use of insulin, other antidiabetic treatments, and the prevalence of diabetes-related comorbidities varied widely (or were not reported) among the studies. Each trial used a different goal for intensive glycemic control using a variety of measures of glycemia.

Summary of results

Only the UKPDS trial had sufficient participants to begin to make a precise estimate of mortality. The trial found nonsignificant trends for decreased all-cause and diabetes-related mortality rates with intensive glycemic control at about 10 years follow-up. The other two trials found no difference in mortality. Similarly UKPDS found marginally significant reductions in nonfatal and total myocardial infarctions, and fatal sudden death events. No differences were found for other cardiovascular events and the other two trials found no differences for all cardiovascular events.

Only the Japanese study Shichiri 2000 was designed primarily to investigate retinopathy. They reported that intensive glycemic control resulted in substantial reductions in progression of retinopathy after 8 years; however, no significant differences were found in development of preproliferative or proliferative retinopathy. UKPDS found a significant reduction in the need for retinal photocoagulation after about 10 years with intensive glycemic control, but no difference in vitreous hemorrhage or blindness events. VA CSDM found that patients on intensive glycemic control had increased retinopathy progression over the first year, but reduced progression in the second year.

UKPDS found no difference in rates of kidney failure over 10 years, but the other trials reported slower progression of microalbuminuria after 2 years and less progression of nephropathy at 8 years with intensive treatment. No statistically significant differences were reported in a wide range of neuropathy events in two trials.

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The studies do not provide evidence for any improvements in retinopathy or kidney function with intensive glycemic control.

Correlation of level of glycemic control and clinical outcomes

From the three trials, there is evidence to suggest long-term reductions in microvascular events (i.e., retinopathy and kidney disease) and macrovascular events (i.e., cardiac and stroke events) with progressively improved glycemic control; however, it may be the case that a transient increase in cardiovascular events may occur with the introduction of intensive glycemic control.

Severe hypoglycemia

Study descriptions and applicability to Medicare population

For the purposes of this report, we included all prospective studies of intensive glycemic control in predominantly patients with type 2 diabetes with a minimum sample size of 50 patients followed for at least 3 months.

Nine studies met criteria, of which five were randomized controlled trials, one a nonrandomized controlled study, and three uncontrolled cohort studies. Two of the trials (both from UKPDS) included only subjects with newly diagnosed type 2 diabetes. The mean HbA1c reported ranged from about 7% to 10%. There was a wide range across studies of insulin use and other antidiabetic treatments; one study did not report how many subjects had type 2 diabetes and likely included at least some with type 1 diabetes. The prevalence of diabetes-related comorbidities varied widely (or were not reported) among the studies. All studies included at least some patients 65 years or older, but the largest trials (UKPDS) set 65 years old as a maximum age at enrollment. No study performed separate analyses for older patients. Each study used a different goal for intensive glycemic control using a variety of measures of glycemia.

Summary of results

All studies reported on "severe" hypoglycemic episodes, sometimes defined as grade 3 or 4, sometimes as "requiring assistance," but sometimes not further defined. The two UKPDS trials and the nonrandomized controlled study, all relatively large, provide evidence that severe hypoglycemic episodes are statistically significantly (or at least substantially) more common among patients being treated with intensive glycemic control. On the order of 1-2 percent of patients using intensive glycemic control had episodes of severe hypoglycemia. Among the studies that reported any severe hypoglycemic events and reported results per 100 patient-years, the rates with multidose insulin were less than 1 event per 100 patient-years. This can be contrasted with the 62 severe hypoglycemic episodes per 100 patient-years found in DCCT among patients with type 1 diabetes.[51] It is unclear whether the lack of difference in effect of the other comparative trials was due to differences in the studies or to an insufficient number of subjects to detect possible differences. However, it is notable, that the three studies (possibly) conducted most recently both report no episodes of severe hypoglycemic episodes among a large number of subjects.

Correlation of level of glycemic control and hypoglycemia

Four studies analyzed correlations between either achieved HbA1c or change in HbA1c and hypoglycemia outcomes. Importantly, though, none analyzed the outcome of interest, grade 3 or higher episodes of hypoglycemia. While one study suggests an exponential increase in hypoglycemia episodes with continually decreasing HbA1c below approximately 8%, overall the

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evidence weakly suggests only a possible correlation between tightness of glycemic control and frequency of hypoglycemia episodes.

Question B

Through the systematic review process, describe the applicability of the literature to the non-dialysis-dependent Medicare population in regards to

The effect of frequency of glucose monitoring on clinical outcomes in patients with type 2 diabetes.

Clinical events

For the purposes of this report, we searched for all prospective studies of self-monitoring of blood glucose (SMBG) in predominantly patients with type 2 diabetes with a minimum sample size of 100 patients followed for at least 1 year. No study met eligibility criteria.

Severe hypoglycemia

Study descriptions and applicability to Medicare population

For the purposes of this report, we included all prospective studies of intensive glycemic control in predominantly patients with type 2 diabetes with a minimum sample size of 50 patients followed for at least 3 months.

Three uncontrolled cohort studies met criteria. The frequency of monitoring ranged from about 14 to 28 times per week. All patients used insulin, but only one study explicitly included only patients with type 2 diabetes. This latter study had a mean age of 65 years, though no subanalyses were performed in this group. It is likely that the other two studies included at least some patients with type 1 diabetes, particularly since the mean age at enrollment was about 40 in both studies. The mean duration of diabetes in all studies was about 14 to 19 years. The mean baseline HbA1c levels ranged from about 8% to 10%. None of the studies was clear about how patients and clinicians changed diabetes management based on the SMBG readings.

Summary of results

In one study, about half of the patients suffered from symptomatic hypoglycemia (probably including episodes not requiring assistance from others) and in a second study about three-quarters of the patients reported grade 3 or 4 hypoglycemia episodes. In the third study, the number of weekly hypoglycemic episodes increased by an average of four episodes during the study.

Correlation of SMBG frequency and hypoglycemia

No study attempted to correlate SMBG frequency with hypoglycemia episodes.

Question C

Through the systematic review process, describe the applicability of the literature to the non-dialysis-dependent Medicare population in regards to

The effect of frequency of glucose monitoring on glycemic control (HbA1c) in patients with type 2 diabetes.

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Study descriptions and applicability to Medicare population

For the purposes of this report, we included all prospective studies of intensive glycemic control in predominantly patients with type 2 diabetes with a minimum sample size of 50 patients followed for at least 3 months.

Five randomized controlled trials, one nonrandomized controlled study, and five single-arm, uncontrolled cohort studies met eligibility criteria. The frequency of glucose monitoring in the experimental arms or the cohort studies was highly variable, ranging from 2-3 daily measurements every two weeks to about six measurements per day. Only one of the trials and two of the other studies report that adjustments to antidiabetic treatments were made based on SMBG readings. The nonrandomized comparative study was an observational study, with no specific protocol regarding SMBG.

In the randomized trials, fewer than half the participants were aged 65 years or older at enrollment; most of the other studies also included a majority of patients under age 65. One of the cohort studies may have included patients with type 1 diabetes. Among the randomized trials, the mean duration of diabetes ranged from about 5 to 10 years; among the other studies some included only patients with newly diagnosed diabetes. The data on comorbidities was generally not reported. Across studies, the mean baseline HbA1c levels ranged from 7% to 10%.

Summary of results

The randomized trials provide inconclusive evidence that use of SMBG may result in a small, possibly clinically nonsignificant, decrease in HbA1c, on the order of a 0.25% to 0.5% decrease. Although some of the nonrandomized studies found larger decreases in HbA1c with SMBG use, these studies were generally in agreement with the randomized trials regarding the change in HbA1c. There was no clear pattern across studies regarding how the intensity of the SMBG protocols (frequency of monitoring) or baseline HbA1c related to net changes in HbA1c. The studies were each very different in how frequently (and on which days) SMBG was performed. In addition, given that most of the studies did not report how patients or clinicians changed their behavior or treatments, these analyses do not explain how the use of SMBG resulted in improved HbA1c.

As a point of reference, the prospective trials generally found smaller net effects of SMBG than the two large retrospective database analyses from Kaiser Permanente[23] and Harvard Pilgrim[24] health maintenance organizations. The Kaiser Permanente study reported that people with type 2 diabetes who filled prescriptions equivalent to at least 0.75 strips per day had HbA1c levels between 0.4% and 0.6% lower than those with "inadequate" use, depending on their diabetes treatment regimen (approximately 23,000 subjects).[23] The Harvard Pilgrim study evaluated a mix of people with types 1 and 2 diabetes (725 subjects) and reported that initiation of SMBG was not associated with improved HbA1c levels in those with good (HbA1c $\leq$ 8.0%) or adequate (8-10%) baseline glycemic control, but among those with poor baseline glycemic control (>10%), initiators of SMBG lowered their mean HbA1c level by 0.63% compared with noninitiators (P = .03).[24]

Of note, no eligible study evaluated continuous glucose monitoring or other home blood glucose measurement techniques.

Correlation of SMBG frequency and HbA1c

Two of the studies on SMBG reported analyses correlating SMBG frequency with achieved HbA1c. The two studies suggest that increased frequency of SMBG is associated with better HbA1c levels.

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Discussion

The eligibility criteria for this report were strict, requiring relatively large numbers of subjects and long-term follow-up. Thus, this report only reviews the studies that are likely to provide the "strongest" evidence. Many studies were not reviewed because of small sample size or shorter-term follow-up. The report included only five randomized trials of intensive glycemic control, only three of which provided data on clinical events, and five randomized trials of SMBG, none of which provided data on either clinical events or hypoglycemic episodes. In fact, no study met eligibility criteria that evaluated SMBG and clinical events. A small number of studies evaluated correlations between either intensity of glycemic controlled (measured by HbA1c) or frequency of self-monitoring and outcomes of interest for this report. No eligible study evaluated continuous glucose monitoring.

The applicability of these studies to the nondialysis-dependent Medicare population is debatable. Using only age as a criterion, most studies included only a minority of participants of age 65 years or older at enrollment. Studies commonly had only a small percentage of older patients, where mean age was less than about 55 years. The largest study, UKPDS (trial 1) enrolled patients with a maximum age of 65 years. No study performed subanalyses of the Medicare-eligible population. The applicability of this trial to the Medicare population is further limited by the fact that only patients with newly diagnosed diabetes (thus with "moderate" HbA1c of about 7%) were enrolled. Other than the UKPDS trials, the duration of diabetes in most studies was on the order of 10 years and most studies had mean HbA1c levels at enrollment of about 8% to 10%. However, it is difficult to compare most of the studies to Medicare population based on other factors. Prevalence of comorbidities, such as cardiovascular, kidney, eye, and peripheral nerve disease, were generally not reported. In addition, insulin use at baseline ranged widely from 0 to 100 percent of subjects, based on varying eligibility criteria and treatment practices. As highlighted by the Japanese study of relatively thin patients with type 2 diabetes, it is likely that the studies varied in the degree to which patients were insulin deficient compared with their insulin sensitivity. It was difficult to pinpoint when most studies were performed since this was generally not reported. However, the UKPDS trial was run from 1977 to 1991 and only three cohort studies were definitely conducted in the last decade (although four other cohort studies and four randomized trials were probably conducted in the last decade).

Regarding the effect of these two interventions among patients with type 2 diabetes, the reviewed studies generally found that intensive glycemic control may result in reduced mortality and certain cardiac events, progression of retinopathy (after about 1 year), and progression of nephropathy. No effect was found for various cardiovascular events, blindness events, kidney failure, or neuropathy. No evidence was reported regarding possible improvement in retinopathy or kidney function with treatment. Among older studies, there is evidence that intensive glycemic control is strongly associated with episodes of severe hypoglycemia; however, since no episodes were reported among more recent studies, it is possible that with newer treatment protocols or training methods, the risk of severe hypoglycemic episodes is now very low. The reported rates of severe hypoglycemia were orders of magnitude smaller than the rates found in DCCT among patients with type 1 diabetes. Similarly, uncontrolled cohort studies suggest that SMBG use is associated with symptomatic or severe hypoglycemia episodes. Evidence from randomized and uncontrolled studies were inconclusive about whether SMBG use results in clinically significant reductions of HbA1c; the two largest randomized trials found statistically significant net reductions of less than 0.5%. Furthermore, the studies of SMBG are generally

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difficult to interpret since the links between SMBG use and changes in antidiabetes management, resulting in changes in glycemia, are not described and the SMBG protocols varied widely across studies. No clear association across studies was found between the intensity of the SMBG protocols and net reduction of HbA1c.

Over the long term, three studies did find that the level of glycemic control achieved correlated with improved micro- and macrovascular outcomes, although there may be a transient increase in cardiovascular events with the introduction of glycemic control. The studies that analyzed intensity of glycemic control and risk of hypoglycemia did not specifically evaluate severe hypoglycemic episodes. Similarly two studies found that the frequency of SMBG use was continuously associated with better achieved HbA1c levels.

Overall, the assessed studies generally found that among patients with type 2 diabetes, that intensive glycemic control results in reduces risks for various clinical events, but there are no data on the effects of SMBG on clinical outcomes. SMBG use may result in only clinically nonsignificant improvements in achieved glycemic control, but both intensive glycemic control and SMBG may result in increased episodes of severe hypoglycemia. Also, more intensive glycemic control and more frequent use of SMBG are more strongly associated with outcomes than lesser interventions. However, the degree to which these studies are applicable to patients 65 years of age and older, who may have more severe comorbidities, a shorter life expectancy, and more cognitive, visual, and social difficulties than study patients is unclear

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Appendix A. List of Rejected Articles

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(N too small)

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Anonymous. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group. . Journal of Pediatrics. 1994 Aug . UI 8040759
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(Type 1 DM)

Abraira C;Duckworth W;McCarren M;Emanuele N;Arca D;Reda D;Henderson W;VA Cooperative Study of Glycemic Control and Complications in Diabetes Mellitus Type. Design of the cooperative study on glycemic control and complications in diabetes mellitus type 2: Veterans Affairs Diabetes Trial. Journal of Diabetes & its Complications. 2003 Nov . UI 14583175
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Allen BT;DeLong ER;Feussner JR. Impact of glucose self-monitoring on non-insulin-treated patients with type II diabetes mellitus. Randomized controlled trial comparing blood and urine testing. Diabetes Care. 1990 Oct . UI 2170088
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(Duration too short)

Cox D;Gonder-Frederick L;Polonsky W;Schlundt D;Julian D;Clarke W. A multicenter evaluation of blood glucose awareness training-II. . Diabetes Care. 1995 Apr . UI 7497863
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(Retrospective)

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Gebhart SS;Wheaton RN;Mullins RE;Austin GE. A comparison of home glucose monitoring with determinations of hemoglobin A1c, total glycated hemoglobin, fructosamine, and random serum glucose in diabetic patients. Archives of Internal Medicine 151(6):1133-7,. 1991 Jun . UI 2043015
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Hendra TJ;Taylor CD. A randomised trial of insulin on well-being and carer strain in elderly type 2 diabetic subjects. Journal of Diabetes & its Complications. 2004 May . UI 15145325
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Hoffman RM;Shah JH;Wendel CS;Duckworth WC;Adam KD;Bokhari SU;Dalton C;Murata GH;Diabetes Outcome in Veterans Study. Evaluating once- and twice-daily self-monitored blood glucose testing strategies for stable insulin-treated patients with type 2 diabetes : the diabetes outcomes in veterans study. Diabetes Care. 2002 Oct . UI 12351471
(Duration too short)

Holman RR;Dornan TL;Mayon-White V;Howard-Williams J;Orde-Peckar C;Jenkins L;Steemson J;Rolfe R;Smith B;Barbour D;McPherson K;Poon P;Rizza C;Mann JI;Knight AH;Bron AJ;Turner RC. Prevention of deterioration of renal and sensory-nerve function by more intensive management of insulin-dependent diabetic patients. A two-year randomised prospective study. Lancet. 1983 Jan 29 . UI 6130244
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Horton ES;Clinkingbeard C;Gatlin M;Foley J;Mallows S;Shen S. Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes. Diabetes Care. 2000 Nov . UI 11092289
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Kawachi I;Conaglen JV;Bryson LR;Kilpatrick JA. An assessment of home monitoring of blood glucose levels in Dunedin. New Zealand Medical Journal. 1983 Aug 24 . UI 6348610
(N too small)

Kawamori R;Kamada T. Determination of the glycemic threshold for the regression or prevention of diabetic microangiopathies, and the insulin injection regimen to establish strict glycemic control in NIDDM. Japanese Journal of Medicine. 1991 Nov . UI 1798230
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Klein CE;Oboler SK;Prochazka A;Oboler S;Frank M;Glugla M;Winters S. Home blood glucose monitoring: effectiveness in a general population of patients who have non-insulin-dependent diabetes mellitus. Journal of General Internal Medicine. 1993 Nov . UI 8289098
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Laakso M. Glycemic control and the risk for coronary heart disease in patients with non-insulin-dependent diabetes mellitus. The Finnish studies. Annals of Internal Medicine. 1996 Jan 1 . UI 8554204
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Lazar HL;Chipkin SR;Fitzgerald CA;Bao Y;Cabral H;Apstein CS. Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events. . Circulation. 2004 Mar 30 . UI 15006999
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Martin S;Schneider B;Heinemann L;Lodwig V;Kurth HJ;Kolb H;Scherbaum WA. Self-monitoring of blood glucose in type 2 diabetes and long-term outcome: an epidemiological cohort study. Diabetologia. 2006 Feb . UI 16362814
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Metzger M;Leibowitz G;Wainstein J;Glaser B;Raz I. Reproducibility of glucose measurements using the glucose sensor. . Diabetes Care. 2002 Jul . UI 12087017
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Muchmore DB;Springer J;Miller M. Self-monitoring of blood glucose in overweight type 2 diabetic patients. Acta Diabetologica. 1994 Dec . UI 7888692
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Murata GH;Hoffman RM;Shah JH;Wendel CS;Duckworth WC. A probabilistic model for predicting hypoglycemia in type 2 diabetes mellitus: The Diabetes Outcomes in Veterans Study (DOVES). Archives of Internal Medicine. 2004 Jul 12 . UI 15249354
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Murata GH;Shah JH;Hoffman RM;Wendel CS;Adam KD;Solvas PA;Bokhari SU;Duckworth WC;Diabetes Outcomes in Veterans Study (DOVES). Intensified blood glucose monitoring improves glycemic control in stable, insulin-treated veterans with type 2 diabetes: the Diabetes Outcomes in Veterans Study (DOVES). Diabetes Care. 2003 Jun . UI 12766106
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Murata GH;Shah JH;Wendel CS;Hoffman RM;Adam KD;Bokhari SU;Solvas PA;Duckworth WC. Risk factor management in stable, insulin-treated patients with Type 2 diabetes: the Diabetes Outcomes in Veterans Study. Journal of Diabetes & its Complications. 2003 Jul . UI 12810241
(Duplicate publication, no additional information)

Nathan DM;McKitrick C;Larkin M;Schaffran R;Singer DE. Glycemic control in diabetes mellitus: have changes in therapy made a difference?. American Journal of Medicine. 1996 Feb . UI 8629649
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Nerenz DR;Repasky DP;Whitehouse FW;Kahkonen DM. Ongoing assessment of health status in patients with diabetes mellitus. Medical Care. 1992 May . UI 1583926
(<50% Type 2)

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Nicer T;Mardarowicz G;Lopatynski J. Usefulness of glucose levels determination with glucometer in epidemiologic research. Annales Universitatis Mariae Curie-Sklodowska - Sectio d - Medicina. 2003. UI 15315026
(Not Int/Pred of interest)

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(Retrospective)

Ostgren CJ;Lindblad U;Melander A;Rastam L. Survival in patients with type 2 diabetes in a Swedish community: skaraborg hypertension and diabetes project. Diabetes Care. 2002 Aug . UI 12145224
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