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14. ABSTRACT

The overall aim of this proposal was to test the clinical effects of a Computer Assisted Decision Support (CADS) System for the management of Type 2 diabetes (T2D) by primary care providers (PCPs) and to compare longitudinal patterns of change within and between patients who are managed with the CADS system for differing durations. This comparison was intended to help us to understand the clinical utility of using the CADS system continuously or up to a certain threshold of patient improvement. To achieve these aims, we requested a second year of funding (first year funded through United States Army Medical Research Acquisition Activity [USAMRAA], contract number W81XWH-09-2-0196, for a prospective, cluster, randomized controlled trial (RCT). The ongoing project is a multi-site study including the Walter Reed National Military Medical Center, Fort Belvoir Community Hospital (FBCH), and the Kimbrough Ambulatory Care Center.

The proposal herein is not duplicative of any current study but rather an extension of the already funded one. A detailed, technical explanation of the software and hardware elements of this study are included in reports for the original CADS study and available upon request.

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Introduction

Diabetes mellitus (DM) affects more than 29 million people in the United States and is associated with devastating complications in both personal and financial terms. Diabetes is the leading cause of blindness, non-traumatic amputations, and renal failure in adults and reduces life expectancy by 5-10 years and quality of life years by 11 to 23 years in adults 65 years of age and older. The estimated total economic cost of diagnosed diabetes in 2012 was $245 billion, a 41% increase from the previous estimate of $174 billion (in 2007 dollars) with direct costs at $177 billion and indirect at more than $68 billion. People with diagnosed diabetes incur average medical expenditures of about $13,700 per year, of which about $7,900 is attributed to diabetes. Their average medical expenditures are approximately 2.3 times higher than their expenditures would be in the absence of diabetes. Hospital inpatient care comprises 43% of the total medical cost (1).

The Diabetes Control and Complications Trial (DCCT), the United Kingdom Prospective Diabetes Study (UKPDS), and the "Kumamoto" study conclusively proved that improved glycemic control is important in reducing microvascular complications (2-4). Together, these studies showed that for every 1% decrease in A1C, there is a 25% decrease in microvascular complications. Based on these studies, the American Diabetes Association (ADA) recommends that the goal for A1C should be below 7% (normal = 4 - 6.1%) (5), and the American Association of Clinical Endocrinologists (AACE) recommends that it should be below 6.5%, corresponding to an average blood glucose (BG) values of 150 and 135 mg/dL, respectively, [normal = 70 - 126 mg/dl] (6). Furthermore, years of improved glycemic control appear to have a legacy effect and not only reduce the future rate of microvascular complications but also decrease the incidence of macrovascular complications in both Type 1 and Type 2 diabetes (7-8).

Hypertension is one of the most common co-morbidities associated with DM and substantially contributes to the macrovascular disease that occurs in up to 80% of patients with DM (9). Several large randomized clinical trials (RCTs), including the UKPDS, demonstrated that, independent of the effects of glycemic control, improving blood pressure (BP) control significantly reduced macrovascular complications and cardiovascular-related deaths (9--13). Similarly, the UKPDS showed a 13% reduction in microvascular complications for every 10 mmHg reduction in systolic pressure. This finding was confirmed and extended to DM patients who were "normotensive" (3). Gaede et al. showed the marked benefit of aggressive blood pressure, lipid, and blood glucose management achieved through multifactorial intervention (14). There also appears to be a legacy effect of blood pressure control in Type 2 diabetes as recently shown by Holman et al. (15).

Despite the well-documented benefits of glycemic and BP control, these are still sub-optimal in most patients. Although there is a trend toward improved glycemic control, the Centers for Disease Control (CDC) estimates that approximately 48% of patients with DM have A1Cs over 7% (16). The military healthcare system (MHS) - where there is no cost to the patient for care and testing supplies - has similar results with hemoglobin A1C's over 7% in 42% and over 9.0% in 23.3% of all patients with diabetes. In 2009, data from the Walter Reed Health Care System (WRHCS) indicated that 51% had an A1C above 7%. Furthermore, BP control in our patients is similar to the national

average with 62% of our patients having either systolic over 140 mmHg and/or diastolic over 90 mmHg under current treatment. Recommended levels to reduce the risk of cardiovascular mortality and morbidity are less than 130/80 mm/Hg.

Reasons for Sub-optimal Achievement of Diabetes Control

The reasons why more patients do not reach appropriate goals for glycemic control are multiple and complex. First, due to an insufficient number of Endocrinologists and Certified Diabetes Educators in both military and civilian health care settings (17), the vast majority of patients with DM are managed by primary care providers (PCPs), including family practitioners, nurse generalists, nurse practitioners, and physicians' assistants, who are not necessarily equipped with the latest information and tools to provide optimum care nor have the time required to evaluate relevant data necessary to do so. The patient may bring his/her handwritten logbook and/or meter to the clinic where the data must be reviewed manually or the patient will bring his/her memory-equipped meter to the clinic, where it may be uploaded to the provider's computer and analyzed. Manual review of the records precludes any statistical and graphical analysis of the data and often limits the provider's ability to recognize patterns and trends. Moreover, this approach is a time-consuming and an inefficient use of both the provider's and patient's time. Uploading of the glucose data provides the requisite statistical and graphical analysis. However, all the major glucose meter manufacturers have their own proprietary software – none of which are integrated into the electronic medical record (EMR) - and each of the meters has its own unique connecting cable. Thus, the multiplicity of non-integrated programs and connecting cables prevent the provider from efficiently reviewing BG data thus creating a significant barrier to using this technology.

Second, the introduction of new oral and parenteral agents has exponentially increased the complexity of the management of T2DM in the last 10-15 years. Prior to the introduction of metformin in 1995, the only available class of oral agents was sulfonylureas. Now there are fifteen classes of oral medications, insulins, and non-insulin injectables. Recombinant human insulin and analog insulins have come into common use and the long-acting insulin analogs (insulin glargine and Detemir) have been incorporated into many regimens for type 2 diabetes either alone or in combination with oral agents. The enormous number of possible combinations of therapeutic agents makes it difficult for physicians to be familiar with all available approaches. Making matters more complex is that for each class there may be several options, e.g. for insulin secretagogues one can choose sulfonylureas like glipizide, glipizide-XL, or glyburide or a meglitinide such as nateglinide or repaglinide.

Third, self–monitoring of blood glucose (SMBG) on the part of the patient is an essential tool in achieving improved glycemic control. Several studies have shown that improved glycemic control is cost effective in both Type 1 and Type 2 DM (T1DM and T2DM) despite the increase in cost of supplies, a greater number of clinic visits, and more pharmaceuticals used. Yet, many patients do not monitor as recommended, in part because of the barriers noted above (e.g., they perceive that their providers cannot or do not review the SMBG results), a lack of understanding of how to use their glucose data to improve their glycemic control, as well as social and personal barriers.

The Case for Systematic, Rigorous Examination of a Computer Assisted Decision Support System for Diabetes Management

Although many studies have demonstrated the potential advantages of telemedicine, web-based, and/or web-assisted DM management, most have used the web for patient education, performance monitoring, risk stratification, and case management by nurses (18-21). Only a few studies have shown that using the web and/or e-mail improves glycemic control (22-24) or can reduce the number of clinic visits (23) while others have not been able to show such an effect (24-25).

Computer-assisted algorithms to provide decision support for interpretation of the glucose profile have been previously developed and published by the collaborators on this project as well as others (26-29). We and our colleague (Berger) have previously developed methods to automatically select regimens and doses of insulin for patients with T1DM (30). Lehmann has adopted and slightly modified the models of Rodbard and Bergman, and used it to develop "AIDA" – http://www.2aida.org – a program intended for education of health care providers and patients (31). This has not been employed therapeutically and no controlled trials have been performed.

There are only a few studies investigating decision support in the management of diabetes. Holman (32) and Chiarelli (33) reported that portable decision support devices used by patients with T1DM resulted in improved glycemic control. A web-based decision support system (DSS) improved compliance with generally recognized process measures of DM care (e.g. the number of A1C and low density lipoprotein [LDL] tests obtained) but did not improve the actual A1C level (34). Cleveringa et al. were unable to show that a DSS used by a practical nurse improved A1C in T2DM although it did improve cardiovascular risk factors (35). Recently, the IDEATel consortium study showed that a telemedicine application improved A1C, BP and lipids in an older, ethnically diverse and underserved population (36). Salzsieder and colleagues used their Diabetiva® program to apply continuous glucose monitoring (CGM) data to a DSS to improve A1C (37). Decision support systems that been used in blood pressure management have shown conflicting results (38-39).

Building on our prior experience in developing methods to select regimens and doses of insulin for patients with T1DM, we developed a CADS system for management of T2DM by PCPs to overcome many of the aforementioned barriers to the appropriate management of T2DM. The key feature of CADS is that it simplifies the work of the PCP by automatically integrating the essential factors necessary to make a recommendation for management - the patient's SMBG data from their uploads, current and previous medication, the presence or absence of certain co-morbidities, and current relevant laboratory data – and then making a recommendation based on established consensus algorithms (40).

Body

The use of a computer assisted decision system (CADS) has been described in detail in the quarterly, annual, and final reports that have been submitted. The goal of the first study (Year 1 or Months 1-12) was to determine whether or not the use of CADS by

PCPs, i.e. Internists, Family Practitioners, Nurse Practitioners, and Physician's Assistants, can improve glycemic and other outcomes in patients with poorly controlled T2DM over one year. The theoretic construct for establishing the hypotheses is that non-endocrinologist providers have neither the time nor expertise to address critical issues of management for patients with T2DM and that a CADS system will help them do so. Additionally, a CADS system will, because it saves time in the management of glycemic-related outcomes and permits providers to give more attention to management of the important co-morbidities of T2DM. Finally, a patient with improved glycemic control and comorbidities will be more satisfied with their overall treatment.

This study entitled, "Extension of a Computer Assisted Decision Support (CADS-X) Study to Improve Outcomes in Patients with Type 2 DM Treated by Primary Care Providers" (CADS-X) was designed with two primary aims: (1) To provide those providers who were not assigned to the CADS arm in the initial study an opportunity to "cross-over" to CADS in a subsequent year provided that: a) CADS is shown to produce statistically significant improvements in A1C or other response variables (fasting plasma glucose {FPG}, post-prandial plasma glucose {PPG}, post prandial excursions, rate of hypoglycemia) and b) funding is available for continuation of the trial) and (2) to determine the legacy effect of CADS by providing primary care providers (PCPs) and their patients who were initially randomized to CADS an opportunity to use CADS for an additional year for a total of 2 years. However, significant challenges in the approval and implementation of the original study, "The Use of a Computer-Assisted Decision Support (CADS) System to Improve Outcomes in Patients with Type 2 Diabetes Who Are Treated by Primary Care Providers" (the CADS study), delayed our ability to implement the extension study. An overview of the original study and the challenges that have prevented us from completing the first study are detailed in the 2013 Annual Report. The 2014 Annual Report dated 12 December 2014 summarized the activity relevant to the continuation of the original study. This report summarizes the activity relevant to the continuation of the original study. **Information that is new since the submission of the 2014 Annual Report is bolded.**

Key Research Accomplishments

1. Enrollment

The Project Officer (PO) completed enrollment of 18 Primary Care Providers (PCPs) and 76 patients before closing enrollment on 30 September 2014. **Data collection ceased on 15 January 2015.**

2. Progress of Patients in the Study

a. Completed the study (6 visits): 6 patients/1 provider

b. Completed Visit 5: **10** patients

c. Completed Visit 4: **18** patients

d. Completed Visit 3: **17** patients

e. Completed Visit 2: **35** patients (visit 2 marks the beginning of the intervention part of the study; it is after this visit that patients are asked to upload their

glucometers before each quarterly visit with their PCPs and follow protocol instructions for SMBG frequency.

f. Completed Visit 1:76

3. Withdrawn from Study: 2 Providers; 25 Patients

a. Reason for provider withdrawal

(1) One left practice

(2) One was a contractor and research involvement was not in his contract

b. Reasons for patient withdrawals

(1) Too busy

(2) Diabetes care transferred from PCP to diabetes NP or endocrinologist

(3) Too much difficulty uploading glucometer data

(4) Personal issues

(5) Well controlled and doesn't want to change treatment plan

(6) Too many fingerstick blood glucose tests required

(7) Initiation of dialysis

(8) Initiation of prandial insulin

(9) Left area

(10) No reason or other

(11) Lost to follow-up

4. Study challenges

Study challenges have been described in detail in previous reports. With few exceptions, patients were somewhat consistently challenged when attempting to upload their glucose data. Access to the patient portal, Diabetes Mellitus Everywhere (DME) in CDMP required installation of JAVA with each upload. This was a step that confused several patients. Providers often needed assistance with a password reset or were unable to access CDMP from their desktop computers even though the research study staff was consistently able to access CDMP from their desk top computers. Additional challenges included getting patients to return for their follow-up appointments within a 2-week window and the high drop-out rate.

CDMP and CADS Maintenance and Enhancements

CDMP and CADS continue to be hosted on a password-protected, secure server maintained by Estenda Solutions. Despite efforts since 2010 to acquire the Department of Defense (DoD) Information Assurance Certification and Accreditation Process (DIACAP) approval, CDMP remains in the approval process without a clear indication if and when approval may occur. Estenda Solutions

worked closely with the research staff to maintain CDMP and CADS and to assist with patient and provider problems that could not be solved by the research staff.

Reportable Outcomes

Preliminary Data Analysis

Patient demographics are representative of the Washington metropolitan area. All of the patients who participated were adults at least 18 years of age with type 2 diabetes and A1C levels between 7% & 11%. Eligible patients were using lifestyle measures (diet and exercise), oral hypoglycemic agents, and/or injectable glucose lowering agents with the exception of prandial (meal-time) insulin or combination insulins (combination of basal and prandial insulins) to manage their diabetes. There were insufficient data to draw conclusions based on age, gender, race, or level of glucose control. Fourteen providers were physicians, three were nurse practitioners, and one was a physician's assistant. Five were male (all physicians), the rest were female.

There are very few reportable outcomes from this study due to the inadequate number of patient visits, the relatively few times that providers actually accessed CADS, or if they did run the CADS analysis, used the recommendations. The protocol required patients to check a finger stick blood glucose (FSBG) level twice a day 6 days/week, 4 times/day once a week, and 8 times/day once a month. Although the majority of patients tested once or twice daily, very few tested 4 times/day once weekly, and even fewer 8 times/day once monthly. Although corrected by Estenda, accuracy of glucometer readings was confounded when patients did not "inform" their glucometers when they performed control tests which resulted in high and/or low glucose values that were not patient values. An inadequate amount of data to inform findings was also compromised by a larger than expected drop-out rate and missed visits.

The efficiency of CADS was compromised by the lack of an interface with AHLTA, the electronic medical record (EMR) in the DoD. The research staff had to manually update specific laboratory values and medications prior to each patient visit; providers would never have or take the time to enter this information. Nine of the 18 providers enrolled at least 5 patients, the minimum number established to begin using CADS. The drop-out rate is evident (see 2. Progress of Patients in the Study) as patients progressed through the study. One reason for this is that many patients who were among the first patients enrolled for a specific provider may have lost interest or been lost to follow-up by the time the 5th patient was enrolled. Unfortunately for both providers and patients the exhaustion of study funds occurred at a time when more providers had finally enrolled their 5th patient and were anticipating beginning the study.

The CADS application worked well once control glucose levels were removed from the patient data. Several providers who had begun to use the program were disappointed when informed that the study had to be terminated. Invitations to participate in one of two focus groups that were designed to determine the

feasibility and usability of the program were extended to the 16 providers who were still in the study. Only two providers, both physicians and both females, responded. Both liked the program, but one believed its value was diminished because she had access to a diabetes specialist and a registered dietitian (RD). Without that support she would have been more likely to use it more often. Neither accepted one of the recommendations all of the time. Reasons for not using the recommendations included their belief the recommendation was too aggressive and reluctance to intensify treatment in older patients. Suggestions to improve the application included removing medications that were not commonly used and adding medications that have been approved since the study was implemented. Another suggestion was to elaborate on the justification for the recommendation.

Limitations

As mentioned previously, a limitation of the study design was the requirement that the provider enroll 5 patients before using CADS. It is likely that we would have had more data had providers been given access to CADS with their first consented patient. Several providers had just begun using CADS when we terminated the study. Additional limitations included the difficulty that many patients experienced when uploading their glucose data, the provider difficulty with accessing CDMP and subsequently, CADS, and the patient non-adherence to both the scheduled visits and the self-monitored blood glucose (SMBG) test times. Finally, the lack of interface between CADS and AHLTA required the research staff to manually enter relevant data. Although not particularly time-consuming, it is another "task" that would have discouraged provider use if they had to enter the data.

Conclusions

Diabetes mellitus is a significant cause of morbidity and mortality in the United States, and the leading cause of new blindness, chronic kidney disease, and non-traumatic amputation in the working-aged American population. Although the financial costs to individuals, communities, and health care systems are measurable, the devastating costs in terms of quality of life personal costs are not easily measured. A computer assisted decision support system that makes available the knowledge and expertise of endocrinologists to primary care providers who care for the majority of people with Type 2 diabetes has the potential to significantly improve the level of care provided to people with T2 DM, thus preventing or delaying the onset of and/or reducing the severity of diabetes-related complications. Reducing the risk and/or severity of complications promises to improve the quality of life for people with T2 diabetes and decrease the financial impact on the individual as well as both the military and civilian health care systems.

CADS is a web-based interactive application that enables primary care providers to aggressively and systematically use available medications to help their patients move increasingly and safely toward a level of glycemic control that minimizes their risk of developing diabetes-related complications and/or the severity of these complications.

The findings of this study demonstrate that a computer assisted decision support system can be utilized in primary care, especially if it interfaces with an EMR and, as one provider suggested, it is available to a practice that does not have ready access to a diabetes specialist. Patient non-adherence with the scheduled BG tests may have been mitigated with a less rigorous, but equally informative schedule such as paired testing (before and after a different meal each day) or 3600 testing (7 times/day 3 days/quarter). An easier method of uploading glucometer data may also have enabled providers to make recommendations without seeing the patients, thus reducing the number of patient visits. Termination of the study occurred as more providers were either just beginning to use CADS or were becoming more comfortable with using CADS. Several providers and patients were disappointed when informed that the study was ending. Additional time for providers to explore the different features of CADS, e.g. graphs, summaries, links to professional diabetes websites, may also have facilitated provider use and appreciation of the program.

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