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Meta-analysis of Telemonitoring to Improve HbA1c Levels: Promises for Stroke Survivors

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Abstract

Background: Diabetes mellitus predisposes to ischemic stroke, a major cause of death in this population, and worsens the post-stroke prognosis. Monitoring glycemic control is useful not only in the primary prevention of stroke in diabetics, but also in the rehabilitation from and secondary prevention of stroke. In an often functionally and neurocognitively impaired population, however, poor compliance to treatment regimens is a major problem. Digital, wireless telemonitoring glucometers offer a solution to the compliance issue—not only do they give patients a dynamic experience of their own glycemic control via digital monitors, but many also have an integrated alert system with healthcare providers and more real-time feedback than traditional self-monitoring methods.

Objective: To evaluate effectiveness of telemonitoring technologies in improving long-term glycemic control.

Methods: A search on www.clinicaltrials.gov on November 2013, using keywords "telemonitoring" (n=103), "self-care device" (n=50), and "self management device" (n=210), revealed trials investigating a range of chronic disease including heart disease, diabetes, COPD, asthma, and hypertension. Some of the cardiac-oriented trials utilized varying outcome measurements. Therefore, we only selected published diabetes trials comparing HbA1c levels of a group receiving standard of care to a group receiving a telemonitoring intervention. Using a random effects model of mean difference, a meta-analysis was conducted on five trials that measured differences in HbA1c levels between the two groups at six months follow-up.

Results: Five clinical trials were identified. Four of the five studies showed a greater reduction in HbA1c in the intervention group compared to controls at 6 months, although only one was statistically significant. There was considerable heterogeneity between studies (I2= 69.5%, p=0.02). The random effects model estimated the aggregate effect size for mean difference in reduction of HbA1c levels in the treatment group vs. control to be 0.08% [-0.12-0.28%], which was not statistically significant (p=0.42).

Conclusions: The varying results may be due to specific factors in the trials that contributed to their large heterogeneity. Although there is great potential to use telemonitoring in stroke patients, further trials are needed to support its role in improving diabetes management in this population. Nonetheless, in the future telemonitoring may substantially help patients at risk of ischemic stroke and those who require close glucose monitoring.

Keywords: Telemonitoring; Compliance; Adherence; HbA1c; Diabetes; Stroke; Prevention; Mobile health; m Health

Introduction

Stroke is the cause of death in roughly 20% of patients with diabetes mellitus-two to three times that of non-diabetics [1] and each year of diabetes increases the risk of stroke by approximately 3% [2,3]. Diabetes is also associated with a poorer prognosis in stroke survivors [4-6], and higher rates of post-stroke functional and cognitive impairment worsen patient compliance to diabetic regimens [7-9]. Although great progress has been made with respect to cardiovascular disease, less attention has been paid to the relationship between diabetes and stroke [10]. Since diabetes currently affects over 26 million people in the U.S. and will likely double in prevalence over the next several decades, this represents a growing healthcare crisis [11,12]. Mobile, telemonitoring glucometers can continuously provide feedback on glucose levels to patients and physicians, although their benefit on long-term glycemic control is less established.

The major modifiable risk factors for cerebrovascular disease include diabetes mellitus, hypertension, smoking, and dyslipidemia [13]. Diabetes is a unique problem in stroke patients because diabetics are more likely to present with completed stroke and have a higher mortality rate. In addition, diabetics who survive a stroke are more likely to be debilitated post-ictus and have poorer functional outcomes than non-diabetics [6,9,14]. The relationship between stroke and diabetes is bidirectional, as stroke and transient ischemic attacks (TIAs) predispose patients *without* pre-morbid diabetes to long-term impaired glucose tolerance and diabetes [15,16].

The neurocognitive effects of stroke and diabetes are also a major cause of disability, which impairs adherence to often complicated diabetic regimens [7-9]. In addition to motor and sensory deficits, stroke patients are also commonly left with deficits in attention, memory, and executive function, and have a high incidence of

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dementia. These post-stroke neurocognitive deficits occur at even higher rates in patients with comorbid diabetes [17]. Diabetes on its own causes insidious damage to the brain as small-vessel disease, and neuropsychological studies have shown that poor long-term glycemic control has a deleterious effect on cognition [18,19]. In effect, the post-stroke population with diabetes represents a large cohort that is at high risk of subsequent strokes (and other complications), yet is challenging to manage effectively.

Tight glucose control, often measured by hemoglobin A1c (HbA1c), is a cornerstone of treatment that reduces many of the diabetic complications, and better adherence to diabetic regimens is generally associated with improved long-term glycemic control in terms of HbA1c [20]. However, diabetes is often poorly controlled because time-sensitive regimens, pill burden, test strips, and frequent doctor visits frequently leave patients confused and non-compliant, leading to otherwise preventable disease burden [21,22]. This compliance is a major concern in the many diabetic stroke patients who are neurocognitively impaired, and especially in the elderly, who often have less access to primary care. As a result, these patients may not be able to adhere to such regimens without costly nursing care.

Recent advances in affordable, mobile telemonitoring devices provide hope of improving not only patient compliance, but also communication between the patient and physician to facilitate a tailored regimen of care for that specific patient. Telemonitoring has already been used with favorable results in other chronic conditions including hypertension [23], COPD [24] and atrial fibrillation [25], to provide longitudinal data and certain outcomes including blood pressure, oximetry, spirometry and abnormal heart rhythms.

The search is on not only for the ideal technology that is easy-to-use, communicates effectively with the patient's provider, and promotes patients engagement, but also for a clinically effective protocol with which to use the device that would overcome obstacles such as determining the patient population that would receive the most benefit, and developing the ideal algorithm for treatment modifications, frequency of glucose testing, and follow-up care. This may provide a practical means of monitoring and altering regimens to achieve glycemic control in the often cognitively-impaired post-stroke population. We hypothesized that telemonitoring devices improve long-term glycemic control in terms of HbA1c, and in this meta-analysis, we review five randomized clinical trials which have assessed whether the addition of certain telemonitoring devices to diabetic regimens has resulted in better glycemic control compared to standard of care. We further discuss the implications this may have on post-stroke patients in their recovery process.

Methods

A search on www.clinicaltrials.gov in November 2013, using keywords "telemonitoring" (n=103), "self-care device" (n=50), and "self management device" (n=210), revealed trials investigating a range of chronic disease, such as heart disease, diabetes, COPD, asthma, and hypertension. Trials with all statuses, such as recruiting, completed, ongoing and not yet open were included in the search. Each trial (Figure 1) was then evaluated for its use of a telemonitoring device to enhance patient care with chronic disease. Randomized trials were included if they assessed the effect of telemonitoring devices-those with an ability to digitally communicate or relay recorded data that provided an opportunity for patient engagement-on the clinical outcome of long-term glycemic control (in terms of HbA1c) in patients with diabetes mellitus at a minimum of 6 months following randomization. Trials were excluded if the study did not provide this outcome (i.e. only outcomes of COPD, hypertension, etc.), if the results were not yet published, if only medication management of the disease of interest was assessed, if the device used was purely for injection (without telemonitoring capability), if the endpoints were only transient hypo- or hyperglycemia (as opposed to long-term glycemic control), or if the trial was a pilot study that only assessed the ability of the device to accurately measure glucose levels. In addition, trials were excluded if the device was not used to record patient data in the home environment, or if not enough information about the device was provided-including not knowing whether the device had telemonitoring capability, not knowing if the subjects were able to see their own recorded data at some point or if the device provided feedback (patient engagement), or if there was no indication of the device's name or brand.

Certain heart disease trials with published results utilized varying outcome measurements. Therefore, we focused on published diabetes trials comparing HbA1c levels of a group receiving standard of care, which followed guidelines either by the American Diabetes Association [26] or equivalents (Italian Standards for Diabetes Mellitus, 2007; Korean Diabetes Association, 2007), to a group receiving intervention with a telemonitoring device. A meta-analysis was then conducted on five trials that measured a change in HbA1c levels at six months using a random effects model of mean difference.

Results

Five clinical trials [27-31] were identified that measured the change in HbA1C levels during a minimum of a 6-month follow-up period between diabetic patients receiving standard of care and those receiving the additional telemonitoring intervention (Table 1). Four trials demonstrated a further reduction in HbA1c in the intervention group compared to controls [28-30], but only one was statistically significant [27]. In one trial, there was an increase in HbA1c that was not statistically significant [32].

There was considerable heterogeneity between studies (I^2 = 69.5%, p=0.02). The random effects model estimated the aggregate effect size for mean difference in reduction of HbA1c levels in the telemonitoring group to be 0.08% [-0.12-0.28%], which trended towards, but did not reach, statistical significance (p=0.42) (Figure 2).

Discussion

We performed a meta-analysis assessing the use of telemonitoring devices to reduce mean HbA1c. Overall, our meta-analysis showed that telemonitoring interventions tended to reduce HbA1c greater than in the control groups, but only one of the five trials showed a statistically significant difference. The reasons may be rooted in the wide variation of each of the study's protocols, demographics, and treatment regimens. Certain features of each study, however, highlight the benefits of telemonitoring, which in the future will likely prove useful to a large subset of the population.

The varying telemonitoring devices, protocols for using them, and follow-up care were major factors that would need to be optimized in the future. Although all five studies measured HbA1c at 6 months in subject and control groups, some also measured outcomes at 12 months [27,28], and the follow-up protocols varied in the frequency of visits, method of communication with physician, and presence of nursing care. In addition, the education, algorithms, and goals given to physicians who were treating patients in the intervention group varied widely. In each study, the glucometers had a screen (to display serum glucose), but the data was downloaded in different locations-at

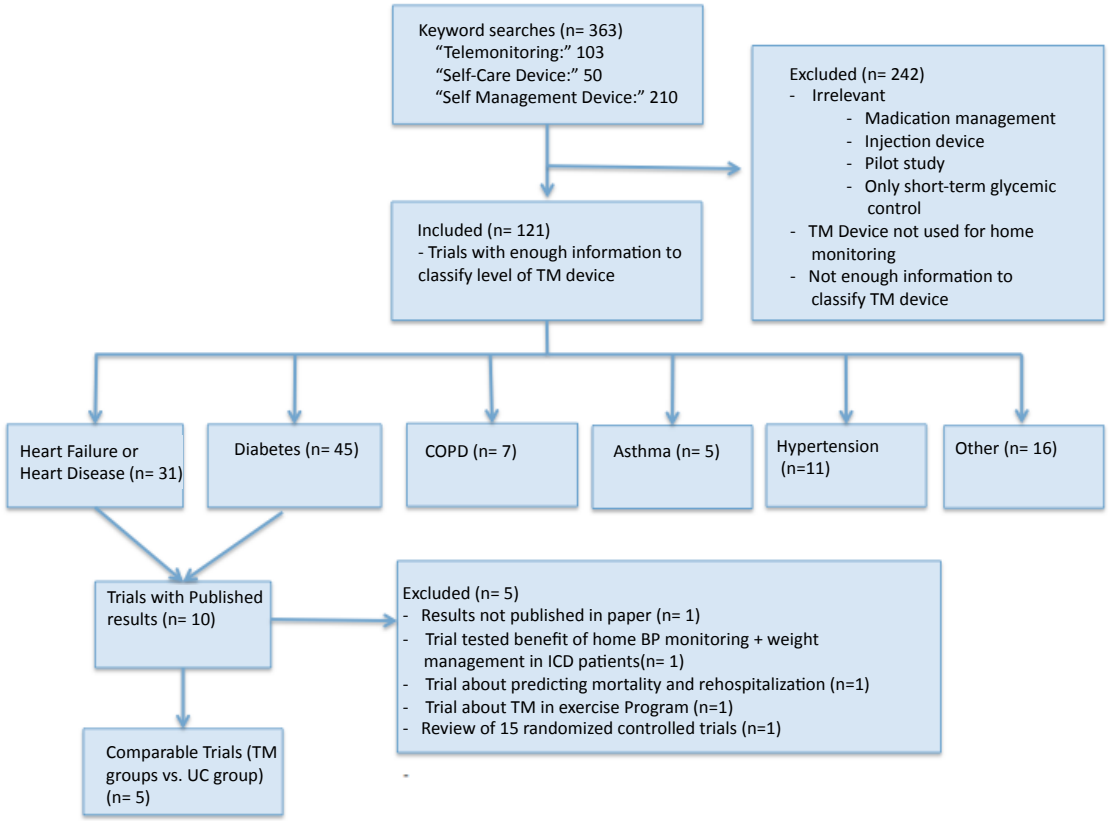

Figure 1: Flow Chart of Search Results for Randomized Controlled Trials Assessing the Efficacy of Telemonitoring in Patients with Diabetes Mellitus

Trial	Sample Size (N)	Type of Diabetes	Insulin Dependence	Duration of Diabetes (Years) (Mean or Median, SD or IQR)	Age (Years)	Device	Follow-up period
Polonsky et al. [27]	483	Type 2	Independent	TM: 7.5 (6.1) Controls: 7.6 (6.1)	>25	Accu-Chek	12 Months
Bosi et al. [28]	1024	Type 2	Independent	TM: 6.2 (3.2-8.8) Controls: 6.2 (3.4-8.8)	35-75	Accu-Chek	12 months
Lim et al. [29]	144	Type 2	Mostly Independent	TM: 14.1 (10.1) Controls: 15.8 (10.7)	>60	GlucoDr SuperSensor	6 Months
McKee et al. [30]	55	Type 2	Mostly Independent	Not Provided	>30	Cardicom equipment	12 Months
Chase et al. [31] (DIRECNET)	200	Type 1	Dependent	TM: 5.3 (3.4) Controls: 5.4 (3.1)	7-18	GlucoWatch G2 Biographer	6 months

Table 1: Characteristics of the Randomized Studies Included in the Meta-Analysis

home, in the office-and at different frequencies. Interestingly, in the Lim trial the device was integrated into the hospital server, physician's office, and patient's mobile phone, so that the patient would receive directions via SMS messaging to measure glucose or even make conservative adjustments to their medications based on predetermined algorithms. The regimens for testing serum glucose also varied among the studies from some that were seven times per day only immediately prior to a follow-up visit [27] to others that were on a weekly basis [33]. Theoretically, more frequent communication and follow-up visits would improve compliance in the post-stroke diabetic population and lead to a reduction of HbA1c, although this was unclear in the trials.

Treatment changes were generally more common in the telemonitoring groups than in controls, and were as much as 3-fold [27]. Changes in medications, dosing, and regimens are common in diabetics in order to achieve glycemic control, and these changes can be more frequent in light of the impaired glucose tolerance that may occur for months after a stroke [15]. Treatment intensification, therefore, may be a beneficial effect of the increased attention to glucose control that results from telemonitoring. However, in all but one study [27], the treatment intensification did not provide a clear overall benefit in HbA1c reduction. In fact, in the DIRECNET study [31], the HbA1c actually trended slightly upwards in the intervention group, although this was likely in part due to the significant skin irritation that the device caused in the majority of subjects, which resulted in poorer compliance. The utility of telemonitoring as a means of intensifying treatment may be further limited in stroke patients because despite the fact that diabetes is an independent risk factor for ischemic stroke, randomized trials have failed to show a reproducible benefit of tight glucose control in decreasing the risk of stroke [34]. This is in contrast to studies that have shown that improved glycemic control improves the microvascular complications of diabetes, including retinopathy, nephropathy, and neuropathy [34]. It may be the case that randomized studies have been underpowered to detect a significant benefit in

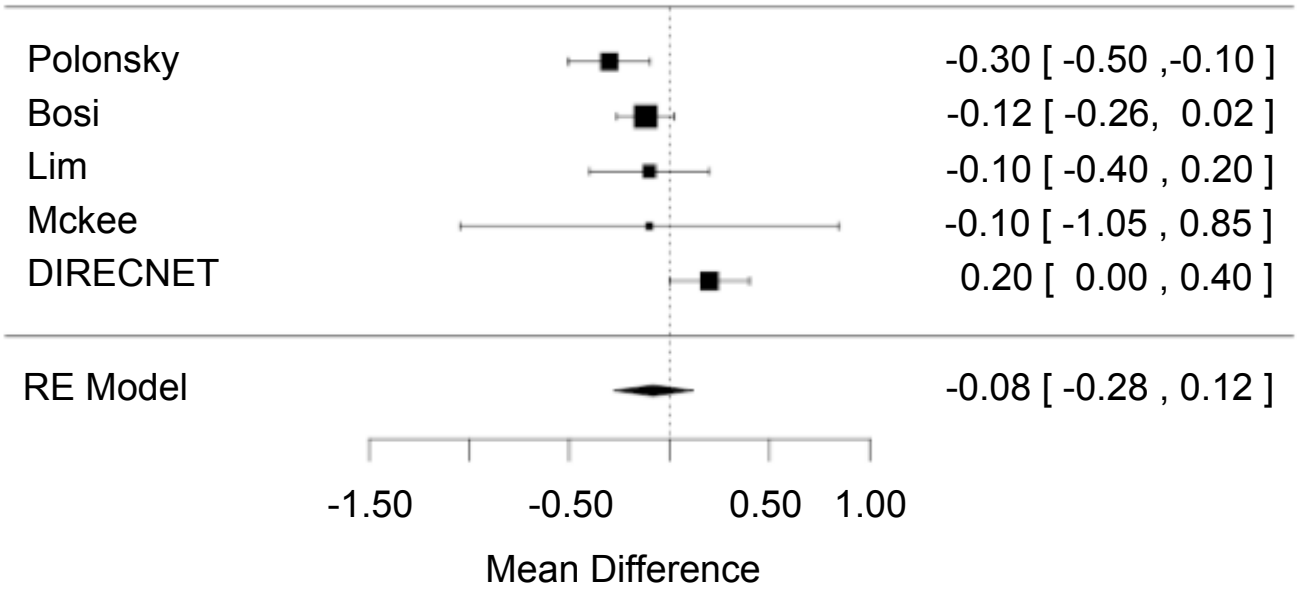

Figure 2: Forest Plot of the Differences in Mean HbA1c between Controls and Telemonitoring Group of Each Trial

glycemic control, or that it may take longer than the study follow-up period for glycemic control to noticeably impact stroke risk [16,34]. Nevertheless, the benefits of telemonitoring may, at the very least, include mitigation of preventable microvascular sequelae.

The medications used in the studies, however, were seldom specified, so it is unclear which treatment algorithm would be ideal. Treatment intensification may also increase the risk of hypoglycemia [35], which not only is dangerous on its own, but can worsen compliance as diabetics come to fear the symptoms of hypoglycemia and frequently under-dose their medications [36]. Furthermore, in the post-stroke population, it may cause focal neurologic deficits which can mimic a recurrent stroke [37]. Luckily, hypoglycemia was not significantly more common in the telemonitoring groups compared to controls, although this was not unexpected as most of the subjects were insulin-independent (with the exception of the DIRECNET trial) (Table 1).

Variations in education level, age, access to healthcare, and socioeconomic status may confer differences in patient adherence to diabetic regimens. In addition to stroke-specific factors such as functional and cognitive impairment, determinants of poor compliance to diabetes regimens include depression, cost, increased dosing frequency, adverse family dynamics, drug abuse, and advanced age [38]. The Lim trial, for example, included the frequently-disadvantaged older population (Mean age: 67.2 years). The elderly population has a several-fold higher prevalence of stroke, and risk of recurrent stroke increases from 10-15% in the 45-64 age range to 20-25% in patients over 65 [39,40]. Also, most likely due to the older age group, the subjects' duration of diabetes in the Lim trial (Table 1) was approximately twice that of the Polonsky or Bosi trials (14-16 vs. 6-8 years, respectively), which, as mentioned, is related to the incidence of many diabetic complications. In the McKee trial, the majority of patients was economically disadvantaged, and earned less than $20,000 per year. Indeed, the heaviest burden of stroke is in the elderly and minority groups [10]. Most notably however, the trials excluded patients with significant cognitive impairment or psychosis-common in post-stroke patients [17].

Nonetheless, there are certain features of telemonitoring that may make it more successful in the future. We hypothesized that telemonitoring improves HbA1c at 6 months, and a finding consistent among most of the five trials is that patients in both the control and placebo groups all tended to achieve better glycemic control when compared to their baseline at the studies' initiation, albeit with varying statistical significance. A component of this improvement may be secondary to increased compliance and adherence because patients are aware they are being studied, a phenomenon known as the Hawthorne effect [41]. In essence, patients are aware that the healthcare provider is watching and monitoring them, which compels them to achieve favorable results in order to impress the physician. There is also likely to be an effect as described by the Health Beliefs Model, a model that uses psychological principles to predict patient behavior in taking health-related action, which has already been shown to have a significant effect on compliance and metabolic control in diabetics [42,43]. Since the Hawthorne effect and Health Beliefs Model were also apparent in the control groups, as their HbA1c tended to improve as well, the differences in HbA1c between the control and intervention groups may be a conservative estimate relative to the general population, which was not included in the studies. This may confound and artificially diminish the interpretation of telemonitoring efficacy.

Even though telemonitoring may not yet be optimized to significantly improve glycemic control, the Hawthorne effect, Health Beliefs Model, and patient engagement may improve patient lifestyle choices such as diet and exercise. Not only are lifestyle changes a core of treatment in diabetes [44], but certain aspects of a patient's lifestyle-smoking, obesity, unhealthy diets-are overall associated with a substantial decrease in stroke incidence (HR: 0.62, 95% CI: 0.39-0.98) [44]. In addition, telemonitoring may also help raise awareness about the increased risk of stroke in patients with diabetes.

Certain limitations should be noted. As mentioned, the studies included in our meta-analysis were heterogeneous in terms of the sample size, device used, and primary outcome of assessing glycemic control (reduction in HbA1c, proportion reaching HbA1c goal, etc.). To address these issues, we statistically accounted for variations such as sample size, and to standardize the outcome of long-term glycemic control, our definition was the change in HbA1c between the intervention and control groups at 6 months follow-up, which each study reported regardless of their primary outcome. We did our best to control for the devices used in the study, by only including trials that used devices with telemonitoring capabilities.

In the future, longitudinal studies with effective protocols will be needed so that this technology can be used to measure and intervene in patients at risk for recurrent stroke and diabetic complications. Although there is great potential in using this technology among stroke patients, further work needs to be done to show its efficacy in terms of long-term glycemic control.

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