Cost-effective strategies for the long-term management of diabetes mellitus

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Boston University
COST-EFFECTIVE STRATEGIES FOR THE LONG-TERM MANAGEMENT
OF DIABETES MELLITUS

by

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A.B., Dartmouth College, 2012

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requirements for the degree of
Master of Science
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DEDICATION

I would like to dedicate this work to my parents—Venkata and Savitri—who never stopped believing in my mission and my vision.
ACKNOWLEDGMENTS

I would like to thank Dr. Elliot Sternthal and Dr. James Burgess for the opportunities that they have given me in exploring more about the intersection between clinical science and health economics and for the guidance they have offered me in crafting this thesis.
COST-EFFECTIVE STRATEGIES FOR THE LONG-TERM MANAGEMENT OF DIABETES MELLITUS

KEDAR N. MULPURI

ABSTRACT

Diabetes mellitus (DM) is a significant public health problem that afflicted approximately 29.1 million Americans in 2012 (CDC, 2014). The estimated cost of diabetes in the United States in 2012 was $245 billion, including $176 billion in direct medical costs and $69 billion in reduced productivity (ADA, 2013a). To reach a diagnosis of DM, a clinician generally relies on fasting plasma glucose (FPG), the oral glucose tolerance test (OGTT), and/or the Hemoglobin A1c (HbA1c) test (ADA, 2013b). Current noninsulin antidiabetic medications include sulfonylureas, GLP-1 analogues, DPP-4 inhibitors, biguanides, thiazolidinediones, and SGLT2 inhibitors (Kaiser & Oetjen, 2014). Insulin therapies include basal (long-acting insulin analogues), biphasic (premixed insulin analogues), prandial (short-acting insulin analogues), and basal bolus (a combination of long-acting and short-acting insulin analogues) (Esposito et al., 2012). The aim of this study is to review the existing literature on the cost effectiveness of diabetes interventions to develop a standardized protocol for early type 2 diabetes care that can be delivered through primary care providers.

The substantial cost effectiveness of preventative measures, including ad campaigns and outreach programs, has already been established (Mendis & Chestnov, vi
2013). Screening for impaired glucose tolerance early and implementing lifestyle and pharmacological changes at an early stage are also considered cost effective approaches for the long-term management of diabetes mellitus (Gillies et al., 2008). This study utilizes six cost effectiveness analyses on both clinical and non-clinical interventions to determine a standardized protocol for screening, diagnosing, and treating DM.

Noninsulin antidiabetic drugs accounted for 78.4% of the 154.4 million prescriptions for antidiabetic drugs filled in 2012 (Hampp et al., 2014). Approximately half of the noninsulin antidiabetic drugs filled in 2012 was for metformin, whereas roughly a quarter of the same category was for sulfonylureas (Hampp et al., 2014). In decreasing order, long-acting human analog insulin and fast-acting human analog insulin were the most popular insulin variants in the insulin antidiabetic drug market (Hampp et al., 2014). Of the noninsulin antidiabetic drugs, the highest proportion of diabetic patients who achieved the HbA1C target of <7% were those taking sustained release exenatide (a GLP-1 analog) (63.2%) (Esposito et al., 2012). Of the insulin varieties, the highest proportion of diabetic patients who achieved the HbA1C target of <7% were those using basal bolus insulin (50.2%) (Esposito et al., 2012). While there are some concerns about the ability of diabetic patients with chronic kidney disease to clear metformin via renal excretion, extensive clinical experience supports its use in diabetic patients with mild to moderate renal impairment (Inzucchi et al., 2014).

From the cost effectiveness studies, lifestyle modification (i.e., changes in diet and exercise) beginning at any age was determined to be a cost-effective approach in preventing and treating DM and may be cost saving for adults between the age of 25 to
44 (Herman et al., 2005). Screening for DM beginning at age 45 and repeating every three years if negative provides the best balance of effectiveness and cost effectiveness (Kahn et al., 2010). As a first-line clinical intervention, metformin was established to be cost-effective as well in treating DM (but less so compared to lifestyle modification) (Herman et al., 2005). Bariatric surgery for diabetics with a BMI greater than or equal to 35 kg/m$^2$ has also been established as cost effective (Hoerger et al., 2010). Next, in considering the ideal frequency of clinical consultations, diabetics with a stable condition (assessed as HbA1c $\leq$ 7.5%, blood pressure $\leq$ 145 mmHg, and total cholesterol $\leq$ 201 mg/dL) can safely be seen by a primary care provider every six months compared to every three months with no noticeable decline in long-term health outcomes (Wermeling et al., 2014). For cases of T2D that cannot be simply controlled with metformin, sulfonylurea has shown that it is overall more cost-effective and effective as a second-line therapy when compared to DPP-4 inhibitors and GLP-1 analogs (Zhang et al., 2014). Cost effectiveness analysis of the long-acting analogue insulin detemir across different countries reveals substantially different cost effectiveness for the medication in terms of both nominal and purchasing power terms (Home et al., 2014).

The results of these studies were parsed to establish a long-term clinical protocol for primary care providers in screening, diagnosing, and treating type 2 diabetes. Future studies should focus on integrating cost effectiveness and comparative effectiveness research in implementing even more nuanced clinical decisions through a structured protocol. The cost effectiveness of existing and new interventions—both clinical and non-clinical in nature—will also need to be continuously assessed to ensure that the
measurements incorporate the most accurate set of assumptions on costs and effectiveness.
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LIST OF ABBREVIATIONS

ADA ............................................................ American Diabetes Association
ADD ............................................................ Antidiabetic drug
CDC ........................................................... Centers for Disease Control and Prevention
CKD ............................................................ Chronic kidney disease
CVD ............................................................ Cardiovascular disease
DM ............................................................ Diabetes mellitus
HbA1c ........................................................ Hemoglobin A1c
ICER ........................................................ Incremental cost effectiveness ratio
NCD ........................................................ Non-communicable disease
NIADD ....................................................... Noninsulin antidiabetic drug
OGLD ........................................................ Oral glucose lowering drug
QALY ........................................................ Quality-adjusted life year
T2D ........................................................... Type 2 diabetes
WHO ........................................................ World Health Organization
INTRODUCTION

Diabetes mellitus (DM) is a significant public health problem worldwide that afflicts both developed and developing countries and accounts for a significant portion of healthcare costs for any country. Since the discovery of this pathological state, the diagnosis and treatment of diabetes have improved a great deal. While there is an ever-expanding armamentarium of effective interventions in managing diabetes mellitus, it is important to also identify the treatments that are most cost-effective so as to reduce the burden of healthcare costs attributable to this disease state. This review aims to assimilate the current body of research on the pharmacologic approaches to managing diabetes mellitus and on the cost-effectiveness analysis of these interventions among others. The clinical effectiveness and cost effectiveness of both clinical and non-clinical interventions for managing type 2 diabetes (T2D) determined through cost effectiveness studies will be utilized in developing a standardized treatment protocol for primary care providers. Finally, the predicted effectiveness and cost effectiveness of antidiabetic drugs in the pipeline will also be briefly discussed.

Overview of Diabetes

In 2012, 29.1 million persons in the United States were estimated to have DM, including 21.0 million diagnosed cases and 8.1 million undiagnosed cases (CDC, 2014). According to the World Health Organization (WHO), the leading causes of death across the world were high blood pressure (13%), tobacco use (9%), high blood glucose (6%), physical inactivity (6%), and overweight and obesity (5%) (2009). These risk factors are
associated with chronic conditions, such as diabetes, cancer, and heart diseases (WHO, 2009). These conditions impacted countries across all incomes groups (WHO, 2009).

In 2012, the estimated cost of diabetes was $245 billion; of this estimate, direct medical costs and reduced productivity accounted for $176 billion and $69 billion, respectively (ADA, 2013a). Medical expenditures on diabetes can be disaggregated as follows: hospital inpatient care (43%), prescription medications used to treat diabetes-related complications (18%), antidiabetic drugs and supplies (12%), physician office visits (9%), and nursing/residential facility stays (8%) (ADA, 2013a). The average annual medical expenditures for a patient diagnosed with diabetes totaled $13,700 in 2012, of which diabetes accounted for $7,900 (ADA, 2013a). Those with a diabetes diagnosis incurred about 2.3 times the medical expenditures as those without one (ADA, 2013a).

A successful treatment protocol for the long-term management of diabetes requires a multifaceted approach in addition to traditional clinical interventions, including group counseling programs, self-management education, and lifestyle modification (ADA, 2013b). The American Diabetes Association (ADA) strives to identify and assess the validity of published studies in order to develop a standard of care for the treatment of diabetes mellitus (ADA, 2013b). Of notable interest to the ADA is the cost-effectiveness of clinical recommendations for treating DM, including screening, diagnostic exams, and treatment regimens (2013b). The ADA’s Professional Practice Committee releases an annual update of their guidelines for the standard of care (2013b). Given the numerous therapeutics for treating DM that are currently on the market or in the pipeline, it is important to continuously assess the cost-effectiveness of these therapeutics in order to
assist in the decision-making process for the benefit of physicians, patients, and payers. A variety of interventions—both clinical and non-clinical—will be analyzed through cost effectiveness studies to determine which ones are most desirable for controlling blood glucose levels.

Diabetes mellitus describes syndromes associated with dysfunction in the control of blood glucose levels (ADA, 2013b). The ADA currently recognizes four classifications for DM: type 1 diabetes, type 2 diabetes, other specific types of diabetes, and gestational diabetes mellitus (ADA, 2013b). Type 1 diabetes is associated with the destruction of pancreatic beta cells, which means that the pancreas has virtually no way of creating endogenous insulin (ADA, 2013b). On the other hand, type 2 diabetes is associated with both insulin resistance and a gradual decline in the pancreas’s ability to release insulin with bidirectional exacerbation (ADA, 2013b). In some situations, it is difficult to clinically discern whether a patient has type 1 diabetes or type 2 diabetes (ADA, 2013b).

To reach a diagnosis of DM, a clinician generally relies on the fasting plasma glucose (FPG) or the oral glucose tolerance test (OGTT), the latter of which requires a 2-hour reading following the ingestion of 75 grams of glucose (ADA, 2013b). An A1C test is also utilized in clinical practice because it is more convenient albeit with a lower sensitivity compared to the other tests (ADA, 2013b). The diagnosis of diabetes requires A1C ≥6.5%, FPG ≥126 mg/dL, 2-hour plasma glucose ≥200 mg/dl with OGTT, or random plasma glucose ≥200 mg/dL (ADA, 2013b). Controlling blood glucose levels (glycemic control) within an individualized optimal range is the focus of most clinical
interventions for type 2 diabetes (ADA, 2013b). Because of frequently associated cardiovascular risk factors and comorbidities, controlling blood glucose levels within an acceptable range is not necessarily a guarantee of higher quality of life or expected life years, which are the effectiveness measures employed in cost-effectiveness analysis.

**Biochemical Approaches of Noninsulin Antidiabetic Drugs**

The broadest categorizations of drugs for treating type 2 diabetes include those that act on pancreatic beta cells and those that operate by other means (Kaiser & Oetjen, 2014). Sulfonylureas, GLP-1 analogues, DPP-4 inhibitors, biguanides, thiazolidinediones, and SGLT2 inhibitors are some of the noninsulin antidiabetic drugs that work to modulate blood glucose levels by utilizing various biochemical strategies independent of insulin stimulation or provision (Kaiser & Oetjen, 2014).

Sulfonylureas inhibit ATP-dependent potassium channels, which depolarizes the cell membrane and allows an influx of calcium through voltage-dependent L-type calcium channels (Kaiser & Oetjen, 2014); this has the effect of stimulating insulin release in pancreatic beta cells, which results not only in lower blood sugar levels but also weight gain (Kaiser & Oetjen, 2014). Also of significance is the greater incidence of cardiac events with the use of glibenclamide (glyburide in North America)—a sulfonylurea (Kaiser & Oetjen, 2014).

Glucagon-like peptide-1 (GLP-1) is another insulin secretagogue (activates insulin secretion from beta cells) that is released from intestinal L-cells after eating a meal (Kaiser & Oetjen, 2014). In natural form, GLP-1 has a very short half-life (2 minutes) once it is cleaved by dipetidylpeptidase 4 (DPP-4) (Kaiser & Oetjen, 2014).
Thus administering GLP-1 alone will likely not provide prolonged stimulation of insulin secretion (Kaiser & Oetjen, 2014). Instead, GLP-1 analogues (e.g., exanatide and liraglutide) were developed resistant to cleavage and degradation to increase the half-life of the compounds in the bloodstream when injected subcutaneously (Kaiser & Oetjen, 2014). DPP-4 inhibitors (including sitagliptin, vildagliptin, and saxagliptin) work by inhibiting DPP-4 from cleaving endogenous GLP-1, which boosts its levels and allows it to act in stimulating beta cells (Kaiser & Oetjen, 2014). GLP-1 analogues have been associated with increased activity and greater mass in beta cells (Kaiser & Oetjen, 2014). More importantly, since GLP-1 analogues and DPP-4 inhibitors only act in the presence of elevated blood glucose levels, the risk of a patient suffering from hypoglycemia as a result of their use is low (Kaiser & Oetjen, 2014). Unfortunately, Kaiser and Oetjen note that dysfunction of the pancreas, including pancreatitis, acinar cell death, and dysplasia, have been identified as side effects of GLP-1 analogues in rodent and animal studies (Kaiser & Oetjen, 2014).

Biguanides, including metformin, have held a prominent position in the antidiabetic drug market (Kaiser & Oetjen, 2014). Metformin acts by inhibiting gluconeogenesis in the liver, which helps in lowering blood glucose levels (Kaiser & Oetjen, 2014). Surprisingly given its immense popularity, the mechanism of action for metformin has only recently been elucidated (Kaiser and Oetjen, 2014; Madiraju et al., 2014). Metformin selectively inhibits the mitochondrial isoform of glycerophosphate dehydrogenase, which ultimately increases the cytosolic NADH-NAD ratio and restrains the conversion of lactate to pyruvate—an important precursor of gluconeogenesis.
(Madiraju et al., 2014). Other proposed but less validated mechanisms include inhibition of complex I of the mitochondrial transport chain, which causes a reduction of energy stores (higher ADP/ATP and AMP/ATP ratios) resulting in AMP-dependent kinase activation (Kaiser & Oetjen, 2014). Several other theories involving AMP-dependent kinase and other signaling enzymes that may act to reduce gluconeogenesis in the liver have also been proposed (Kaiser & Oetjen, 2014). In any case, metformin remains an effective tool for managing blood glucose levels (Kaiser & Oetjen, 2014). Some studies even suggest metformin has protective effects, including lower mortality rates and reduced risk of cancer and CVD (Kaiser & Oetjen, 2014). It is also important to note that metformin is weight neutral, which should mean that diabetic patients who are obese can potentially benefit from it (Kaiser & Oetjen, 2014).

The mechanisms of action for thiazolidinediones (TZD), including rosiglitazone and pioglitazone, are complex (Kaiser & Oetjen, 2014). They not only improve the sensitivity of skeletal muscle and liver to insulin but also inhibit gluconeogenesis in the liver and promotes anti-inflammatory responses in some organs (Kaiser & Oetjen, 2014). Unfortunately the side effect profile of TZD drugs make them much less attractive as treatment options: commonly cited adverse effects include fluid retention due to abnormal sodium/water balance following kidney reabsorption, long bone fractures, and weight gain likely are contraindications to many patients receiving TZD treatment (Kaiser & Oetjen, 2014). This could potentially be problematic for patients with chronic kidney disease, osteoporosis, and obesity. TZD drugs generally act as agonists for PPARγ, a nuclear receptor associated with retinoid X receptors (Kaiser & Oetjen, 2014).
Regulatory process for PPARγ activity include phosphorylation, acetylation, sumoylation, and ubiquitination (Kaiser & Oetjen, 2014). As previously noted, one of challenges facing the use of TZD drugs in clinical practice is the potentially serious side effect profile (Kaiser & Oetjen, 2014); recent research on TZD drugs has focused on more selective modulation of PPAR (Kaiser & Oetjen, 2014). In addition, potential dual PPARγ/α agonists have been explored to benefit from the decrease of blood glucose levels through PPARγ agonists and the decrease of lipid levels through PPARα (Kaiser & Oetjen, 2014).

Finally, another important current class of noninsulin antidiabetic drugs is the SGLT2 inhibitors, such as dapagliflozin (Kaiser & Oetjen, 2014). The sodium-glucose transporter 2 (SGLT2) is located in the proximal tubule of the kidney (Kaiser & Oetjen, 2014). When SGLT2 (a low-affinity, high-capacity glucose transporter) is inhibited, glucose reabsorption in the kidney is impeded, resulting in lower blood glucose levels (Kaiser & Oetjen, 2014). It should be noted that hypoglycemia is not a concern because SGLT1 (a high-affinity, low-capacity transporter) is still free to reabsorb glucose once the filtrate reaches SGLT1-rich areas in more distal parts of the kidney and the mode of action is independent of insulin (Kaiser & Oetjen, 2014). For convenience, a schematic that depicts the site of action for the described classes of noninsulin antidiabetic drugs is shown in Figure 1 below (Kaiser & Oetjen, 2014).
Figure 1: Mechanisms of action for existing and experimental antidiabetic drugs. Among other strategies, antidiabetic drugs primarily seek to reduce glucose release from the liver, decrease resorption of glucose in the kidneys, and amplify the secretion of insulin. Adapted from Kaiser and Oetjen, 2014.

Biochemical Approaches of Experimental Noninsulin Antidiabetic Drugs

Experimental approaches to treating DM have included the following: G-protein coupled receptor/free fatty acid receptor 1 (GPR40/FFAR1) activators, glucokinase activators, glucagon-receptor blockers, 11β-hydroxysteroid dehydrogenase 1 (11β-HSD 1) inhibitors, IL-1β neutralizing antibodies, and recombinant TNF-α receptor 2 (Kaiser & Oetjen, 2014). The mechanisms of action for these therapies are also shown in Figure 1 above (Kaiser & Oetjen, 2014). The cost effectiveness of these therapies is impossible to predict because all of them are novel approaches to targeting modulators of blood glucose levels without any broad consensus of their effectiveness and, furthermore, do not have
any established cost data for estimating cost assumptions. The ones most similar to existing therapeutics are glucagon-receptor blockers (Kaiser & Oetjen, 2014); while glucagon-receptor blockers block glucagon receptors in order to prevent glucagon from stimulating gluconeogenesis and increasing blood glucose levels, GLP-1 analogues and DPP-4 inhibitors inhibit glucagon secretion (Kaiser & Oetjen, 2014). Glucagon-receptor blockers and glucagon-secretion inhibitors are essentially different approaches with the same overall goal of preventing glucagon from modulating blood glucose levels (Kaiser & Oetjen, 2014). Therefore, the effectiveness of these approaches in lowering blood glucose levels are likely comparable to each other, and the use of these therapeutics in combination might even offer synergistic effects.

Effectiveness of Antidiabetic Therapies in Achieving HbA1c Targets

Esposito et al. assessed the effectiveness of the following eight drug classes utilized in the treatment of type 2 diabetes in reducing Hemoglobin A1C (HbA1C) levels to <7%: metformin, sulphonylureas, α-glucosidase inhibitors, thiazolidinediones, glinides, DPP-4 inhibitors, GLP-1 analogues, and insulin analogues (2012). The authors conducted a systematic review of randomized controlled trials that met rigorous criteria for selection (Esposito et al., 2012). The goal of the study was to track the proportion of patients with Hemoglobin A1C levels below <7% (Esposito et al., 2012). According to the ADA, the optimal HbA1c level is under 7% for non-pregnant adults with type 2 diabetes, so the ADA recommends that devising or revising a treatment regimen for a type 2 diabetic patient should primarily focus on attaining this outcome if it can be realistically and safely achieved (as cited in Esposito et al., 2012). In its 2009 estimate,
the National Committee for Quality Assurance reported that about 40% of diabetic patients (including type 1 and type 2) achieved HbA1c <7% in 2009 (as cited in Esposito et al., 2012).

The authors were able to conduct a meta-analysis on 218 randomized controlled trials published between 1994 and 2011 that met their inclusion criteria (Esposito et al., 2012). These study designs included parallel group, crossover, double-blind, triple-blind, single-blind, and open-label structures (Esposito et al., 2012). In addition to mean baseline HbA1C values, the authors also included age, gender, treatment category, trial duration, year of publication, concomitant drug use, duration of diabetes, and their interactions into their meta-regression model (Esposito et al., 2012). In total, the sample included 78,945 patients with a mean age range of 50.2 to 62.7 years, trial duration range of 12 to 134 weeks, and mean baseline HbA1c range of 7.2 to 11.7% (Esposito et al., 2012).

The drug classes reported were further divided into 12 classes from 8 classes to account for the sub-categorization of insulin analogues and GLP-1 analogues (Esposito et al., 2012). Insulin treatment programs were divided into the basal (long-acting insulin analogues), biphasic (premixed insulin analogues), prandial (short-acting insulin analogues), and basal bolus (a combination of long-acting and short-acting insulin) classes (Esposito et al., 2012). GLP-1 analogues were divided into daily (exenatide and liraglutide) and weekly (exantide long-acting release) classes (Esposito et al., 2012). The regression results are displayed in Table 1 below (Esposito et al., 2012).
Table 1: Changes in HbA1C levels divided by antidiabetic drug class. The table includes the outcomes of 342 arms. Adapted from Esposito et al., 2012.

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<tr>
<th>Drugs</th>
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<th>No. of subjects</th>
<th>Basal HbA1c, % Mean (s.d.)a</th>
<th>Δ† HbA1c, % Mean (s.d.)a</th>
<th>HbA1c &lt;7% Pooled prevalence (% and 95% CI)</th>
<th>χ²</th>
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<tr>
<td>Basal</td>
<td>57</td>
<td>21615</td>
<td>8.79 (0.26)</td>
<td>−1.28 (0.36)</td>
<td>58.9 (35.7–42.2)</td>
<td>95.1</td>
</tr>
<tr>
<td>Biphasic</td>
<td>51</td>
<td>11921</td>
<td>9.38 (0.60)</td>
<td>−1.91 (0.64)</td>
<td>34.4 (31.1–37.9)</td>
<td>92.1</td>
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<td>Prandial</td>
<td>13</td>
<td>2597</td>
<td>8.66 (0.54)</td>
<td>−1.08 (0.68)</td>
<td>36.3 (26.3–47.7)</td>
<td>96.1</td>
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<td>Basal bolus</td>
<td>16</td>
<td>2967</td>
<td>8.33 (0.52)</td>
<td>−1.22 (0.58)</td>
<td>50.2 (43.0–57.4)</td>
<td>93.0</td>
</tr>
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<td>GLP-1 agonists</td>
<td>33</td>
<td>5783</td>
<td>8.38 (0.35)</td>
<td>−1.12 (0.23)</td>
<td>45.7 (42.2–49.2)</td>
<td>85.4</td>
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<td>Exenatide LAR</td>
<td>4</td>
<td>668</td>
<td>8.41 (0.13)</td>
<td>−1.61 (0.16)</td>
<td>63.2 (54.1–71.5)</td>
<td>81.7</td>
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<td>DPP-4 inhibitors</td>
<td>60</td>
<td>13847</td>
<td>8.11 (0.55)</td>
<td>−0.74 (0.30)</td>
<td>39.5 (35.7–42.3)</td>
<td>93.2</td>
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<td>1120</td>
<td>8.39 (0.57)</td>
<td>−0.72 (0.41)</td>
<td>25.9 (18.5–34.9)</td>
<td>89.4</td>
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<td>Thiazolidinediones</td>
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<td>6655</td>
<td>8.62 (0.64)</td>
<td>−0.96 (0.32)</td>
<td>33.2 (28.5–38.2)</td>
<td>93.1</td>
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<td>5895</td>
<td>7.91 (0.54)</td>
<td>−0.77 (0.29)</td>
<td>48.2 (43.0–53.5)</td>
<td>93.2</td>
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<td>Glinides</td>
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<td>1050</td>
<td>8.15 (0.38)</td>
<td>−0.64 (0.20)</td>
<td>39.1 (29.3–49.9)</td>
<td>90.4</td>
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<td>Metformin</td>
<td>21</td>
<td>4827</td>
<td>8.55 (0.78)</td>
<td>−1.21 (0.48)</td>
<td>42.0 (35.5–48.9)</td>
<td>94.2</td>
</tr>
</tbody>
</table>

AGL, α-glucosidase inhibitor; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; LAR, long-acting release.
aMean weighted by number of patients.
†Δ denotes change in HbA1c.

As shown in Table 1, the percentage of patients who reached the HbA1C target of <7% was as high as 63.2% (CI 54.1–71.5) for exenatide long-acting release and 25.9% (CI 18.5–34.9) for α-glucosidase inhibitors (Esposito et al., 2012). Of the insulin therapies, the basal bolus class program excelled with 50.2% (CI 43.0–57.0) of diabetic patients reporting HbA1c <7%; in decreasing order, the others included the basal class with 38.9% (CI 35.7–42.2) of users reporting HbA1c <7%, the prandial class with 36.3% (CI 26.3–47.7), and the biphasic class with 34.4% (CI 31.1–37.9) (Esposito et al., 2012). Amongst all GLP-1 agonists, including exenatide long-acting release, 45.7% (42.2–49.2) of diabetes patients reported HbA1c <7% (Esposito et al., 2012). In decreasing order, the percentage of diabetic patients reporting HbA1c <7% for all noninsulin antidiabetic drugs were as follows: sulphonylureas (48.2%), GLP-1 agonists (45.7%), metformin (42.0%), glinides (39.1%), DPP-4 inhibitors (39.0%), thiazolidinediones (33.2%), and α-glucosidase inhibitors (25.9%) (Esposito et al., 2012).
Also shown in Table 1 are mean changes from HbA1c baseline; diabetic patients taking glinides saw the smallest decrease in HbA1c levels (-0.64%) and those taking biphasic insulin saw the greatest decrease in HbA1c levels (-1.91%) (Esposito et al., 2012). The authors also grouped the patients into different tiers of baseline HbA1c levels to see how much noninsulin and insulin antidiabetic drugs contributed to drops in HbA1c levels in all tiers (Esposito et al., 2012). The results for both are shown in Figure 2 and Figure 3, respectively (Esposito et al., 2012).

**Figure 2:** Changes in HbA1c levels from baseline HbA1c for all noninsulin drugs. The white columns represent the proportion of the tier reaching the <7% HbA1c target and the black columns represent the mean decrease in HbA1c levels weighted by number of patients. Adapted from Esposito et al., 2012.
Figure 3: Changes in HbA1c levels from baseline HbA1c for all insulin drugs. The white columns represent the proportion of the tier reaching the <7% HbA1c target and the black columns represent the mean decrease in HbA1c levels weighted by number of patients. Adapted from Esposito et al., 2012.

As shown in Figure 2, noninsulin drugs contribute to progressive declines in HbA1c levels as one moves from lower to higher tiers of HbA1c with the exception of the baseline >10.0% HbA1c tier (Esposito et al., 2012). In Figure 3, insulin drugs demonstrate much more profound declines in HbA1c when scanning from lower HbA1c baseline levels to a higher ones (Esposito et al., 2012). It appears that insulin-based treatments administered to diabetic patients with higher baseline HbA1c levels are more effective than noninsulin treatments at achieving decreases in HbA1c, especially below <7% (Esposito et al., 2012). While metformin is commonly prescribed as a monotherapy in the earlier stages of type 2 diabetes, disease progression often means more therapeutics have to be added to the treatment regimen to control HbA1c (Esposito et al., 2012).
Esposito et al. acknowledge the large amount of interstudy heterogeneity with heterogeneity greater than 80% for all drug classes (2012). This was the primary reasoning for including variables (first-time drug user, gender, mean age, year of publication, trial duration, and concomitant drug use) into the regression to try to explain some of the heterogeneity (Esposito et al., 2012). The authors found that none of these factors significantly explained the interstudy heterogeneity observed in the meta-regression, except for HbA1c baseline levels (Esposito et al., 2012). Esposito et al., however, argue that the heterogeneity amongst the randomized controlled trials were addressed with random effects in the regression model (2012). To conclude, the authors suggest that the tier of baseline HbA1c levels be taken into strong consideration when determining the optimal treatment regimen because there is significant variation in efficacy both between and within noninsulin and insulin antidiabetic drug classes at each of the baseline HbA1c tiers (Esposito et al., 2012).

Usage Rates of Antidiabetic Drugs

In 2012, roughly 18.8 million U.S. adults filled their antidiabetic drug (ADDs) prescriptions at retail pharmacies (Hampp et al., 2014). Given that 13.2 million U.S. adults filled antidiabetic drug prescriptions in 2003, this latest figure represents a 42.9% increase (Hampp et al., 2014). In other terms, 81.3 per 1,000 adults filled prescriptions for ADDs in 2012 compared to 63.1 per 1,000 adults in 2003 (representing an increase of 28.9%) (Hampp et al., 2014). Of these consumers in 2012, 86.7% used noninsulin antidiabetic drugs (NIADDs) and 27.1% used insulin antidiabetic drugs (Hampp et al., 2014). Overall, the use of noninsulin diabetic drugs increased by 36.2% in 2012.
compared to 2003 (Hampp et al., 2014). The usage rates for the remaining antidiabetic drugs are shown in Figure 4 (Hampp et al., 2014).

![Figure 4: Patterns in the filling of antidiabetic drug prescriptions at U.S. retail pharmacies from 2003 – 2012. A: Noninsulin antidiabetic drug prescriptions. B: New entrants to the diabetes drug market. Adapted from Hampp et al., 2014.](image)

As shown in Panel A of Figure 4, the use of biguanides (such as metformin) increased to 60.4 million by 2012 (a 97.0% increase compared to 2003) (Hampp et al., 2014). While the usage of sulfonylureas remains stagnant in absolute terms, its share
amongst all NIADDs dropped from 36.3% in 2003 to 26.7% in 2012 (Hampp et al., 2014). During the same timeframe, thiazolidinediones also saw diminished usage with a decrease of 64.0% amongst its peers (Hampp et al., 2014).

As one can see in Panel B of Figure 4, sitagliptin, a DPP-4 inhibitor, is the fastest growing antidiabetic drug prescription among the new entrants to the market with an astounding increase in market share of 10.5 million prescriptions between 2003 and 2012 (Hampp et al., 2014). Other notable mentions that are increasing its share of the antidiabetic drug market amongst the new entrants are saxagliptin and liraglutide (Hampp et al., 2014). Originally one of the growing products in the same cohort, immediate-release exenatide, a GLP-1 analog labeled as Byetta by Bristol-Myers Squibb, appears to be losing its popularity in utilization amongst physicians in comparison to the other newly minted peers (Hampp et al., 2014); its use reached its peak in 2008 with 2.5 million prescriptions (Hampp et al., 2014). This sharp decline likely can be attributed to the introduction of liraglutide, which gained popularity in utilization amongst GLP-1 analogs (Hampp et al., 2014). In January 2012, however, a once-weekly extended-release exenatide formulation was approved by the U.S. Food and Drug Administration (FDA) and marketed as Bydureon by Bristol-Myers Squibb (Hampp et al., 2014); this formulation would represent 20.3% of all exenatide prescriptions filled at U.S. retail pharmacies in 2012 (Hampp et al., 2014).

As of 2012, 154.5 million prescriptions for antidiabetic drugs were filled with noninsulin varieties accounting for 78.4% of the total (Hampp et al., 2014). Unsurprisingly, single-ingredient metformin accounted for roughly one out of every two
prescriptions for noninsulin antidiabetic drugs (Hampp et al., 2014). It was used by a staggering 11.8 million of the 16.3 million noninsulin antidiabetic drug users (Hampp et al., 2014). Sulfonylureas, including glipizide, glimepiride, and glyburide, accounted for more than a quarter of all NIADDs prescribed (Hampp et al., 2014). Also of importance was how DPP-4 inhibitors were pre-eminent in the utilization of newly introduced incretin-based drugs (Hampp et al., 2014).

5.1 million patients received the 33.4 million insulin prescriptions that were filled in 2012 (Hampp et al., 2014). The most popular preparations in the insulin market in sequential order were long-acting human analog insulin (e.g., insulin glargine) and fast-acting human analog insulin (e.g., insulin aspart and insulin lispro) (Hampp et al., 2014).

In looking at utilization rates, it is important to consider what combinations of therapies are being used (Hampp et al., 2014). In 2012, metformin use as a monotherapy accounted for 44% of prescriptions filled in U.S. retail pharmacies. Its concomitant use with other prescriptions was as follows: sulfonylurea (22.1%), DPP-4 inhibitors (22.0%), and long-acting insulin (9.7%) (Hampp et al., 2014). In the reverse perspective, between 51.9% (GLP-1 analogs) and 66.6% (thiazolidinediones) of noninsulin antidiabetic drug use was in conjunction with metformin (Hampp et al., 2014). Approximately one-third of long-acting insulin use occurred in conjunction with fast-acting insulin use; conversely, two thirds of fast-acting insulin was utilized in conjunction with long-acting insulin (Hampp et al., 2014). It is clear from these data that metformin and long-acting insulin are the primary options of the noninsulin antidiabetic drugs and insulin antidiabetic drugs, respectively (Hampp et al., 2014). As such, a clinician likely utilizes these two
therapies as the benchmark for evaluating the clinical effectiveness of proposed diabetes treatment regimens.

From analyzing these trends, Hampp et al. describe the ease of use of some of these products as the force behind their growth in market share (2014). For example, liraglutide, a GLP-1 analog, requires one injection daily compared to immediate release exanatide, which requires two daily injections (Hampp et al., 2014). This fact could explain some of the decline seen in exanatide’s share of the market from 2003 to 2012 (Hampp et al., 2014). It is also notable that the extended-release exanatide required only one weekly injection and thus gained instant popularity when it was released in 2012, which at least helped to maintain the stability of exanatide prescriptions in nominal terms (Hampp et al., 2014). Also mentioned is the growth of DPP-4 inhibitor use likely propelled by their availability as oral tablets (Hampp et al., 2014).

Hampp et al. also noted that 6.7% of noninsulin antidiabetic drug prescriptions were written for combination products, especially combinations that included metformin in conjunction with sitagliptin and glyburide (2014). Combination therapies of metformin with DPP-4 inhibitors were also a significant part of all DPP-4 inhibitor-containing therapies (Hampp et al., 2014). Also shown was that one-half to two-thirds of sulfonylurea, DPP-4 inhibitor, thiazolidinedione, and GLP-1 analog prescriptions were in conjunction with metformin prescriptions (Hampp et al., 2014). Hampp et al. found this trend peculiar because clinical guidelines generally recommend continuing metformin use in addition to noninsulin antidiabetic drugs unless its use is contraindicated or not well-tolerated by the patient (2014). Finally, the authors acknowledge that
rosiglitazone—a thiazolidinedione—had an abrupt decline when the association between cardiovascular events and rosiglitazone was revealed (as cited in Hampp et al., 2014); rosiglitazone was heavily restricted by the FDA in May 2011 with few exceptions (as cited in Hampp et al., 2014). Pioglitazone-containing medications would then supplant rosiglitazone as the leading thiazolidinedione on the market with 6.8 million prescriptions filled at U.S. retail pharmacies in 2012 (Hampp et al., 2014). In November 2013, however, the FDA lifted the ban on rosiglitazone, which may lead to increased utilization of rosiglitazone in the future (as cited in Hampp et al., 2014).

Complications Arising from Comorbidities

Metformin’s pre-eminence as the primary option for treating type 2 diabetes can be attributed to its low cost, safety profile, and prospective cardiovascular benefits (Inzucchi et al., 2014). Metformin use, however, can be problematic for patients with cardiovascular, renal, hepatic, and pulmonary diseases (Kaiser & Oetjen, 2014). In most cases, metformin will suffice for a patient with few comorbidities, but diabetic patients with kidney disease, in theory, are believed to struggle to clear metformin via renal excretion, which may lead to the eventual accumulation of lactate (resulting in lactic acidosis) (Inzucchi et al., 2014). Of the 21 million patients estimated to have type 2 diabetes, roughly 12% of them are also estimated to have impaired kidney function concurrently (as cited in Inzucchi et al., 2014). While drug labeling warns of metformin-associated lactic acidosis based on moderate pharmacokinetic research, the incidence of lactic acidosis in patients with metformin is estimated to be 1 per 23,000 to 30,00 person-years, which is even lower than the estimate of 1 per 18,000 to 21,000 person-years for
patients using other medications (as cited in Inzucchi et al., 2014). Inzucchi et al. sought to review existing literature studies to discover the true incidence of metformin-associated lactic acidosis in clinical studies with special attention given to those with chronic kidney disease to see whether the results warrant a change in clinical guidelines (2014).

It is believed that biguanides, including metformin, inhibit the mitochondrial respiratory chain, which limits aerobic respiration and thus energy production (Inzucchi et al., 2014). This should favor lactate synthesis and lead to elevated levels of lactate in the bloodstream (Inzucchi et al., 2014). Inzucchi et al., however, found in their review that the levels of lactate circulating in the bloodstream for diabetic patients taking metformin were fairly normal for each patient, including for those patients also having chronic kidney disease (2014). While metformin levels in the bloodstream of diabetic patients with chronic kidney disease are elevated compared to those without it, the levels of lactate in the bloodstream do not increase significantly when metformin is added to the treatment regimen (Inzucchi et al., 2014). In most cases, the clinical guidelines warning of metformin use in diabetic patients with chronic kidney disease are ignored (as cited in Inzucchi et al., 2014); even when metformin is prescribed for this population, its use is not associated with any additional occurrence of adverse effects and may even be associated with additional clinical benefits for this subpopulation compared to the overall population of diabetic patients (as cited in Inzucchi et al., 2014).

The fear of metformin use in diabetic patients with chronic kidney disease likely originates from the discontinuation of phenformin—another biguanide—almost 40 years
ago (as cited in Inzucchi et al., 2014). In the case of phenformin, the drug was associated with significant increased risk of lactic acidosis, but its metabolism pathway is much different from that of metformin (as cited in Inzucchi et al., 2014). While metformin is cleared entirely by the kidney (with a half-life of 6.5 hours), phenformin metabolism undergoes both hepatic and renal clearance processes, resulting in a larger half-life of 7-15 hours compared to metformin (as cited in Inzucchi et al., 2014). Phenformin’s lipophilic tendency compared to metformin also accounts for its affinity to mitochondrial membranes, which could result in the inhibition of aerobic respiration and potentially higher lactate levels (Inzucchi et al., 2014). In comparison, metformin is not demonstrably associated with lactate release in the muscle and lactate oxidation seen with phenformin (Inzucchi et al., 2014). In short, the evidence against metformin use in patients with chronic kidney disease in order to avoid the risk of lactic acidosis is dubious at best, and the restrictions on metformin use in this subgroup based on scant clinical evidence of its potential risks could hinder potential clinical benefits and cost savings.
PUBLISHED STUDIES

According to Hicks and Jacobs, “economic evaluation analysis involves the quantification of changes in health resource use and outcomes due to the introduction of new interventions” (2014). The most cost-effective strategies for reducing costs on cardiovascular disease and diabetes seem to be preventative measures taken before the incidence of disease, including ad campaigns and outreach programs designed to discourage tobacco use, alcohol use, unhealthy eating, and sedentary lifestyles (Mendis & Chestnov, 2013). Screening for impaired glucose tolerance in those at risk for diabetes and implementing lifestyle and pharmacological modifications at an early stage is also considered a cost-effective measure in reducing the incidence of diabetes (Gillies et al., 2008). To further explore the cost effectiveness of both clinical and non-clinical interventions, a few choice studies were selected for examination. These cost effectiveness studies include both long-standing and recently published works.

Cost-Effectiveness of Diabetes Screening

Kahn et al. prepared a sample of 325,000 people from the US population who were 30 years of age without a current diabetes diagnosis (2010). The authors then utilized the Archimedes model to compare eight proposed approaches to screening and compared these results to the no-screening approach (Kahn et al., 2010). Each of these strategies had a proposed time to begin screening and a proposed frequency of screening (the latter of which is expressed in parentheses): 30 years (every 3 years), 45 years (every year), 45 years (every 3 years), 45 years (every 5 years), 60 years (every 3 years), hypertension diagnosis (every year), hypertension diagnosis (every 5 years), and
maximum screening (Kahn et al., 2010). The simulation, which was necessitated by the lack of clinical trial data, then accounted for the expected diabetes treatment upon detection and included the incidence of diabetes-related complications (myocardial infarction, stroke, and microvascular disease) in order to determine the impact on quality of life, life expectancy, and costs (Kahn et al., 2010). The comparisons of these eight strategies to the null strategy can be found in **Figure 5** and **Figure 6** (Kahn et al., 2010).

**Figure 5: QALYs added for each of the proposed screening strategies compared to the null strategy.** The error bars represent the 95% confidence interval for the QALYs added per 1,000 people after 50 years of follow-up based on the screening strategy compared to the null strategy. Adapted from Kahn et al., 2010.
Figure 6: Cost per QALY (US$/QALY) for each of the proposed screening strategies compared to the null strategy. The error bars represent the 95% confidence interval for the cost per QALY (undiscounted) after 50 years of follow-up based on the screening strategy compared to the null strategy. Adapted from Kahn et al., 2010.

Figure 5 reveals that maximum screening (i.e., screening starting at age 30 and repeated every 6 months until age 75) added the most QALYs per 1,000 people after a 50 year follow-up period as one would expect (Kahn et al., 2010). In a society with unlimited healthcare resources, this strategy could be pursued, but in reality, this approach is simply not practical. Screening at age 60 repeated every 3 years, on the other hand, added the least number of QALYs of the eight proposed strategies (Kahn et al., 2010). This result suggests that screening at 60 years is likely too late to substantially alter the health outcome of the patient. Figure 6 reveals the cost per QALY for each of the strategies in comparison to the control (i.e., the null strategy of no screening) (Kahn et al., 2010). The results reveal the impracticality of maximum screening with an incremental cost effectiveness ratio of $40,778/QALY (Kahn et al., 2010). The strategy for screening at hypertension diagnosis repeated every year (i.e., once blood pressure exceeds 140/90 mmHg and repeated every year thereafter) had the most attractive
incremental cost effectiveness ratio ($6,287/QALY) (Kahn et al., 2010). Unfortunately, this strategy only added 78 QALYs per 1,000 people, which is significantly lower than five of the proposed strategies (Kahn et al., 2010). Kahn et al. instead were drawn to the strategies of screening at age 30 or age 45 and repeating every 3-5 years thereafter because these strategies resulted in both attractive cost-effectiveness and clinical effectiveness (2010). The three relevant strategies resulted in an incremental cost-effectiveness ratio of around $10,500 or less (Kahn et al., 2010).

Cost-Effectiveness of Diabetes-Related Appointments

Another study compared the cost-effectiveness of a 6-month monitoring scheme to that of a 3-month monitoring scheme through primary care providers for stable type 2 diabetes patients (Wermeling et al., 2014). The researchers looked at 2,215 patients between the ages of 40 and 80 years of age under the care of 233 general practitioners across the Netherlands (Wermeling et al., 2014). To be eligible, the patients could not be on insulin treatment, had to be in a stable condition (defined as HbA1c ≤7.5%, blood pressure ≤145 mmHg, and total cholesterol ≤201 mg/dL), and had to have a type 2 diabetes diagnoses for at least a year (Wermeling et al., 2014). Finally, the patients selected did not have a strong preference for which treatment group they joined and were randomized (Wermeling et al., 2014). At the 18-month follow-up period, Wermeling et al. then assessed the percentage of patients with a stable condition as previously defined (2014).

Surprisingly, the percentage of patients who met the criteria for a stable condition at the 18-month follow-up was 69.5% for the 3-month group to 69.8% for the 6-month
group (Wermeling et al., 2014). This meant that the 6-month group actually had marginally better outcomes under this criteria compared the 3-month group even though they were seen half as many times by the general practitioner (Wermeling et al., 2014). Given that 6-month monitoring scheme was €387 (~$580) cheaper than the 3-month monitoring scheme, these results demonstrate that the 6-month monitoring scheme was cost saving (better outcomes and lower costs) compared to the 3-month monitoring scheme (Wermeling et al., 2014). It should be noted, however, that the 95% confidence interval for the difference in outcomes between the two groups indicates there is significant ambiguity in what the difference likely is for the real population (95% CI: -6.2 to 6.7%) (Wermeling et al., 2014).

Interestingly, Wermling et al. chose not to include a QALY measure in determining cost effectiveness, even though they collected that data as well (2014). The EQ-5D—a quality-of-life measure—indicates that the follow-up EQ-5D for the 3-month group was the same as the baseline EQ-5D for the 3-month group (the mean for both was 0.87 with different standard deviations for each) (Wermeling et al., 2014). For the 6-month group the follow-up EQ-5D was also the same the baseline EQ-5D (the mean for both was 0.86 with different standard deviations for each) (Wermeling et al., 2014). Given the short frame of the study, the long-term quality of life and life expectancy could not be determined for the two treatment groups (Wermeling et al., 2014). In any case, the results at least indicate that the outcomes between the 3-month and 6-month groups are comparable, so patients who remain stable at an appointment could reasonably schedule
their next appointment 6 months later without any noticeable difference in outcomes compared to scheduling their next appointment 3 months later (Wermeling et al., 2014).

**Cost-Effectiveness of Established Diabetes Therapies**

Herman et al. published a seminal study on the cost-effectiveness of lifestyle modification and metformin therapy following diabetes diagnosis by using lifetime costs for their calculations (2005). The target population included patients 25 years or older collected from the Diabetes Prevention Program data set (Herman et al., 2005). The study included the health system and the societal perspectives (Herman et al., 2005). The results are shown in Table 2 (Herman et al., 2005).

**Table 2: Sensitivity analyses of lifestyle intervention and metformin intervention.**
The cost-effectiveness of lifestyle modification and metformin are assessed in relation to the placebo intervention. Adapted from Herman et al., 2005.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lifestyle Intervention vs. Placebo Intervention</th>
<th>Metformin Intervention vs. Placebo Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Δ Cost, $</td>
<td>Δ QALY</td>
</tr>
<tr>
<td>Base-case analysis</td>
<td>635</td>
<td>0.57</td>
</tr>
<tr>
<td>Age 25–44 y</td>
<td>489</td>
<td>0.63</td>
</tr>
<tr>
<td>Age 45–54 y</td>
<td>1,807</td>
<td>0.53</td>
</tr>
<tr>
<td>Age 55–64 y</td>
<td>2,617</td>
<td>0.39</td>
</tr>
<tr>
<td>Age ≥ 75 y</td>
<td>2,508</td>
<td>0.21</td>
</tr>
<tr>
<td>Reduced cost–</td>
<td>3,696</td>
<td>0.57</td>
</tr>
<tr>
<td>20% reduced effectiveness</td>
<td>1,417</td>
<td>0.46</td>
</tr>
<tr>
<td>50% reduced effectiveness</td>
<td>213</td>
<td>0.30</td>
</tr>
<tr>
<td>Reduced cost and 20% reduced effectiveness</td>
<td>−2,181</td>
<td>0.41</td>
</tr>
<tr>
<td>0% discount rate</td>
<td>−1,526</td>
<td>0.99</td>
</tr>
<tr>
<td>5% discount rate</td>
<td>1,382</td>
<td>0.42</td>
</tr>
<tr>
<td>Societal perspective</td>
<td>4,967</td>
<td>0.97</td>
</tr>
</tbody>
</table>

As shown in Table 2, Herman et al. establish the base-case cost-effectiveness of lifestyle modification (through the Diabetes Prevention Program) and metformin therapy as $1,124/QALY and $31,286/QALY, respectively, in comparison to the placebo intervention (2005). For adults age 55–64, the cost-effectiveness of lifestyle modification and metformin therapy are $3,409/QALY and $64,904/QALY, respectively (Herman et
Lifestyle modification was by far the most cost-effectiveness intervention under any set of assumptions (Herman et al., 2005); in many cases, lifestyle modification even produced costs savings, especially for the 25-44 year age group under the base-case analysis (Herman et al., 2005). Lifestyle modification was estimated to prolong the type 2 diabetes incidence by 11 years compared to 3 years for metformin (Herman et al., 2005). Finally, lifestyle modification and metformin decreased the incidence of diabetes and the incidence of any diabetes-related complications with lifestyle modification again arising as the more effective of the two (Herman et al., 2005). The results from this well-cited study likely solidified lifestyle modification and metformin therapy as the predominant treatments for type 2 diabetes as seen today.

**Cost-Effectiveness of Insulin Analogues**

Oral glucose-lowering drugs (OGLDs) are not always effective in controlling blood glucose levels alone, so an insulin therapeutic must be added to help bring blood glucose levels back to an acceptable range (Home et al., 2014). The administration of insulin analogues is one amongst various strategies to manage diabetes mellitus (Cameron & Bennett, 2009). Endogenous insulin secretion includes both bolus and basal components that insulin analogues try to replicate (Cameron & Bennett, 2009). Thus, there are rapid-acting analogues designed to satisfy bolus demands (around mealtime) and long-acting analogues for maintaining basal insulinization (Cameron & Bennett, 2009). Cameron and Bennett found that the use of these insulin analogues correlates with a decrease in diabetes-related complications and a greater number of QALYs compared to conventional insulin therapy (2009); however, the researchers also found that costs
associated with using insulin analogues are significantly greater than the costs associated with recombinant DNA human insulin therapy (Cameron & Bennett, 2009). Cameron and Bennett determined that the use of insulin analogues are only necessary for patients with a high risk of entering a hypoglycemic state, and thus, the mass administration of insulin analogues would not be prudent for all diabetics (2009).

Home et al. decided to use the results of the A1cHieve study in their own cost-effectiveness analysis to examine whether a treatment protocol consisting of OGLDs and insulin is not only more effective but more cost-effective than a treatment protocol of only OGLDs in patients with type 2 diabetes (2014). The A1cHieve study was an observational/non-interventional cohort study that followed 44,872 insulin-naïve and 21,854 insulin-experienced patients with type 2 diabetes beginning insulin aspart 30, insulin detemir, or biphasic insulin aspart over the course of 24 weeks (Home et al., 2014).

For the purposes of their study, Home et al. studied populations who were beginning insulin detemir in Mexico (n=109), India (n=487), Indonesia (n=109), India (n=1491), and Algeria (n=473) (2014). In addition, individuals who had HbA1C measurements both at baseline and 24 weeks after receiving insulin detemir therapy were included in the study (Home et al., 2014). The authors then used a discount rate of 3.0% throughout the 24-week period (Home et al., 2014). To examine the health outcomes, Home et al. utilized EQ-5D HRQoL measures assessed at baseline and at 24 weeks (Home et al., 2014). The authors then projected the financial and clinical consequences of adding insulin detemir to the treatment regimen compared to just taking OGLDs for each
of the countries over 30 years (Home et al., 2014). Finally, the authors also utilized the IMS Centre for Outcomes Research (CORE) Diabetes Model—constructed using a arrangement of Markov models—to establish the long-term health outcomes and costs associated with beginning insulin detemir for people who are not able to achieve appropriate blood glucose levels on OGLDs alone (Home et al., 2014). This includes the costs of a wide range of complications, such as cardiovascular disease, eye disease, and hypoglycemia to name a few (Home et al., 2014). The CORE Diabetes Model utilized Monte Carlo simulations to estimate the probabilities of developing these complications (Home et al., 2014).

By beginning insulin detemir in addition to these OGLD treatments, subjects in the five countries all experienced an increase in life expectancy in the 30-year base case: Mexico (1.9 years), India (1.6 years), Algeria (0.8 years), Indonesia (1.0 year), and South Korea (1.0 year) (Home et al., 2014). In addition, beginning insulin detemir was also associated with decreased incidence of diabetes-related complications in comparison to taking OGLDs alone: 25% to 38% for vision loss, 48% to 68% for late-stage renal disease, 2% to 17% for foot ulcers, and 12% to 22% for myocardial infarction (Home et al., 2014). Overall, the QALY improvements were as follows: Algeria (1.2), India (5.0), Mexico (2.5), Indonesia (1.8), and South Korea (1.0) (Home et al., 2014). The additional cost of taking insulin detemir in addition to OGLDs was anywhere between two and five times greater than taking OGLDs alone (Home et al., 2014). The authors decided to also express the numerator of their incremental cost effectiveness ratios (ICERs) in terms of their fraction of GDP per capita (Home et al., 2014). It seemed this approach was meant
to account for differences in purchasing power amongst people of these different countries (Home et al., 2014). The results of the study are shown in Table 3 (Home et al., 2014).

**Table 3: Short-term and long-term cost effectiveness of adding insulin detemir to OGLDs as a treatment protocol for those unresponsive to OGLDs.** The 1-year and 30-year ICER calculations are shown as costs per patient. Adapted from Home et al., 2014.

<table>
<thead>
<tr>
<th></th>
<th>Mexico</th>
<th>South Korea</th>
<th>Indonesia</th>
<th>India</th>
<th>Algeria</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-year ICER (cost per QALY gained) (base case)</td>
<td>2867 MXP (dominant)</td>
<td>15,139 KRW</td>
<td>3,995,329 IDR</td>
<td>39,214 INR</td>
<td>368,200 DZD</td>
</tr>
<tr>
<td>Local currency</td>
<td>62,952 MXP</td>
<td>4,273,409 KRW</td>
<td>22,920,222 IDR</td>
<td>58,454 INR</td>
<td>617,858 DZD</td>
</tr>
<tr>
<td>USD</td>
<td>4836</td>
<td>3935</td>
<td>2381</td>
<td>1054</td>
<td>7758</td>
</tr>
<tr>
<td>GDP fraction</td>
<td>0.48</td>
<td>0.18</td>
<td>0.68</td>
<td>0.71</td>
<td>1.48</td>
</tr>
<tr>
<td>Incremental cost</td>
<td>9443 MXP</td>
<td>289,225 KRW</td>
<td>544,145 IDR</td>
<td>18,422 INR</td>
<td>39,530 DZD</td>
</tr>
<tr>
<td>Incremental QALY</td>
<td>0.15</td>
<td>0.06</td>
<td>0.11</td>
<td>0.322</td>
<td>0.064</td>
</tr>
<tr>
<td>Incremental LE (years)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

As shown in Table 3, the cost effectiveness of these treatments varied significantly across the five countries for both the 30-year ICER and 1-year ICER calculations (Home et al., 2014). The following are the 30-year ICER calculations for these five countries: Mexico (-0.02), South Korea (0.00), Indonesia (0.12), India (0.48), and Algeria (0.88) (Home et al., 2014). In addition, the following are the 1-year ICER calculations for these five countries: Mexico (0.15), South Korea (0.06), Indonesia (0.68), India (0.71), and Algeria (1.48) (Home et al., 2014).

As one can see, the addition of insulin detemir to the treatment regimen of those who are unresponsive to OGLDs is a cost saving approach in the 30-year calculation.
since incremental costs are lower and incremental QALYs are increasing (Home et al., 2014). For South Korea, the addition of insulin detemir is nearly insignificant to incremental costs in USDs and as a fraction of GDP (Home et al., 2014); therefore, ICER as a fraction of GDP is 0.00 to indicate the low incremental cost of medication coupled with significant increases in QALYs (Home et al., 2014). It is important to note that while the ICER calculations for both the 1-year and 30-year periods in terms of USDs never exceeded $10,000/QALY, the cost of medications in Algeria and India were significantly higher in real terms (Home et al., 2014). The average Indian patient who was unresponsive to OGLDs, for example, would have to pay 48% of his income (with the assumption that GDP per capita roughly translates to income per capita) to achieve one more QALY, even though this number is only $707/QALY in USD terms (Home et al., 2014). In Algeria, the 30-year ICER was $4,625/QALY in terms of USDs and 0.88/QALY in terms of GDP fraction, which were the highest of any of the countries in both (Home et al., 2014). Overall, Home et al. deemed the addition of insulin detemir to the treatment regimen to be cost-effective (2014). Given the short window of the 1-year ICER, it is likely not worth discussing the practical implications of these calculations.

In another study, Zhang et al. sought to assess the cost effectiveness of adding additional medications as second-line therapies to the standard metformin and insulin regimen for treating diabetes mellitus from the patient perspective (2014). A total of four treatments arms were studied: metformin, sulfonylurea, and insulin (T1); metformin, DPP-4 inhibitor, and insulin (T2); metformin, GLP-1 agonist, and insulin (T3); metformin and insulin (T4) (Zhang et al., 2014). The patients began metformin
monotherapy once the target HbA1c level had been reached (Zhang et al., 2014). Following that point, other agents (DPP-4 inhibitors, GLP-1 analogs, and sulfonylureas) were added to the treatment protocol as shown in T1-T3 if the HbA1c target was ever exceeded, and insulin was added to the treatment regimen as a tertiary line of therapy if patients still exceeded their HbA1c target first-line and second-line therapies alone (Zhang et al., 2014).

The authors then classified ten Markov states in their Markov model based on the specific HbA1c level corresponding to one of ten tiers (Zhang et al., 2014). The period of each cycle in their model was 3 months, and the authors used an annual discount rate of 3% (Zhang et al., 2014). To gather patient data, the authors used the claims data and clinical data from a large U.S. health plan that services patients across the country (Zhang et al., 2014). By the end of their selective process for identifying patients who met their criteria, Zhang et al. had 37,501 patients who were all at least 40 years of age and received their type 2 diabetes diagnosis between 1995 and 2010 (2014). The base-case results of the four treatment regimens are shown in Table 4 for both women and men when glycemic control goal was ignored (Zhang et al., 2014). It is important to note that these are listed as simple cost effectiveness ratios (not incremental cost effectiveness ratios) (Zhang et al., 2014).
Table 4: Base-case results of the four treatment arms. The base-case results, including expected life years, expected QALYs, expected medication cost (USD) per QALY, and mean time to use insulin (years), are shown for the four treatments arms. The expected medication cost (USD) per QALY is a simple cost effectiveness ratio. Adapted from Zhang et al., 2014.

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1</td>
<td>T2</td>
</tr>
<tr>
<td>Expected LYs</td>
<td>68.66</td>
<td>68.63</td>
</tr>
<tr>
<td>Expected QALYs</td>
<td>68.41</td>
<td>68.39</td>
</tr>
<tr>
<td>Expected medication cost (USD) per QALY</td>
<td>2,600</td>
<td>2,741</td>
</tr>
<tr>
<td>Mean time to use insulin (years)</td>
<td>2.76</td>
<td>2.33</td>
</tr>
</tbody>
</table>

Comparison of the expected LYs, expected QALYs, expected medication cost per QALY, and mean time from diagnosis to insulin initiation for men and women. Four treatment regimens are T1, metformin plus sulfonylurea plus insulin; T2, metformin plus DPP-4 inhibitor plus insulin; T3, metformin plus GLP-1 agonist plus insulin; and T4, metformin plus insulin.

As shown in Table 4, the expected QALYs of all four treatments are very similar amongst men and women, but the differences in expected medication cost (USD) per QALY are more discernable (Zhang et al., 2014). For men, the simple cost effectiveness ratios were as follows in decreasing order: T3 ($2,791/QALY), T4 ($2,750/QALY), T2 ($2,741/QALY), and T1 ($2,600/QALY) (Zhang et al., 2014). For women, the simple cost effectiveness ratios were as follows in decreasing order: T3 ($2,891/QALY), T4 ($2,845/QALY), T2 ($2,835/QALY), and T1 ($2,675/QALY) (Zhang et al., 2014). For both men and women, T1—metformin, sulfonylurea, and insulin—seemed to provide the best value for patients in terms of expected cost of medication per QALY, whereas T3—metformin, GLP-1 agonist, and insulin—seemed to provide the worst value for patients in terms of expected cost of medication per QALY (Zhang et al., 2014).
Also of importance is the fact that T1 allowed both men and women to remain insulin independent for the longest mean period of time (2.76 years for men; 2.59 years for women) compared to the other treatment groups (Zhang et al., 2014). Remaining insulin independence for as long as possible is likely a significant consideration to the patient for the sake of convenience if nothing else. The results are more nuanced when visualized with blood glucose level targets (Zhang et al., 2014). In Figure 7, one can see the simple cost effectiveness ratios of the four treatment regimens for men and women divided into three HbA1c targets (6.5%, 7.0%, and 8.0%) (Zhang et al., 2014).

**Figure 7:** Cost effectiveness ratios for the four treatment arms divided into three HbA1c targets. The x-axis shows the expected medication cost per QALY, whereas the y-axis shows the expected QALYs prior to the first event (i.e., a diabetes-related complication or death). Adapted from Zhang et al., 2014.

The results in Figure 7 provide a more personalized approach to deciding which of the four treatment regimens is best suited for the given HbA1c target (Zhang et al., 2014). As one can see, T1—metformin, sulfonylurea, and insulin—still has the most desirable expected medication cost per QALY and expected QALYs prior to the first event in men and women and amongst all three HbA1c targets (Zhang et al., 2014). The
effectiveness (given as expected QALYs prior to the first event) of T1 was superior to that of other treatment arms for the 6.5% and 7% HbA1c targets but fell just short of the effectiveness of T2 (metformin, DPP-IV, and insulin) for the HbA1c target of 8.0% (Zhang et al., 2014). The difference at the 8.0% HbA1c target is likely statistically insignificant, and the cost-effectiveness of T1 is still significantly more attractive compared to T2 (Zhang et al., 2014). Overall, T1 was not only the most cost effective approach in terms of $/QALYs but also the most effective approach in terms of expected QALYs prior to the first event (with the exception of the 8% HbA1c target for the latter) (Zhang et al., 2014). Therefore, implementation of sulfonylurea in a patient’s treatment regimen as a second-line therapy should appeal to all parties (clinicians, patients, and payers) for the 6.5% HbA1c and 7% HbA1c targets at the very least (Zhang et al., 2014). Sensitivity analyses in comparison to the base case assumptions—given later in the study—also confirm this overall trend (Zhang et al., 2014).

Bariatric surgery for severely obese type 2 diabetics is also an important consideration for clinicians in improving the life expectancy and quality of life for that subpopulation of type 2 diabetic patients (Hoerger et al., 2010). Heorger et al. expanded on the Centers for Disease Control and Prevention-RTI Diabetes Cost-Effectiveness Model to assess the cost-effectiveness of performing bariatric surgery on severely obese patients (defined as BMI $\geq 35$ kg/m$^2$) (2010). The authors believed that bariatric surgery could lead to diabetes remission and an overall improvement in the quality of life for these patients by reducing the incidence of diabetes-related complications (Hoerger et al., 2010). In their simulation, Hoerger et al. estimated the costs, QALYs, and cost-
effectiveness of both gastric bypass surgery and gastric banding surgery with respect to traditional diabetes patient care (2010). All costs were expressed as 2005 U.S. dollars under the medical-care component of the Consumer Price Index, and both costs and QALYs were discounted by 3% (Hoerger et al., 2010). The results of the cost-effectiveness analysis are shown in Table 5 (Hoerger et al., 2010).

**Table 5: Cost effectiveness ratios bypass surgery and banding surgery.** The cost effectiveness of bypass surgery and banding surgery are compared to the control of no surgery (the current standard of care). The table separates the estimates for patients with a new diabetes diagnosis from those with an already established diabetes diagnosis. Adapted from Hoerger et al., 2010.

<table>
<thead>
<tr>
<th>Patients with newly diagnosed diabetes</th>
<th>Total costs*</th>
<th>Remaining life-years</th>
<th>QALYs*</th>
<th>Cost-effectiveness ratio ($/QALY)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No surgery (standard care)</td>
<td>$71,130</td>
<td>21.62</td>
<td>9.55</td>
<td></td>
</tr>
<tr>
<td>Bypass surgery</td>
<td>$86,665</td>
<td>23.34</td>
<td>11.76</td>
<td></td>
</tr>
<tr>
<td>Incremental (vs. no surgery)</td>
<td>$15,536</td>
<td>1.72</td>
<td>2.21</td>
<td>$7,000</td>
</tr>
<tr>
<td>Banding surgery</td>
<td>$89,029</td>
<td>22.76</td>
<td>11.12</td>
<td></td>
</tr>
<tr>
<td>Incremental (vs. no surgery)</td>
<td>$17,900</td>
<td>1.14</td>
<td>1.57</td>
<td>$11,000</td>
</tr>
<tr>
<td>Patients with established diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No surgery</td>
<td>$79,618</td>
<td>16.86</td>
<td>7.68</td>
<td></td>
</tr>
<tr>
<td>Bypass surgery</td>
<td>$99,944</td>
<td>17.95</td>
<td>9.38</td>
<td></td>
</tr>
<tr>
<td>Incremental (vs. no surgery)</td>
<td>$20,326</td>
<td>1.09</td>
<td>1.70</td>
<td>$12,000</td>
</tr>
<tr>
<td>Banding surgery</td>
<td>$96,921</td>
<td>17.80</td>
<td>9.02</td>
<td></td>
</tr>
<tr>
<td>Incremental (vs. no surgery)</td>
<td>$17,304</td>
<td>0.94</td>
<td>1.34</td>
<td>$13,000</td>
</tr>
</tbody>
</table>

*Costs and QALYs are discounted at a 3% annual rate. †Cost-effectiveness ratios are rounded to the nearest $1,000/QALY.

As shown in Table 5, the QALYs for no surgery, bypass surgery, and banding surgery were 9.55 QALYs, 11.76 QALYs, and 11.12 QALYs, respectively, for patients with a new diagnosis of diabetes (Hoerger et al., 2010). The total costs for no surgery, bypass surgery, and banding surgery were $71,130, $86,665, and $89,029, respectively, for patients with a new diagnosis of diabetes (Hoerger et al., 2010). Using these numbers, the incremental cost-effectiveness ratio of bypass surgery and banding surgery for
patients with an established diabetes diagnosis were determined to be $7,000/QALY and $11,000/QALY, respectively (Hoerger et al., 2010). Given that they are both compared to the standard of care (no surgery), one can infer that bypass surgery is both a more cost-effective and effective strategy than banding surgery for patients with a new diabetes diagnosis and a BMI greater than or equal to 35 kg/m² because it results in lower costs and better outcomes (Hoerger et al., 2010).

The relative cost-effectiveness of bariatric surgery compared to banding surgery is roughly similar for patients with an already established diabetes diagnosis (Hoerger et al., 2010). As shown in Table 5, the QALYs for no surgery, bypass surgery, and banding surgery were 7.68 QALYs, 9.38 QALYs, and 9.02 QALYs, respectively, for patients with an established diabetes diagnosis (Hoerger et al., 2010). The total costs for no surgery, bypass surgery, and banding surgery were $79,618, $99,944, and $96,921, respectively, for patients with an established diabetes diagnosis (Hoerger et al., 2010). Using these numbers, the incremental cost-effectiveness ratio of bypass surgery and banding surgery for patients with an established diabetes diagnosis were determined to be $12,000/QALY and $13,000/QALY, respectively (Hoerger et al., 2010). Given that they are both compared to the standard of care (no surgery), one can infer that bypass surgery is both a more cost-effective and effective strategy than banding surgery for patients with an established diabetes diagnosis and a BMI greater than or equal to 35 kg/m² because it results in lower costs and better outcomes (Hoerger et al., 2010).

Therefore, regardless of whether the patient has a newly established diabetes diagnosis or a previously established diabetes diagnosis, a patient with a BMI greater
than or equal to 35 kg/m² should always be considered for bariatric surgery after evaluating the patient’s individual risk factors for surgical complications (Hoerger et al., 2010). Sensitivity analyses provided by Hoerger et al. indicate that under any set of assumptions the cost-effectiveness of bariatric surgery and banding surgery is always under $40,000/QALY in comparison to the current standard of care (no surgery) (2010). The authors also list some of the perceived limitations of the study: selection of health parameters, limited data on long-term effects of bariatric surgery, assumption of quality of life improvement based on BMI decrease based on cross-sectional data, poor data on diabetes remission, limited data on surgical outcomes for patients with established diabetes diagnoses, and homogenous diabetes progressions rates based on HbA1c levels for both obese and non-obese persons (Hoerger et al., 2010).
RESULTS

The main findings of the six studies reported are as follows: 1) lifestyle modification is the most cost-effective intervention for treating DM at any age and under any set of assumptions compared to metformin and the placebo intervention and could be cost saving for adults between the age of 25 to 44 (Herman et al., 2005), 2) screening for DM beginning at age 30 or 45 and continued every 3 or 5 years thereafter is acknowledged as a cost-effective ($\leq 10,500/QALY) (Kahn et al., 2010), 3) scheduling a six-month follow-up appointment with a primary care provider is more cost-effective than scheduling a three-month follow-up appoint for stable diabetics (HbA1c $\leq 7.5\%$, blood pressure $\leq 145$ mmHg, and total cholesterol $\leq 201$ mg/dL) (Wermeling et al., 2014), 4) metformin has proven its cost-utility as a first-line therapy (i.e., the default option for a patient diagnosed with DM) (Herman et al., 2005), 5) sulfonylurea is a significantly better second-line therapy compared to DPP-4 inhibitors and GLP-1 analogs (Zhang et al., 2014), 6) insulin detemir, even though it has a desirable cost effectiveness overall, has variable cost effectiveness across countries in terms of both nominal and purchasing power terms (Home et al., 2014), 7) bariatric surgery for patients with a previously established or newly established diabetes diagnosis and a BMI greater than or equal to 35 kg/m$^2$ is more cost-effective when compared to both banding surgery and no intervention (Hoerger et al., 2010). Combining these findings could help establish a cost-effective standard of care for the long-term management of diabetes mellitus for all patients.
DISCUSSION

The key to establishing a cost-effective standard of care that satisfies healthcare providers who always strive to provide the best quality care and healthcare managers who are focused on controlling costs is finding a balance between cost-effectiveness and clinical effectiveness. A screening test that is repeated every day, for example, might result in maximal effectiveness (i.e., highest expected number of QALYs out of any other screening strategies), but it would be impractical and costly to conduct a screening test every single day, especially if there were no statistically significant benefit compared to testing every year. Therefore, through input from both clinicians and health economists, an ethical, practical approach that balances cost effectiveness and clinical effectiveness should be devised.

In addition, following an established protocol could allow primary care providers to exclusively manage stable prediabetic and early stage DM patients with no diabetes-related complications, allowing endocrinologists to focus on managing DM patients who are not responsive to the established protocols or have diabetes-related complications that require specialized attention. For all patients, the primary care provider should reinforce the importance of lifestyle modification (including diet and exercise) in preventing debilitating chronic diseases later in life (Herman et al., 2005). As previously noted, this preventative strategy would produce cost savings if initiated earlier in life (Herman et al., 2005). The PCP should also screen patients for diabetes beginning at age 30 and repeat screening every three years thereafter unless a diabetes diagnosis has been established (Kahn et al., 2010). The cost-effectiveness of screening at age 30 and repeating testing
every three years is comparable to that of screening at age 45 and repeating testing every three years or five years in terms of $/QALYs (Kahn et al., 2010); however, the clinical effectiveness of beginning screening at 30 and repeating every three years is markedly greater than those of the other two strategies previously mentioned (Kahn et al., 2010). Therefore, a primary care provider would be most comfortable with screening at age 30 and repeating every three years to ensure both cost considerations and effectiveness considerations are balanced in the joint interest of the patient and society.

Upon reaching a diagnosis of DM, the clinician should initially prescribe metformin to the patient given its proven effectiveness in numerous clinical trials as a first-line therapy for the treatment of DM and its proven cost effectiveness amongst health economists (Herman et al., 2005). The primary care provider should then check the patient’s BMI to see if it is greater than or equal to 35 kg/m$^2$ (Hoerger et al., 2010); if the patient’s BMI exceeds this threshold, the primary care provider should recommend the patient for bariatric surgery after reviewing the patient’s individual risk factors for this type of surgery (Hoerger et al., 2010). Upon assessing the stability of the patient’s condition ($\text{HbA1c} \leq 7.5\%$, blood pressure $\leq 145$ mmHg, and total cholesterol $\leq 201$ mg/dL), the primary care provider can decide whether to schedule the next follow-up appointment three months or six months from that date (Wermeling et al., 2014). A primary care provider could be reasonably confident that a diabetic patient assessed as stable could be seen again in six months as opposed to three months with no significant deterioration in the patient’s condition over that time period, whereas an unstable diabetic
patient or a patient changing his or her diabetes treatment regimen would require a follow-up appointment in 3 months (Wermeling et al., 2014).

At the next follow-up appointment, the primary care provider should once again assess the stability of the patient’s condition. If the patient is not meeting a set HbA1c target from 6.5% to 8% with metformin alone, the primary care provider should consider adding a sulfonylurea to the patient’s treatment along with the existing metformin prescription (Zhang et al., 2014). As previously noted, however, the primary care provider will have to be cautious of the increased risk of cardiac events and weight gain observed with sulfonylurea medications (Kaiser & Oetjen, 2014). At the next visit, if the patient still fails to show response to metformin and sulfonylurea treatments in reaching the HbA1c target, insulin therapy, such as insulin detemir, should be utilized in the patient’s treatment regimen to help the patient reach the HbA1c target (Zhang et al., 2014; Home et al., 2014). Once the patient has achieved the HbA1c target and the patient’s overall condition is stable, the primary care provider can then see the patient every six months thereafter to monitor the stability of the patient’s DM condition and overall health. If at any point the patient requests more personalized care or if the primary care provider believes a standardized treatment protocol would be ineffective for the specific case, the primary care provider should refer the patient to an endocrinologist.

In summary, the treatment protocol is as follows:

1. Always emphasize the importance of lifestyle modification (including diet and exercise) to all patients regardless of age. (Herman et al., 2005)
2. Screen for diabetes mellitus every 3 years starting at age 30 unless a diabetes diagnosis is established. (Kahn et al., 2010)

3. After a diabetes diagnosis has been established, prescribe metformin and set an achievable HbA1c target for the patient. (Herman et al., 2005; Zhang et al., 2014)

4. Consider recommending the patient for bariatric surgery if the patient’s BMI is greater than or equal to 35 kg/m². (Hoerger et al., 2010)

5. Assess the stability of the patient’s condition (HbA1c ≤ 7.5%, blood pressure ≤ 145 mmHg, and total cholesterol ≤ 201 mg/dL). (Wermeling et al., 2014)

6. Schedule a follow-up appointment 3-months later to reassess the stability of the patient’s condition and the patient’s progress in achieving the HbA1c target. (Wermeling et al., 2014)

7. If the patient has been responding to the metformin therapy, schedule a follow-up every 6 months unless the patient’s condition becomes unstable (in which case the patient should be seen every 3 months until a stable condition is achieved). If the patient is not responding to the metformin therapy alone, add a sulfonylurea to the patient’s treatment regimen and schedule a follow-up appointment in 3 months. (Wermeling et al., 2014; Zhang et al., 2014)

8. If the patient has been responding to the metformin and sulfonylurea therapy, schedule a follow-up every 6 months unless the patient’s condition becomes unstable (in which case the patient should be seen every 3 months until a stable condition is achieved). If at the follow-up appointment, a patient currently taking metformin and sulfonylurea is still not responding to those treatments in reaching
the set HbA1c target, add insulin therapy to the patient’s treatment regimen and schedule a follow-up appointment in 3 months. (Home et al., 2014; Wermeling et al., 2014; Zhang et al., 2014)

9. If the patient has been responding to the metformin, sulfonylurea, and insulin therapies, schedule a follow-up every 6 months unless the patient’s condition becomes unstable (in which case the patient should be seen every 3 months until a stable condition is achieved). If at the follow-up appointment, a patient currently taking metformin, sulfonylurea, and insulin is still not responding to those treatments in reaching the set HbA1c target, assess the patient’s compliance to the treatment regimen and refer the patient to an endocrinologist to explore other ways to manage their specific diabetes mellitus condition. (Home et al., 2014; Wermeling et al., 2014; Zhang et al., 2014)

Future studies on cost effectiveness analysis should focus on analyzing more combinations of established and new antidiabetic drug treatments, including both insulin and noninsulin varieties. Comparative effectiveness studies are also important to consider in tandem with cost effectiveness studies because proposed interventions that have the highest comparative effectiveness and the most desirable cost effectiveness are attractive to all parties, including clinicians, payers, and patients. It is important to continue conducting cost effectiveness (and comparative effectiveness) studies as new treatments enter the market for the treatment of diabetes mellitus because the paradigm of the treatment regimen that balances clinical effectiveness and cost effectiveness is naturally going to be in flux.
REFERENCES


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EDUCATION

May 2015  BOSTON UNIVERSITY, Boston, MA
M.S. Medical Sciences, GPA: 3.61
M.P.H. Health Policy & Management, GPA: 3.69
Thesis: Cost-Effective Strategies for the Long-Term Management of Diabetes Mellitus
Activities: Boston Medical Center, Volunteer

Dec. 2012  DARTMOUTH COLLEGE, Hanover, NH
B.A. Economics with Honors, GPA: 3.54
Thesis: Healthcare Expenditures and Trade
Honors: Order of Omega (Greek Honor Society), Dartmouth Cancer Scholar
Activities: Dartmouth Business Journal, Editor-in-Chief; Dartmouth Investment & Philanthropy Program, Member; College Fed Challenge – FRB of Boston, Team Participant; Sigma Nu Fraternity, Academic Chair

Summer 2012  TUCK SCHOOL OF BUSINESS AT DARTMOUTH
Business Bridge Program
• Participated in a business transition program to enrich skills in financial accounting, financial economics, marketing, spreadsheet modeling, and business strategy
• Team Valuation Project: Analyzed the WD-40 Company, requiring economic, marketing, financial, and strategic evaluation; Presented a recommendation to senior executives
EXPERIENCE

Mar.–June 2013

IBM INTELLECTUAL PROPERTY LAW, Alexandria, VA

Independent Contractor

• Conducted comprehensive searches for existing claims in a variety of intellectual property databases to assist IBM with filing patent disclosures relating to electronic patient records, telecommunications, and other fields through the US Patent & Trademark Office


CURIE LEARNING, LLC, Herndon, VA

Director

• Provided strategic advice to a $1M+ revenue family business focused on tutoring K-12 students for test prep, school admissions, and additional coursework to better compete with similar educational businesses in the area
• Researched potential locales for company expansion in the DC metro area; Resulted in the opening of two new branches and a preschool
• Participated in various fundraising initiatives to help Ekal Vidyalaya, a non-profit organization that provides access to education and health care in rural parts of India

Summer 2011

GEORGE MASON UNIVERSITY, Fairfax, VA

Research Assistant, Krasnow Institute of Advanced Study

• Studied blood flow and oxygenation in patients with myofascial trigger points (MTrPs) and control subjects to develop new tools for diagnosis
• Presented preliminary regression results at the 2011 Biomedical Engineering Society Conference for undergraduate students in Hartford, CT (“Understanding Dynamics of Oxygenation and Blood Flow in the Upper Trapezius Muscle During Exercise”)

Summer 2011
Summer 2009

Naval Research Laboratory, Washington, DC

Research Assistant, Center for Bio-Molecular Science and Engineering

- Investigated properties of novel synthetic polymers and traditional suit materials developed to optimally restrict the flow of toxins through a hypothetical biohazard suit
- Co-authored a poster presented at the 2009 DTRA Physical Science and Technology Conference in Dallas, TX (“Controllable Chemical Protection – Electroactive Tethered Membranes”)