



**The New England Comparative Effectiveness Public Advisory Council
Public Meeting – October 29, 2014**

**Controversies in the Management of Patients with
Type 2 Diabetes**

Draft Report – September 2014

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1. Introduction

To make informed health care decisions, patients, clinicians, and policymakers must consider many different kinds of information. Rigorous evidence on the comparative clinical risks and benefits of alternative care options is always important; but along with this information, decision-makers must incorporate other considerations. Patients and clinicians must weigh patients' values and individual clinical needs. Payers and other policymakers must consider information about current patterns of utilization, and the impact of any new policy on access, equity, and the overall functioning of systems of care. All decision-makers, at one level or another, must also take into account the costs of care, and make judgments about how to gain the best value for every health care dollar.

The goal of the New England Comparative Effectiveness Public Advisory Council (CEPAC) is to provide a forum in which all these different strands of evidence, information, and public and private values are discussed together, in a public and transparent process. Funded by a consortium of state Medicaid agencies, private payers, and integrated provider groups, and backed by a diverse set of New England state policymakers, the mission of CEPAC is to provide objective, independent guidance on how information on comparative effectiveness can best be used across New England to improve the quality and value of health care services. The Council is an independent body composed of clinicians and patient or public members from each New England state with skills in the interpretation and application of medical evidence in health care delivery. Representatives of state public health programs and of regional private payers are included as ex-officio members of CEPAC. The latest information on CEPAC, including conflict of interest policies and guidelines for submitting comments, is available online: cepac.icer-review.org.

The Institute for Clinical and Economic Review (ICER) manages CEPAC and is responsible for developing evidence reviews for CEPAC consideration. ICER is a trusted non-profit organization that evaluates scientific evidence on the value of medical tests, treatments, and delivery system innovations and helps translate that evidence into action to improve patient care and control costs. By working collaboratively with patients, clinicians, manufacturers, insurers and other stakeholders, ICER develops tools to support patient decisions and medical policy that share the goals of empowering patients and improving the value of health care services. More information about ICER is available at www.icer-review.org.

ICER has produced this evidence review and policy analysis in response to increasing stakeholder interest in the management of type 2 diabetes, driven in large part by the rising prevalence of this condition, its significant clinical burden, and escalating out-of-pocket and overall costs of treatment in New England and across the country.

Increasing costs are in part due to the emergence of novel therapies and management tools for diabetes, including newer and costlier forms of insulin, insulin pump therapy, new classes of oral and injectable medications, and devices for the intensive monitoring of blood glucose. For patients unable to manage their type 2 diabetes with lifestyle modifications alone, oral medications or insulin therapy are necessary to achieve target blood glucose levels. Though metformin is widely accepted as an appropriate first-line medication for type 2 diabetes, a number of questions remain regarding management options for patients with more complex disease, including: the relative advantages and risks associated with different pharmacologic combination therapies, including newer drug classes like Dipeptidyl Peptidase-4 (DPP-4) inhibitors and Glucagon-like Peptide-1 (GLP-1) receptor agonists; the best strategies for initiating insulin treatment; the comparative clinical effectiveness and value of different types and delivery methods of insulin; and the role of more intensive glucose monitoring in comparison to conventional monitoring approaches.

To address these concerns, ICER has undertaken a systematic literature review to examine the evidence on different management approaches for patients with type 2 diabetes. This report will support CEPAC's deliberation and attempts to answer some of the key issues confronting patients, physicians, provider organizations, payers, and other policymakers. This review summarizes the evidence on different management approaches for type 2 diabetes management and provides an overview of existing clinical guidelines and payer coverage policies impacting the delivery of care in New England and nationally. Several systematic reviews used in our assessment have found remarkably consistent treatment effects among individual drugs within a class (CADTH 2013a; CADTH 2013b); following the approach used in these reviews, we have also conducted our analyses at the class level. ICER also used a simulation model to explore the potential clinical and economic impact of various management strategies. The overall purpose of this report is to help enhance the use of evidence in practice and policy, and comments and suggestions to improve the work are welcome.

2. Background

2.1 The Condition

The management of type 2 diabetes has received significant attention over the past decade due to the increasing prevalence of this condition and the rise in costs associated with its treatment. Approximately 29 million Americans have diabetes, of whom 95% have the type 2 form (CDC, 2014a). In 2012, the annual cost of managing diabetes was estimated to total \$245 billion, including both direct medical costs and lost productivity resulting from complications (CDC, 2014a). This estimate represents a 41% increase in diabetes-related expenditures since 2007 (ADA, 2013).

Diabetes mellitus is a metabolic disorder that is characterized by hyperglycemia (high blood sugar) in the context of the body's resistance to insulin and a relative insufficiency of insulin production in the pancreas. Insulin is a hormone that is required to control blood glucose levels by supporting the movement of blood glucose into cells to be used as energy. The two main forms of diabetes are type 1 (formerly termed insulin-dependent diabetes) and type 2 (formerly termed non-insulin dependent diabetes). Type 1 diabetes occurs when the body's immune system causes beta cells in the pancreas to be destroyed, reducing or completely eliminating the secretion of insulin. Individuals with type 1 diabetes require insulin-replacement therapy, either delivered by injection or pump, to survive. Type 1 diabetes accounts for about 5% of all diagnosed cases of diabetes, and its onset typically occurs in childhood.

Unlike type 1 diabetes, the type 2 form is categorized by insulin resistance, a condition in which the body is not using insulin effectively. Typically, liver cells react to the presence of insulin by suppressing the release of glucose. However, insulin resistance causes the liver to release glucose, which then accumulates in the blood rather than being absorbed and used by cells, leading to hyperglycemia. The body responds by producing more insulin, but eventually, the insulin-producing beta cells in the pancreas are unable to produce enough hormone to overcome insulin resistance. Type 2 diabetes develops gradually, and is generally considered to be caused by a combination of lifestyle factors, such as obesity, sedentary lifestyle, and alcohol consumption, as well as genetic factors (CDC, 2014b). A number of risk factors are associated with type 2 diabetes, including age, family history, excess weight, inactive lifestyle, high blood pressure, and certain ethnicities such as African American, Hispanic/Latin American, American Indian and Alaska Native, Asian-American, and Pacific Islander (CDC, 2014b). Though more common in adults, type 2 diabetes is becoming increasingly prevalent in younger populations due to the rise in childhood obesity. Presentation of type 2 diabetes symptoms varies, but may include thirst, frequent urination, hunger, weight loss, and fatigue (ADA, 2004).

Chronic hyperglycemia caused by diabetes can increase the risk of several serious complications, many of which can be delayed or prevented with appropriate treatment. Complications include:

- Retinopathy – an inflammatory condition of the eyes that can lead to blindness if untreated
- Neuropathy – nerve damage which may result in numbness in the hands, feet, legs, or arms
- Diabetic ketoacidosis – life-threatening condition brought on by the body burning fat for energy in the absence of sufficient glucose
- Kidney disease - progressive condition that can lead to kidney failure and dialysis
- Macrovascular complications - high blood pressure, cardiovascular disease, and stroke
- Hyperosmolar Hyperglycemic Nonketotic Syndrome (HHNS) – a condition characterized by severe dehydration that may lead to seizures, coma, or death
- Gastroparesis – disorder in which the vagus nerve is damaged, resulting in delayed or stopped passing of food through the stomach.

2.2 Management Options for Type 2 Diabetes

The primary aims of treatment for type 2 diabetes are to control blood sugar levels and manage the patient's risk of major complications. Close monitoring of blood sugar and glycated hemoglobin (HbA1c) levels are a key aspect of type 2 diabetes management. Multiple randomized controlled trials (RCTs) have demonstrated the benefit of tight glycemic control in reducing the risk of microvascular complications in patients with diabetes. The UK Prospective Diabetes Study (UKPDS) assessed patients over a period of ten years and found that intensive glycemic control (median HbA1c = 7%) reduced the risk of microvascular disease by 25% compared to standard treatment (median HbA1c = 7.9%) in patients with type 2 diabetes (King et al., 1999). The Diabetes Control and Complications Trial (DCCT) also investigated the relationship between glycemic control and microvascular complications, finding that tighter glycemic control (mean HbA1c ~7%) in patients with type 1 diabetes was associated with a ~60% reduction in retinopathy, neuropathy, and nephropathy compared to patients in the standard group (HbA1c ~9%) (DCCT, 1987). As such, conventional practice standards emphasize lowering HbA1c levels to less than 7% for most patients with type 2 diabetes (AACE, 2013; Skylar et al., 2003).

The benefits of treating to specific thresholds have also recently been questioned, however (Teoh, 2011). Both the UKPDS and DCCT trials found an increased risk of hypoglycemia associated with intensive glycemic control due to the primary mechanism of action of some diabetes medications (described in more detail below). Hypoglycemia involves a wide range of symptoms, including dizziness, shakiness, confusion, hunger, and weakness brought on by dangerously low levels of blood glucose (below 70 mg/dl) (NIH, 2014). Hypoglycemia is a common occurrence for many patients with diabetes, and is usually treated easily without complication (Briscoe et al., 2014). If

left untreated, however, hypoglycemia can reach severe levels and result in seizures, comas, or death in very rare circumstances (Briscoe et al., 2014).

Healthy lifestyle changes (improved diet and level of exercise) are also a standard part of type 2 diabetes management, and for some individuals with early stage disease modifications in behavior are sufficient to achieve healthy blood glucose levels and/or delay the onset of complications (Ripsin, 2009). Given the progressive nature of type 2 diabetes, however, many patients will eventually require antidiabetic medications to help control blood sugar levels and manage other aspects of the condition.

There is general consensus that metformin – a biguanide that works by decreasing the amount of glucose absorbed from food and the amount of glucose produced by the liver – is the most effective first-line medication option available for most patients (Holman, 2007; Roumie, 2012). Metformin is generally regarded as safe as it does not result in weight gain or hypoglycemia (too-low blood sugar), side effects commonly associated with some other diabetes management options. However, for many patients with type 2 diabetes additional medications are required to control blood glucose, and a second or sometimes third pharmacologic option will be added to the treatment regimen. Additional management options include sulfonylureas, GLP-1 inhibitors, DPP-4 inhibitors, and insulin. These agents are described below, and a summary table comparing the different medications can be found on page 14.

Part of the complexity of managing type 2 diabetes is the number of treatment approaches available. After consultation with external stakeholders regarding those aspects of type 2 diabetes treatment associated with the most variation and controversy, we have limited the scope of our review to a discussion of the second- and third-line medications listed above. Numerous other pharmacologic treatment options are available, including thiazolidinediones, meglitinides, and alpha-glucosidase inhibitors. In addition, bariatric surgery and other interventions seeking to modify risk factors for the progression of type 2 diabetes and its complications are also important considerations for many patients, but for practical reasons these other management options have not been included within the scope of this review.

Pharmacological options

Sulfonylureas

Sulfonylureas have been used in the treatment of type 2 diabetes for over 50 years (Aquilante, 2010). These oral medications work by binding to channels on pancreatic cells, increasing the release of insulin from the pancreas to control blood glucose levels. Sulfonylureas are available in a number of generic and branded forms, and include different generations of agents (full details

available in Table 1 on page 14). Sulfonylureas are generally used at earlier stages of the condition, given their reliance on functioning beta cells in the pancreas to stimulate the release of insulin (Aquilante, 2010). They may be used as first-line agents or in combination with metformin, thiazolidinediones, and other anti-hyperglycemic medications. The most common adverse effects include weight gain (though in some formulations this effect is less pronounced), water retention, and hypoglycemia (Micromedex® Healthcare Series, v. 2.). Hypoglycemia is of particular concern given the medication's main mechanism of action. Sulfonylureas cannot be used with a number of medications that decrease their effectiveness, including beta blockers, calcium channel blockers, oral contraceptives, and thyroid medications (Micromedex® Healthcare Series, v. 2.). Sulfonylureas should also be avoided during pregnancy (Micromedex® Healthcare Series, v. 2.).

Glucagon-like Peptide 1 (GLP-1) receptor agonists

GLP-1 receptor agonists are part of new group of injectable drugs that control blood glucose with three different mechanisms: 1) by mimicking natural GLP-1 hormones to increase insulin secretion; 2) by suppressing pancreatic glucagon secretion (glucagon typically raises blood glucose levels); and 3) by slowing gastric emptying, or the passage of food from the stomach to the small intestine (Garber, 2011; Shyangdan, 2011). GLP-1 agonists can be used as a monotherapy, or in combination with sulfonylureas, metformin, thiazolidinediones, or insulin glargine, a long-acting basal insulin analog (described in more detail later in this section). Available versions of GLP-1 include exenatide (Byetta®, Bydureon®, and Bydureon Pen®, AstraZeneca plc) and liraglutide (Victoza®, Novo Nordisk A/S). Byetta was approved in 2005 and is administered twice daily prior to morning and evening mealtimes. Bydureon, approved in 2012, is a newer long-acting formulation that only requires a weekly injection. Victoza is injected once daily and received FDA approval in 2010. Potential advantages of GLP-1 agonists include their selective effects on insulin (i.e., insulin secretion is only stimulated when blood glucose levels are elevated, thereby reducing the risk of hypoglycemia when taken alone), and the promotion of weight loss given their mechanism of action (Garber, 2011). The most common side effects include nausea, diarrhea, and vomiting (Cernea, 2011). Serious adverse events may include pancreatitis, though a direct association with GLP-1 agonist treatment is not well established (Cernea, 2011). Available GLP-1 agonists also include black box warning labels for thyroid tumors due to studies done in animals suggesting a correlation (Micromedex® Healthcare Series, v. 2.). This effect in humans remains unknown, but the drug is contraindicated in individuals with a family or personal history of certain thyroid cancers (Micromedex® Healthcare Series, v. 2.).

Dipeptidyl peptidase-4 inhibitors (DPP-4 Inhibitors)

DPP-4 inhibitors, or gliptins, are a relatively new class of oral anti-hyperglycemic medications, first approved by the FDA in 2006. Like GLP-1 agonists, DPP-4 inhibitors target the hormones that decrease blood glucose levels. Specifically, DPP-4 inhibitors interrupt DPP-4 enzymes, which destroy beneficial GLP-1 hormones (see above). By inhibiting the action of DPP-4 enzymes, the DPP-4 inhibitors allow GLP-1 hormones to promote the release of insulin and the suppression of glucagon, leading to better blood glucose control (Karagiannis, 2014). DPP-4 inhibitors can be used as a monotherapy or as an adjunctive therapy with metformin, sulfonylurea, or thiazolidinedione (Dricker, 2011). Several DPP-4 agents are available, including sitagliptin (Januvia®, Merck), saxagliptin (Onglyza®, AstraZeneca plc) and linagliptin (Tradjenta®, Boehringer Ingelheim Pharmaceuticals). The most common side effects include upper respiratory infection, nasopharyngitis, and headaches (Reid, 2012). DPP-4 inhibitors do not increase risk of severe hypoglycemia or weight gain (Reid, 2012). Links have also been established between DPP-4 inhibitors and pancreatitis, though a direct association is not well established (Cernea, 2011).

Insulin

Insulin therapy is designed to mimic the normal release of insulin from pancreatic beta cells in patients with uncontrolled hyperglycemia. Coming in many different forms, insulin can either be human synthetic, meaning that it is based on recombinant human DNA and therefore identical to the structure of natural insulin, or an insulin analog, which molecularly alters insulin to allow for more predictable cell absorption (UCSF, 2014). Both versions come in different formulations that affect the drug's onset and duration of action. Insulin can be short- or rapid-acting (bolus), which involves administering insulin at different times in relation to meals, or it can be long- or intermediate-acting (basal) to seek consistent blood glucose levels throughout the day. Fast-acting insulin formulations include regular human insulin (Humulin R®, Eli Lilly and Company; Novolin R®, Novo Nordisk, A/S) and analogs insulin aspart (NovoLog®, Novo Nordisk, A/S), insulin glulisine (Apidra®, Sanofi-Aventis U.S. LLC), and insulin lispro (Humalog®, Eli Lilly and Company). Long- or intermediate acting insulin formulations include neutral protamine Hagedorn (NPH) (Humulin N®, Eli Lilly and Company; Novolin N®, Novo Nordisk, A/S) and analogs insulin detemir (Levemir®, Novo Nordisk, A/S) and insulin glargine (Lantus®, Sanofi-Aventis U.S. LLC). Insulin is also available in a range of concentrations; high concentration formulations (i.e., U-500) allows for a large dose of insulin to be administered using a small volume of the medication (Clark, 2010). Pre-mixed formulations, which combine rapid- and long-acting insulin, are also available to improve patient convenience and minimize multiple daily injections (Qayyum, 2008). Analog insulins are both newer and costlier, but offer some patient advantages such as more flexible dosing, since human insulin has more varied duration of action and can take longer to have an effect after administration (Lipska, 2014). Some long-acting analogs may also reduce the risk of nocturnal hypoglycemia

(Horvath, 2007). Table 2 on page 15 describes the key differences between insulin types in greater detail. There are no generic versions of insulin available, although a biosimilar (i.e. generic formulation of biopharmaceutical product) for insulin glargine recently received first approval in Europe (Hull, 2014).

Insulin can be incorporated at different stages in the management of type 2 diabetes, but is commonly added as a second- or third-line treatment option after the failure of oral anti-hyperglycemic medications to control blood glucose levels. ICER's literature review focused on long-acting insulins, as these are most often employed when patients are using insulin in combination with other medications. Hypoglycemia and weight gain are the most common adverse effects associated with insulin therapy.

Impact of diabetes pharmacotherapy on macrovascular outcomes

As noted previously, intensive glycemic control appears to have a beneficial impact on microvascular complications such as retinopathy and nephropathy. However, the impact of diabetes pharmacotherapy on long-term macrovascular outcomes such as stroke and myocardial infarction (MI) remains a controversial topic. As previously discussed, patients with diabetes are already at an increased risk of adverse cardiovascular outcomes, and findings from some RCTs and observational studies have fueled debate over whether certain medications pose an excess risk of these events. Sulfonylureas in particular have been associated with a modest increase in stroke, acute MI, or death compared to treatment alternatives (Roumie et al., 2012; Muis et al., 2005; Bell, 2006; Monami et al., 2013). Insulin has also been implicated as potentially increasing the risk of cardiovascular disease and cancer (Currie et al. 2012; Smith et al. 2012; Mellbin et al., 2011) although some studies have not shown increased risk of these outcomes (ORIGIN Trial, 2012). Several studies have also found an increased risk of adverse cardiac events, including heart failure, with certain formulations of thiazolidinediones (Erdmann et al., 2009), calling into question their most appropriate role in therapy. A recent publication describes a protocol for the use of the FDA's Mini-Sentinel surveillance database to assess these risks for multiple types of antidiabetic agents (Fireman, 2012). Results are expected to be presented in 2015.

Devices for diabetes management

Insulin delivery – pumps

Insulin can be administered through a variety of mechanisms, including a syringe, a pen, or a pump. Syringes are the conventional method of insulin delivery, involving a subcutaneous injection with a needle. Pens also deliver insulin subcutaneously, but come pre-filled or with cartridges to help manage dosing. Insulin pumps are small devices that can be programmed to provide both

continuous doses of insulin throughout the day and/or fast-acting doses around meal time through a catheter. Pumps are designed to improve patient convenience and glycemic control, and minimize the need for multiple daily injections of insulin (a diabetes management approach requiring the injection of long-acting insulin once or twice daily, in addition to fast-acting insulin near mealtimes for optimal glycemic control). A variety of insulin pumps are available, each with different technological features and accompanying supplies, including tubing, cartridges, dressing, and syringes. The annual costs of pump therapy can be significant, in part because of frequent market upgrades that make certain technology obsolete and require the purchase of new supplies. Popular models of insulin pumps and supplies can cost over \$7,000 at the outset of treatment, with significant additional annual costs to replace supplies required for ongoing care (Rosenthal, 2014).

Glucose monitors

Glucose monitoring is a core part of diabetes management to ensure adequate control of glucose levels, though its role and frequency, particularly for patients on oral medications alone, is controversial (Boutati, 2009). Patients receiving insulin replacement therapy can self-monitor blood sugar levels to determine glycemic control and establish any needed short-term adjustments to therapy. The required frequency of self-monitoring depends on individual factors, including medication choice and risk of hypoglycemia, but typically takes place four times daily for patients using insulin (Babar, 2013; Benjamin, 2002). Self-monitoring of blood glucose involves pricking the finger using a lancet and test strips to manually determine the concentration of glucose in a sample of blood (Benjamin, 2002). Alternatively, individuals can monitor glycemic control with meters that come in a range of models, each with different capabilities and features. Blood glucose meters are small computerized devices that provide automated blood glucose readings. Individuals are still required to prick their finger and provide a blood sample using a test strip, though many versions offer convenience features to support ease of use. Continuous glucose monitors (CGMs) have been developed that use sensors applied subcutaneously to measure and record blood glucose levels in real time throughout the day and signal an alarm if blood sugar concentration is too high or too low. CGMs are more costly than conventional techniques, costing an estimated \$4,335 annually (Huang, 2010). Whether they improve outcomes in patients with type 2 diabetes has been challenged (Jeitler et al., 2008).

Diabetes Management and Rising Costs of Care

The cost of diabetes management has increased substantially in the past decade, in large part due to treatment upgrades that make older versions of medications and devices unavailable or difficult to access. As previously discussed, manufacturers of insulin pumps, glucose monitors, and other diabetes devices frequently replace current technology with new models that require the purchase of updated supplies that are often brand and model specific. Some of the market upgrades have been criticized as convenience features that have little bearing on patient outcomes but which

significantly increase costs (Rosenthal, 2014). Most states, including all six in New England, have legislation in place requiring health insurers to reimburse diabetes treatment, including the costs of equipment and supplies (Cauchi et al., 2013). Even with comprehensive insurance coverage, however, most consumers are responsible for a portion of treatment costs, which can be significant, particularly for ongoing supplies (Kanakakis et al., 2002). Health insurers and consumers are also often pressured to purchase an entire disease management package from manufacturers in order to offer or obtain coverage for specific models of insulin pumps, continuous glucose monitors, and other devices, which can increase costs with unclear added benefit for patients (R. Zavoski, personal communication, 2014).

The price for insulin, which first became available in 1923, has also risen steadily due to the introduction of the newer, costlier analog formulations previously described. Insulin analogs now dominate the diabetes market, with some studies estimating over 90% of insulin-taking type 2 diabetes patients using these formulations (Lipska, 2014). More concentrated versions of insulin (U-500) have also grown more expensive in parallel with an increased demand for formulations that deliver more medication at less volume (Fiore, 2014). The high price of new oral medications, including DPP-4 inhibitors and GLP-1 receptor agonists, also contribute to the escalating costs of diabetes disease management.

Emerging Treatment Options

Investigational treatments for managing type 2 diabetes include imeglimin, the first new oral antidiabetic drug in the glimins class, as well as insulin degludec, an ultralong-acting basal insulin analog. Imeglimin acts to reduce hepatic glucose production and increase muscle absorption of glucose; early trials have shown an efficacy and safety profile similar to metformin (Pirags, 2012), as well as further reductions in HbA1c for patients not adequately controlled on metformin (Fouqueray, 2013). Limited evidence exists showing superiority of insulin degludec over insulin glargine or detemir for improving glycemic control, and some studies have found a significant benefit in reducing the incidence of hypoglycemia in patients with type 2 diabetes compared to long-acting insulin analogs (Wang, 2012). However, the FDA did not approve an original submission for insulin degludec in February 2013 because of concerns regarding a potential safety signal for cardiovascular events, and requested additional data on these outcomes (Tucker, 2013).

Emerging treatment options that have recently been approved by the FDA for type 2 diabetes management include SGLT2 inhibitors, a new class of oral antidiabetic medications; inhaled human insulin (Afrezza®, MannKind Corporation); and devices for insulin delivery such as the insulin patch (OmniPod®, Insulet Corporation) and an “artificial pancreas” device system (MiniMed® 530G with Enlite®, Medtronic, Inc.). SGLT2 inhibitors work to block glucose absorption in the kidneys; three SGLT2s have been approved to treat type 2 diabetes in the U.S. (i.e., dapagliflozin [AstraZeneca plc], canagliflozin [Janssen Pharmaceutical], and empagliflozin [Boehringer Ingelheim]), and there are

several others currently in phase III clinical trials. However, data on their efficacy compared to other oral antidiabetic agents are lacking (Vasilakou, 2013). In June 2014, Afrezza was approved by the FDA as adjunct therapy for type 2 diabetic patients requiring mealtime insulin, and has been shown to significantly reduce HbA1c compared to placebo (Fischer, 2014). The OmniPod insulin patch is designed to benefit certain type 2 subgroups (e.g., elderly patients) because of its small size and simplicity compared to conventional insulin pumps (Pickup, 2012). Finally, the MiniMed 530G System, which can combine an insulin pump and continuous glucose monitor with or without a glucose suspend feature, was approved by the FDA in September 2013, but type 2 patients have not yet been included in clinical trials (Blue Cross Blue Shield Association, 2014).

Table 1. Summary characteristics of non-insulin medications for the treatment of type 2 diabetes.

Characteristic	Sulfonylureas*	GLP-1 receptor agonists	DPP-4 inhibitors
Brand and generic name(s)	<i>First generation:</i> chlorpropamide (Diabinese®), tolbutamide (Orinase®) <i>Second generation:</i> glipizide (Glucotrol®), glyburide (Micronase®), glimepiride (Amaryl®)	exenatide (Byetta®) exenatide extended-release (Bydureon®) liraglutide (Victoza®)	sitagliptin (Januvia®) saxagliptin (Onglyza®) linagliptin (Tradjenta®)
Administration	Oral tablet	Subcutaneous Injection	Oral tablet
Use and effects	Typically taken 20 – 30 minutes before mealtime for optimal blood glucose control	Taken weekly, twice daily before mealtimes, or once daily to control blood glucose levels	Taken once daily with or without food to control blood glucose levels
Usual effective dose	tolbutamide: 500mg – 3000mg chlorpropamide: 100mg – 500mg glyburide: 1.25mg – 5mg glimepiride: 1mg – 8mg glipizide: 5mg – 10mg	exenatide (extended-release): 2mg weekly exenatide (immediate-release): 10mg – 20mcg twice daily liraglutide: 1.2mg – 1.8mg once daily	linagliptin: 5mg once daily sitagliptin: 100 mg once daily saxagliptin: 5mg once daily
Main mechanism of action	Lower blood glucose by stimulating production of insulin by the pancreas.	Slow digestion and lower blood glucose by increasing insulin secretion in presence of elevated glucose levels and suppressing glucagon secretion.	Lowers blood glucose by preventing the degradation of incretin hormones by DPP-4 enzymes, thereby increasing insulin secretion and decreasing the liver's release of glucagon.
Advantages	Generic versions available; most significant reduction in HbA1c levels (although this may cause hypoglycemia).	Lower risk of hypoglycemia (unless taken with sulfonylurea) and weight gain.	Neutral effect on weight, lower risk of hypoglycemia compared to some alternatives.
Potential risks/adverse events	Hypoglycemia, weight gain, heartburn, nausea, cardiac events	Nausea, vomiting, diarrhea, and pancreatitis	Upper respiratory infection, nasopharyngitis, hypoglycemia, headaches, pancreatitis
Price for 30 days of treatment (based on average wholesale price (AWP) estimates)	\$55	\$233	\$326

Micromedex Healthcare Series. RED BOOK® Online. Greenwood Village, CO: Truven Health Analytics, 2014. <http://truvenhealth.com/>. Accessed May, 2014.

Table 2. Summary characteristics of insulin replacement therapies for the treatment of type 2 diabetes.

	Intermediate/Long-Acting Insulin (basal insulin)	
	Human	Analog
Brand and Generic Names	<i>Insulin human isophane (NPH)</i> (Humulin N®, Novolin N®)	<i>Insulin detemir</i> (Levemir®) <i>Insulin glargine</i> (Lantus®)
Administration	Subcutaneous injection;	Subcutaneous injection
Use and Effects	Administered once or twice daily for glycemic control. <ul style="list-style-type: none"> • Onset: 1.5 hours • Peak: 4 -12 hours • Duration: Up to 24 hours 	Administered once or twice daily for glycemic control. <ul style="list-style-type: none"> • Onset: 3-4 hours • Peak: 3-9 hours • Duration: Up to 24 hours
Usual effective dose	Individualized	Individualized
Main mechanism of action	Lowers blood glucose by stimulating glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production.	Insulin binds to insulin receptors. Facilitates uptake of glucose into skeletal muscle and fat tissue and by inhibiting the output of glucose from the liver.
Advantages	Equally effective as analogs in controlling HbA1C	More predictable than human alternatives; decreased risk of nocturnal hypoglycemia
Potential Risk/adverse events	Hypoglycemia, weight gain, low potassium, heart failure if combined with TZDs	Hypoglycemia, heart failure when combined with TZDs, diarrhea if taken with GLP-1 receptor agonist
Price for 30 days of treatment (when used as adjunct to other antidiabetic medications, based on AWP estimates)	~\$80	~\$220

3. Coverage Policies

3.1 Medications

Medicaid

There are many similarities in Medicaid drug coverage policies across the six New England states (see Table 3 on page 19). Prior authorization is typically not required for generic sulfonylureas, though some programs place restrictions on first-generation formulations. Fast-, intermediate-, and long-acting forms of insulin are covered, both in human and analog formulations, though programs vary in which brands require prior authorization.

Differences in policy primarily involve newer drug classes, such as DPP-4 inhibitors and GLP-1 receptor agonists, both of which are available as branded products only. Four of six New England states restrict coverage by requiring patients to fail or have history of use with older medications. For example, Vermont and Massachusetts require patients to fail with metformin monotherapy or combination therapy with insulin, sulfonylurea, or pioglitazone (an oral agent commonly prescribed for type 2 diabetes) before receiving either a DPP-4 or GLP-1 agent. Rhode Island and Maine require patients to demonstrate prior use of metformin (or thiazolidinedione, in the case of Rhode Island) for use of DPP-4 inhibitors. In Rhode Island, the same rules for prior history of use also apply to GLP-1 agonists. Maine also utilizes step-therapy, requiring patients to fail with all other oral medications and insulin before attempting GLP-1 agonists.

Other types of restrictions are less common in New England state Medicaid programs. Three out of six states utilize quantity limits for DPP-4 inhibitors and GLP-1 receptor agonists. Supply limits are mostly similar; Maine, Massachusetts, and Vermont each limit patients to one tablet per day for thirty days of treatment, and patients receive one, three, or four pens/vials of GLP-1 receptor agonist treatment per month, depending on the formulation.

New Hampshire and Connecticut are the only state Medicaid programs in New England that cover at least one DPP-4 inhibitor or GLP-1 agonist without restriction.

Regional Private Payers

Diabetes drug policies among major regional private payers in New England are similar to those of Medicaid agencies (see Table 4 on page 21). All identified policies allow for unrestricted use of generic sulfonylureas. Insulin therapies are typically covered without restriction, though generally require higher co-payments than generic medications. ConnectiCare and Neighborhood Health Plan

of Rhode Island (NHPRI) are exceptions; both require prior authorization for certain insulin formulations. NHPRI also utilizes quantity limits.

Similar to Medicaid programs, regional private insurers place further restrictions on DPP-4 inhibitors and GLP-1 agonists. Five out of seven payer policies identified utilize prior authorization and/or step therapy for most medications in both drug classes, and some formulations are not covered at all. Regional private insurers also universally restrict use for newer diabetes drug classes through tiered co-payments.

National Private Payers

Like regional payers, national private payers generally do not place restrictions on the use of generic sulfonylureas; only Anthem has dose limits in place, and Cigna requires prior authorization for some formulations. Insulin is also typically covered without restriction, though higher co-payments often apply. Humana is an exception by placing quantity limits on certain rapid-acting insulin analogs. Under Humana's formulary, patients are limited to 240 units of Humalog 100 unit/mL cartridge or solution per 30 days (Humana, 2014). Also consistent with the approach of regional insurers, national carriers apply stricter coverage criteria to the newest diabetes drug classes. Humana utilizes step therapy for DPP-4 inhibitors and GLP-1 receptor agonists, and four out of five national payer policies identified apply quantity limits to medications within these classes. Full details of quantity limits are described in Table 4 on page 21, but in general insurers tend to define the maximum allowable supply for medication per period using FDA-approved dosing guidelines. In many cases, certain formulations are entirely excluded from coverage. National private payers also apply higher tiered co-payments to newer diabetes drug classes.

3.2 Devices

Medicare

The Centers for Medicare and Medicaid Services (CMS) has a National Coverage Determination in place for external insulin infusion pumps, which provides coverage for patients with type 1 or type 2 diabetes. To be eligible for coverage, patients must have demonstrated hyperglycemia, as shown through a fasting C-peptide test (a blood test that determines the level of insulin the body is producing) of less than or equal to 10%, or a positive beta cell autoantibody test. Patients must also meet the following requirements:

- Completion of comprehensive diabetes education program; and
- Program of multiple daily injections for previous six months, with frequent self-adjustment of insulin; and
- Documented glucose testing at least four times daily for previous two months; and

- Experience of glycemic events (i.e., uncontrolled HbA1c levels, reoccurring hypoglycemia, etc.)

Patients who have utilized an insulin pump prior to enrollment on Medicare and have a documented two month history of frequent glucose self- testing of at least four times daily may also receive coverage for insulin pumps.

CMS also provides coverage for conventional blood glucose monitors for patients with diabetes. No CMS coverage policies were identified for continuous glucose monitors.

Medicaid

Limited information on durable medical equipment was available from the six New England Medicaid programs. The policies identified all included coverage for insulin pumps, with Maine requiring prior authorization, and Massachusetts adopting the same coverage criteria established by CMS (above). Massachusetts also requires patients to initiate treatment with an insulin pump on a three-month trial basis and document continued medical necessity for ongoing coverage. The policies generally also provide coverage for conventional blood glucose monitors, with Maine requiring prior authorization and Rhode Island limiting coverage to patients with poor diabetic control (i.e., frequent episodes of insulin reaction, ketosis, etc.). No coverage policies for continuous glucose monitors were identified.

Regional Private Payers

Of the policies identified, all provided coverage for insulin pumps with the exception of Blue Cross Blue Shield of Massachusetts, which states that insulin pumps are not medically necessary for patients with type 2 diabetes. Blue Cross Blue Shield of Rhode Island requires documentation of continued medical necessity for long-term use. Regional private insurers generally cover conventional blood glucose monitors, though continuous glucose monitor devices are considered investigational and not clinically necessary in this population.

National Private Payers

Like regional insurers, national insurers generally follow the same CMS criteria for coverage of external insulin pumps. Blood glucose monitors are also generally covered. Continuous glucose monitors are not covered in this population by national payers, with the exception of Cigna, who covers continuous glucose monitors for patients with type 2 diabetes who also have renal insufficiency and a history of severe hypoglycemic events despite demonstrated treatment adherence and compliance with monitoring.

Table 3. Coverage Policies for Type 2 Diabetes Medications: State Medicaid Agencies.

State	Sulfonylureas	DPP-4 Inhibitors	GLP-1 Receptor Agonists	Insulin (Basal)	Insulin (Bolus)
	chlorpropamide; tolbutamide; glipizide ; glyburide ; glimepiride	Januvia®* Onglyza®* Tradjenta®*	Byetta®* Bydureon®* Victoza®*	Humulin N®, Novolin N®* Levemir®* Lantus®*	NovoLog®* Apidra®* Humalog®* Humulin R (U-100® and U-500®)* Novolin R®*
* Brand-only product, no generic available PA: Prior Authorization PDL: Preferred Drug List QL: Quantity Limits ST: Step Therapy					
CT	• <i>Not included on PDL</i>	• Januvia and Onglyza covered	• Covered	• Covered without restrictions	
ME	• PA required for branded formulations (Generic versions covered without restriction) • Glyburide tablets require PA for patients >65 due to risks for severe hypoglycemia in this population	• Januvia and Onglyza are covered in patients with history of metformin use for at least 60 days in previous 18 months • PA required for Tradjenta • QL apply: <u>Januvia</u> : 35 tablets per 35 days <u>Onglyza</u> : 35 tablets per 35 days <u>Tradjenta</u> : 35 tablets per 35 days	• ST and PA required: patients should first fail with all other available oral medications and insulin • QL apply: <u>Byetta</u> : 1.2 mL pen per 30 days <i>No details provided for Bydureon or Victoza</i>	• Covered without restrictions, with the exception of some bolus formulations that require PA (Apidra, a rapid-acting analog, and Humulin R U-500, a concentrated form of short-acting human insulin).	
MA	• PA required for branded formulations (Generic versions covered without restriction) • Glyburide tablets require PA	• PA required: patients must fail with metformin monotherapy and combination therapy, and with insulin, sulfonylureas, and pioglitazone • QL apply: <u>Januvia</u> : 30 tablets/month; maximum dose 100 mg/day <u>Onglyza</u> : 30 tablets/month; 5 mg/day <u>Tradjenta</u> : 30 tablets/month; 5 mg/day	• PA required: patients must fail with metformin monotherapy and combination therapy, and with insulin, sulfonylureas, and pioglitazone • QL apply: <u>Bydureon</u> : four 2 mg vials per 30 days <u>Byetta</u> : 1.2 mL pen or 2.4 mL pen, depending on dose, per 30 days <u>Victoza</u> : two or three 18 mg pens per 30 days, depending on dose	• All formulations covered without restriction with the exception of pens and cartridges, which require PA	
NH	• PA required for branded formulations (Generic versions covered without restriction)	• Januvia and Onglyza covered without restriction • PA required for Tradjenta	• <i>Not included on PDL</i>	• At least one version of human and analog basal or bolus insulin is covered without restriction	

				<ul style="list-style-type: none"> • PA required for some formulations, including: Apidra, Humalog, Humulin R, Humulin N, and Lantus (cartridge and pen versions only)
RI	<ul style="list-style-type: none"> • PA required for branded and first-generation formulations (generic second-generation versions covered without restriction) 	<ul style="list-style-type: none"> • Covered in patients with history of metformin or TZD use in previous 90 days • PA required for Onglyza 	<ul style="list-style-type: none"> • Covered in patients with history of metformin or TZD use in previous 90 days • PA required for Bydureon and Victoza 	<ul style="list-style-type: none"> • Generally all formulations covered without restriction, with the exception of pens and cartridges, which require PA
VT	<ul style="list-style-type: none"> • PA required for branded formulations (Generic versions covered without restriction) • Length of coverage authorization limited to 1 year 	<ul style="list-style-type: none"> • Januvia and Onglyza covered in patients who have failed with metformin • Tradjenta requires additional failure with preferred DPP-4 inhibitors • QL apply: <u>Januvia</u>: 1 tablet per day <u>Onglyza</u>: 1 tablet per day <u>Tradjenta</u>: 1 tablet per day • Length of coverage authorization limited to 1 year 	<ul style="list-style-type: none"> • Covered for patients who are at least 18 years of age and have failed with metformin • PA required for Byetta and Bydureon • QL apply: <u>Bydureon</u>: 4 vials per 28 days <u>Byetta</u>: 1 pen per 30 days <u>Victoza</u>: 3 pens per 30 days • Length of coverage authorization limited to 1 year 	<ul style="list-style-type: none"> • All formulations covered without restriction with the exception of Apidra, which requires PA.

Table 4. Coverage Policies for Type 2 Diabetes Medications: Regional and National Private Insurers.

	<u>Sulfonylureas</u>	<u>DPP-4 Inhibitors</u>	<u>GLP-1 Receptor Agonists</u>	<u>Insulin (Basal)</u>	<u>Insulin (Bolus)</u>
	chlorpropamide; tolbutamide; glipizide ; glyburide ; glimepiride	Januvia®* Onglyza®* Tradjenta®*	Byetta®* Bydureon®* Victoza®*	Humulin N®, Novolin N®* Levemir®* Lantus®*	NovoLog®* Apidra®* Humalog®* Humulin R (U-100® and U-500®)* Novolin R®*
Regional private insurers * Brand-only product, no generic available PA: prior authorization PDL: Preferred Drug List QL: Quantity Limits ST: Step therapy					
Blue Cross Blue Shield MA (BCBS MA)	<ul style="list-style-type: none"> • generics covered without restriction • Tier 1 	<ul style="list-style-type: none"> • ST and PA required (must fail with other oral medications and insulin) • Tier 2 	<ul style="list-style-type: none"> • Byetta covered without restriction • PA required for Victoza Tier 2 and 3	<ul style="list-style-type: none"> • Covered without restrictions; Tier 2 	
Blue Cross Blue Shield Rhode Island (BCBS RI)	<ul style="list-style-type: none"> • Generic versions covered without restriction • Tier 1 	<ul style="list-style-type: none"> • Januvia and Tradjenta are covered without restriction • PA required for Onglyza • QL apply (details not provided) • Tier 2 or 3 	<ul style="list-style-type: none"> • Byetta covered without restriction • Bydureon and Victoza require PA • QL apply (details not provided) Tier 2 or 3	<ul style="list-style-type: none"> • Covered without restriction (some formulations not listed, i.e., Apidra, NovoLog, Novolin); Tier 2 	
Blue Cross Blue Shield Vermont (BCBS VT)	<ul style="list-style-type: none"> • Generic versions covered without restriction • Tier 1 	<ul style="list-style-type: none"> • ST required (patients must fail with metformin) • QL apply to Januvia and Onglyza (details not provided) • Tier 2 or 3 	<ul style="list-style-type: none"> • ST required (patients must fail with metformin) • QL apply to Byetta, Victoza (details not provided) Tier 2 or 3	<ul style="list-style-type: none"> • Covered without restrictions; Tier 2 (Apidra is Tier 3) 	
ConnectiCare	<ul style="list-style-type: none"> • generics covered without restriction • Tier 1 	<ul style="list-style-type: none"> • Januvia and Tradjenta covered without restriction • ST required for Onglyza • Tier 2 or 3 	<ul style="list-style-type: none"> • ST and QL apply 	<ul style="list-style-type: none"> • At least one version of human and analog basal or bolus insulin is covered without restriction • PA required for some formulations, including: rapid-acting analogs Apidra and Novolog, and human insulin Novolin 	
Harvard Pilgrim Health Care (HPHC)	<ul style="list-style-type: none"> • generics covered without restriction • Tier 1 	<ul style="list-style-type: none"> • ST required for Januvia and Tradjenta; Tier 3 • Onglyza covered without restriction; Tier 2 	<ul style="list-style-type: none"> • ST required; Tier 2 	<ul style="list-style-type: none"> • Covered without restrictions; Tier 2 	

Neighborhood Health Plan Rhode Island (NHPRI)	<ul style="list-style-type: none"> • generics covered without restriction • Tier 1 	<ul style="list-style-type: none"> • PA required: must fail with metformin or sulfonylurea (Tradjenta and Onglyza not listed) 	<ul style="list-style-type: none"> • PA required: must fail with metformin or sulfonylurea (Byetta and Bydureon not listed) 	<ul style="list-style-type: none"> • All formulations covered without restriction with the exceptions of pens and cartridges, and Levemir (a long-acting analog insulin) which requires PA
Tufts Health Plan (THP)	<ul style="list-style-type: none"> • generics covered without restriction • Tier 1 	<ul style="list-style-type: none"> • Covered without restriction (Onglyza not listed) • Tier 2 	<ul style="list-style-type: none"> • Covered without restriction (Victoza not listed) • Tier 2 	<ul style="list-style-type: none"> • Covered without restrictions • Tier 2
Regional private insurers therapy * Brand-only product, no generic available PA: prior authorization PDL: Preferred Drug List QL: Quantity Limits ST: Step				
Aetna	<ul style="list-style-type: none"> • generics covered without restriction • Tier 1 	<ul style="list-style-type: none"> • Covered without restriction • Tier 2 	<ul style="list-style-type: none"> • QL apply: <u>Bydureon</u>: 1 mL per week <u>Byetta</u>: 1 pen/month <u>Victoza</u>: 3 pens/month • Tier 2 or 3 	<ul style="list-style-type: none"> • Covered without restrictions • Tier 2, except Apidra, NovoLog, and Lantus (analog) and Novolin N and R (human), which are Tier 3
Anthem	<ul style="list-style-type: none"> • QL apply: <u>glipizide, glimepiride</u>: 60, 120, or 240 tablets per 30 days, depending on dose. <u>tolbutamide</u>: 180 per 30 days • Tier 2 or 3 	<ul style="list-style-type: none"> • QL apply <u>Januvia</u>: 30, 60, or 100 tablets per 30 days, depending on dose <u>Onglyza</u>: 30 or 60 tablets per 30 days, depending on dose • Tier 3; <i>Tradjenta not listed.</i> 	<ul style="list-style-type: none"> • QL apply: <u>Bydureon</u>: 4 per week <u>Byetta</u>: 1.2 or 2.4 per week, depending on dose <u>Victoza</u>: 9 per 30 days • Tier 3 	<ul style="list-style-type: none"> • Covered without restrictions; Tier 3 • <i>NovoLog, Apidra (analog) and Novolin (human) not listed.</i>
Cigna	<ul style="list-style-type: none"> • PA required for chlorpropamide and glyburide; other versions covered without restriction • Tier 1 	<ul style="list-style-type: none"> • QL apply <u>Januvia</u>: 30 tablets per 30 days <u>Tradjenta</u>: 30 per 30 days • Tier 3; <i>Onglyza not listed.</i> 	<ul style="list-style-type: none"> • QL apply: <u>Bydureon</u>: 2.6mL per 28 days <u>Byetta</u>: 3mL per 30 days <u>Victoza</u>: 9 mL per 30 days • Tier 3 	<ul style="list-style-type: none"> • Covered without restrictions; Tier 3 • <i>NovoLog, Apidra (analog) and Novolin (human) not listed.</i>
Humana	<ul style="list-style-type: none"> • generics covered without restriction • Tier 1 	<ul style="list-style-type: none"> • ST and QL apply (30 tablets/30 days) • Tier 2 or 3 	<ul style="list-style-type: none"> • ST and QL apply: <u>Byetta</u>: 1 or 2 pens per 30 days, depending on dosage • Tier 2 • <i>Bydureon and Victoza not listed</i> 	<ul style="list-style-type: none"> • QL apply to Humalog vial and cartridge: 240 for 30 days • All other formulations covered without restriction <u>Tiers</u>: <ul style="list-style-type: none"> • Tier 2: Humalog, NovoLog, Levemir, and Lantus (analog); Humulin N and Humulin R (human) • Tier 3: Novolin N and R (human) Apidra (analog)

United Health Care	<ul style="list-style-type: none"> • generics covered without restriction • Tier 1 	<ul style="list-style-type: none"> • QL apply (details not provided) • Tier 2 or 4 (Januvia) 	<ul style="list-style-type: none"> • QL apply (details not provided) • Tier 2 or 3 	<ul style="list-style-type: none"> • Most bolus and basal insulin vials covered without restrictions. • Novolin (human) and NovoLog (analog) are part of special program requiring patients to switch to lower cost insulin alternatives. <p><u>Tiers:</u></p> <ul style="list-style-type: none"> • Tier 1: Humalog and Levemir (analog); Humulin N and Humulin R (human) • Tier 3: Apidra and Lantus (analog) • Tier 4: Novolin N and R (human) and NovoLog (analog)
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4. Clinical Guidelines and Policy Statements

4.1 Second-Line Medication

American Academy of Clinical Endocrinologists, 2013

<https://www.aace.com/files/consensus-statement.pdf>

Dual therapy should be considered for patients taking metformin (or a metformin alternative, where suitable) whose HbA1c does not reach target with a single oral agent. Patients with an initial HbA1c of >7.5% can also be considered for dual therapy as first-line treatment. Of the medications included in this review, AACE recommends the following hierarchy of oral agents to be used in combination with metformin: GLP-1 agonists, DPP-4 inhibitors, Thiazolidinedione (TZD), Sodium glucose cotransporter 2 (SGLT-2) inhibitors, Basal insulin, Colesevelam, Bromocriptine QR, Alpha-glucosidase (AG) inhibitors, and sulfonylureas/glinides. TZD, SGLT-2 inhibitors, Basal insulin, and sulfonylureas should be administered with caution due to associated risks.

American College of Physicians, 2012

<http://annals.org/article.aspx?articleid=1033354>

The ACP suggests adding a second agent when lifestyle changes and metformin alone do not bring the patient to a reasonable HbA1c target. They do not offer specific preference as to which agents may be most suitable as second-line options.

American Diabetes Association/European Association for the Study of Diabetes, 2012

http://care.diabetesjournals.org/content/37/Supplement_1/S14.full

Dual therapy should be initiated if the patient does not reach their individualized HbA1c target after 3 months of monotherapy with metformin (or an alternative first-line medication, in patients unable to tolerate metformin). ADA/EASD recommends the addition of either a sulfonylurea, TZD, DPP-4, GLP-1 agonist, or basal insulin for dual therapy regimens. They do not offer a suggested hierarchy for second-line prescription; rather the decision should be based on individual patient factors and drug characteristics.

International Diabetes Federation, 2012

<http://www.idf.org/sites/default/files/IDF-Guideline-for-Type-2-Diabetes.pdf>

When HbA1c targets are not achieved using metformin alone, a sulfonylurea can be added as a second-line oral therapy. In patients who are unlikely to meet their HbA1c goal through monotherapy, initial treatment with dual combination therapy may be recommended. Alternative agents should be considered in patients who do not tolerate sulfonylureas, including a DPP-4 inhibitor. IDF notes that the

evidence shows little difference in efficacy between combination therapies, so selection of a second-line medication should be based on access, cost, and side effects.

National Institute for Health and Care Excellence, 2009
<http://www.nice.org.uk/guidance/cg87/chapter/guidance>

If metformin alone is insufficient to bring blood glucose to HbA1c target (typically 6.5%, unless otherwise determined for an individual patient), NICE recommends adding another oral agent, most commonly a sulfonylurea. A DPP-4 can be considered as an alternative second-line medication when a person has a high risk of hypoglycemia or does not tolerate sulfonylureas. When either a DPP-4 or TZD is suitable, the choice should be based on patient preference. NICE does not recommend use of GLP-1 agonists or insulin as second-line therapy.

4.2 Third-Line Medication

American Academy of Clinical Endocrinologists, 2013
<https://www.aace.com/files/consensus-statement.pdf>

For patients taking two oral agents who have an HbA1c <8%, a third-line oral agent may be beneficial in helping the patient to reach his or her target. The recommended hierarchy of third-line agents is as follows: GLP-1 agonists, TZD, SGLT-2 inhibitors, basal insulin, DPP-4 inhibitors, Colesevelan, Bromocriptine QR, AG Inhibitors, and SU/GLNs. AACE notes that TZDs, SGLT-2s, basal insulin, and SU/GLNs should be used with caution due to associated risks. Insulin, as opposed to an additional oral agent, should be considered for patients with HbA1c >8%, patients on two or more oral medications or on GLP-1 therapy, and patients with a long disease history, as these groups are not likely to reach their target HbA1c with additional oral medications.

American Diabetes Association/European Association for the Study of Diabetes, 2012
http://care.diabetesjournals.org/content/37/Supplement_1/S14.full

ADA/EASD suggests that the addition of a third oral agent may benefit some patients, but that most patients will have the best response with the addition of insulin. Of the medications addressed in this review, ADA/EASD suggests the use of DPP-4s, GLP-1 inhibitors, insulin, or sulfonylureas (in no order of preference) as third-line agents, depending on the choice of second-line agent. To reduce the possibility for adverse effects in combining multiple oral agents, the third line agent should share a similar mechanism of action to the agents the patient is already taking. Insulin should be used in circumstances where the degree of hyperglycemia is sufficiently high that it is unlikely an additional oral agent will be effective.

International Diabetes Federation, 2012

<http://www.idf.org/sites/default/files/IDF-Guideline-for-Type-2-Diabetes.pdf>

When the patient does not reach HbA1c target using dual therapy, IDF recommends adding a third oral agent or a basal or premixed insulin. If adding an oral agent, AG-inhibitors, DPP-4 inhibitors, TZDs, or GLP-1 receptor agonists are recommended.

National Institute for Health and Care Excellence, 2009

<http://www.nice.org.uk/guidance/cg87/chapter/guidance>

If a combination of metformin and a sulfonylurea is insufficient to lower HbA1c below 7.5%, a DPP-4 inhibitor can be added as a third-line therapy. DPP-4 inhibitors should only be continued if the patient shows a reduction of at least 0.5 percentage points in HbA1c over a period of 6 months. A GLP-1 can be added as third line in patients who have a body mass index (BMI) of at least 35 accompanied by specific psychological or medical problem associated with weight; patients with a BMI of at least 35 when insulin therapy would impose significant occupational implications; or when weight loss would benefit other comorbidities. Insulin should be considered over addition of a third oral agent for patients on dual therapy with significant hyperglycemia.

4.3 Initiating Insulin and Insulin Choice

American Academy of Clinical Endocrinologists, 2013

<https://www.aace.com/files/consensus-statement.pdf>

Insulin should be considered for patients with HbA1c >8%, patients who are currently on two or more oral medications, patients on GLP-1 therapy, or patients with a long disease history, as these groups are not likely to reach their target HbA1c with additional oral medications. Patients initially presenting with an HbA1c >9% at time of diagnosis may also be considered for insulin therapy as a *first line* treatment. AACE recommends that, in general, patients start on a single daily dose of basal insulin in combination with the patient's existing regimen of oral agents. Dosing should be individualized and regularly adjusted. Premixed insulin can also be considered, but may pose increased risk for some patients. Basal insulin analogues are recommended over NPH insulin, due to a decreased risk of hypoglycemia.

American Diabetes Association/European Association of for the Study of Diabetes, 2012

http://care.diabetesjournals.org/content/37/Supplement_1/S14.full

ADA/EASD suggest introducing a single daily injection of basal insulin when appropriate. Insulin therapy should be strongly considered at time of diagnosis in cases of significant symptomatic hyperglycemia. Insulin should also be used in place of a third oral agent in circumstances where the degree of hyperglycemia is sufficiently high that an additional oral agent is unlikely to bring HbA1c to target.

ADA/EASD suggests that insulin analogues may reduce risk of hypoglycemia as compared to NPH, but notes that they have not been shown to differ significantly from human insulin in lowering HbA1c.

International Diabetes Federation, 2012

<http://www.idf.org/sites/default/files/IDF-Guideline-for-Type-2-Diabetes.pdf>

Insulin should be added when oral blood glucose lowering medications and lifestyle interventions are not sufficient to maintain target HbA1c. Insulin should be introduced at low doses, and dosing should be adjusted upwards as necessary. Patients should be started on basal insulin, such as NPH, insulin glargine, or insulin detemir, or on a premixed insulin.

National Institute for Health and Care Excellence, 2009

<http://www.nice.org.uk/guidance/cg87/chapter/guidance>

Insulin should be considered over addition of a third oral agent for patients on dual therapy with significant hyperglycemia. Patients should be started on human NPH insulin injected once or twice daily, depending on need. An insulin analog may be considered if the patient needs assistance from a health care professional for injection, if the person is at high risk of recurrent hypoglycemic episodes, if the person would otherwise need twice-daily NPH insulin in combination with glucose-lowering drugs, or if the person is unable to use devices needed to inject NPH insulin. Patients may switch from NPH to a long acting analog if they experience recurrent hypoglycemia regardless of whether or not they reach their HbA1c target.

4.4 Strategies for Management and Monitoring

Insulin Pumps

American Academy of Clinical Endocrinologists/American College of Endocrinology, 2014

<https://www.aace.com/files/insulin-pump-management-cs.pdf>

Insulin pumps may be suitable for some insulin-requiring patients with intensively managed type 2 diabetes. Type 2 diabetes patients should be C-peptide positive, but with poor glycemic control on a basal/bolus injection program. They should also have a significant “dawn phenomenon,” or an overnight surge in hormones that can cause glucose levels to spike. Pumps are intended for patients requiring four or more insulin injections daily, as well as four or more glucose measurements. Pumps may be most useful to patients with an erratic lifestyle, such as individuals who frequently travel long distance, perform shift work, or have unpredictable schedules that result in irregular meal timing. Ideal candidates for an insulin pump are those that are currently adherent to their current therapy but are unable to meet their HbA1c target, are struggling with hypoglycemia, or are looking for more ease and flexibility in achieving their HbA1c target.

International Diabetes Federation, 2012

<http://www.idf.org/sites/default/files/IDF-Guideline-for-Type-2-Diabetes.pdf>

IDF suggests that the evidence is insufficient to formulate a recommendation for insulin pump use in type 2 diabetes, though it recognizes its potential on a case by case basis.

Continuous Glucose Monitoring

Endocrine Society, 2011

<https://www.endocrine.org/~media/endosociety/Files/Publications/Clinical%20Practice%20Guidelines/FINAL-Standalone-Color-CGM-Guideline.pdf>

While the Endocrine Society does not offer guidelines specific to type 2 diabetes patients, they do suggest that continuous glucose monitoring may be of benefit to some patients.

American Academy of Clinical Endocrinologists, 2010

<https://www.aace.com/files/continuousglucosemonitoring.pdf>

The AACE does not offer guidelines specific to the use of continuous glucose monitors in patients with type 2 diabetes.

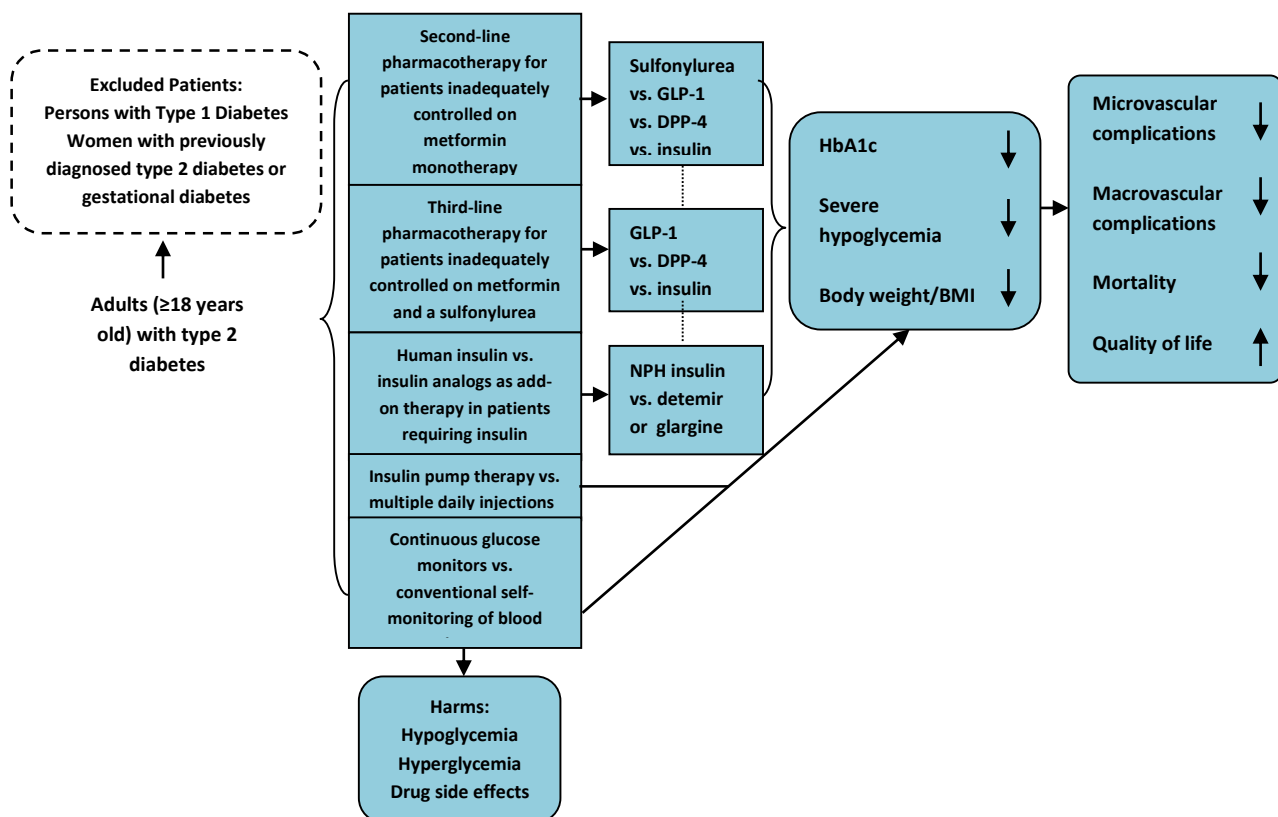
American Diabetes Association

The ADA does not provide clinical guidelines for the use of continuous glucose monitors in patients with type 2 diabetes.

5. Evidence Review

The goal of the evidence review was to evaluate the comparative effectiveness and value of certain treatment options for the management of type 2 diabetes. The sections that follow are organized around five scoping domains of primary interest for this review. These include the comparative effectiveness of (1) use of human insulin vs. insulin analogs as add-on therapy to first-line metformin; (2) second-line pharmacotherapy among patients with inadequate glycemic control on metformin monotherapy; (3) third-line pharmacotherapy among patients with inadequate glycemic control on metformin and sulfonylurea combination treatment; (4) insulin pump therapy vs. multiple daily injections; and (5) continuous glucose monitors vs. conventional self-monitoring of blood glucose for type 2 diabetes management. The comparisons and outcomes of interest are depicted in the analytic framework below. It was anticipated that most available evidence would be restricted to intermediate outcomes such as HbA1c and changes in body weight, so a series of conceptual links would be required to judge the potential effects on longer-term outcomes such as microvascular and macrovascular complications as well as mortality.

Analytic Framework: Type 2 Diabetes Management



Given the very broad scope of this review, we relied on published and authoritative systematic reviews as a starting point for each research domain, as listed below:

- Long-acting insulin analogues versus (human isophane insulin) for type 2 diabetes mellitus (Horvath [Cochrane], 2009)
- Second-line pharmacotherapy for type 2 diabetes (CADTH, 2013)
- Third-line pharmacotherapy for type 2 diabetes (CADTH, 2013)
- Methods for insulin delivery and glucose monitoring (Golden [AHRQ], 2012)

To supplement these reviews, we also identified any additional RCTs, comparative cohort studies, or case series that have been published within three months prior to the end of each literature search (e.g., February 2012 for the CADTH reviews) through August 2014. Case series were limited to those involving 50 or more patients. Additional study exclusions were individualized to each scoping domain, as listed below. Studies were excluded if in their methods or entry criteria:

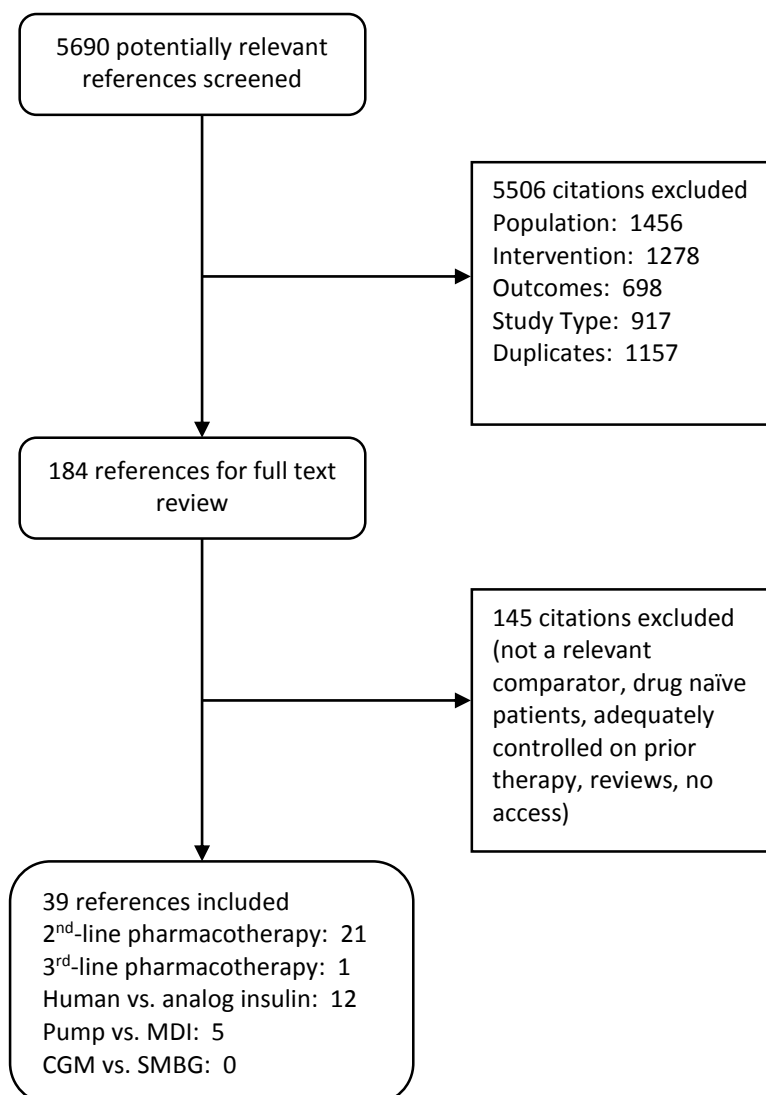
- Inadequate glycemic control was defined as HbA1c <6.5% or fasting plasma glucose <7 mmol/L or two-hour postprandial glucose <10 mmol/L for second- and third-line pharmacotherapy
- Treatment durations were less than 24 hours for evaluation of insulin pump therapy vs. continuous glucose monitoring
- Patients pricked their finger less than three times per day for comparisons of continuous glucose monitoring vs. self-monitoring of blood glucose
- Patients subcutaneously injected insulin less than three times per day for comparisons of insulin pump therapy vs. multiple daily injections

We sought published studies and systematic reviews of antidiabetic therapy among adult (≥ 18 years old) patients with type 2 diabetes. We excluded evidence that evaluated therapies for mixed study populations of type 1 and type 2 patients unless outcomes were reported for a type 2 subgroup, or more than half of the subjects were diagnosed with type 2. We did not evaluate studies conducted specifically in pregnant women with previously diagnosed type 2 or gestational diabetes, or children/adolescents. Interventions of interest included any medications classified as a sulfonylurea, DPP-4, GLP-1, or basal insulin added to metformin monotherapy; any medications classified as a DPP-4, GLP-1, or basal insulin added to metformin and sulfonylurea combination treatment; NPH insulin or the long-acting insulin analogs detemir or glargine; insulin pumps or multiple daily injections via subcutaneous injection; and continuous glucose monitoring or traditional blood glucose monitoring devices. For the purposes of scoping questions 1 and 2, patients that were inadequately controlled on metformin or metformin+sulfonylurea combination therapy, respectively, were eligible for inclusion. Importantly, the CADTH reviews originally specified class-, individual drug-, and drug/dose-level meta-analyses, but found that treatment effect estimates were comparable across the three types of analyses and the greatest precision was

seen with the class-level meta-analysis (CADTH 2010; CADTH 2013). We therefore adopted a similar approach for our supplemental review and economic model (see Section 6 for economic analyses). Finally, we did not assess evidence on rapid or short-acting insulins or insulin analogs, as most type 2 patients typically use long-acting insulins as add-on therapy with one or more oral medications.

Primary outcomes of interest included glycemic control as measured by glycosylated hemoglobin (HbA1c); rate of severe hypoglycemic events; changes in body weight/BMI, incidence of diabetes-related complications including microvascular (e.g., retinopathy, neuropathy) and macrovascular (e.g., coronary heart disease) complications, myocardial infarction, stroke, renal failure, or amputations; and mortality. We also collected information on adherence and health-related quality of life where available. Further details on the literature search strategy for each scoping question can be found in Appendix A.

Figure 1. PRISMA diagram.



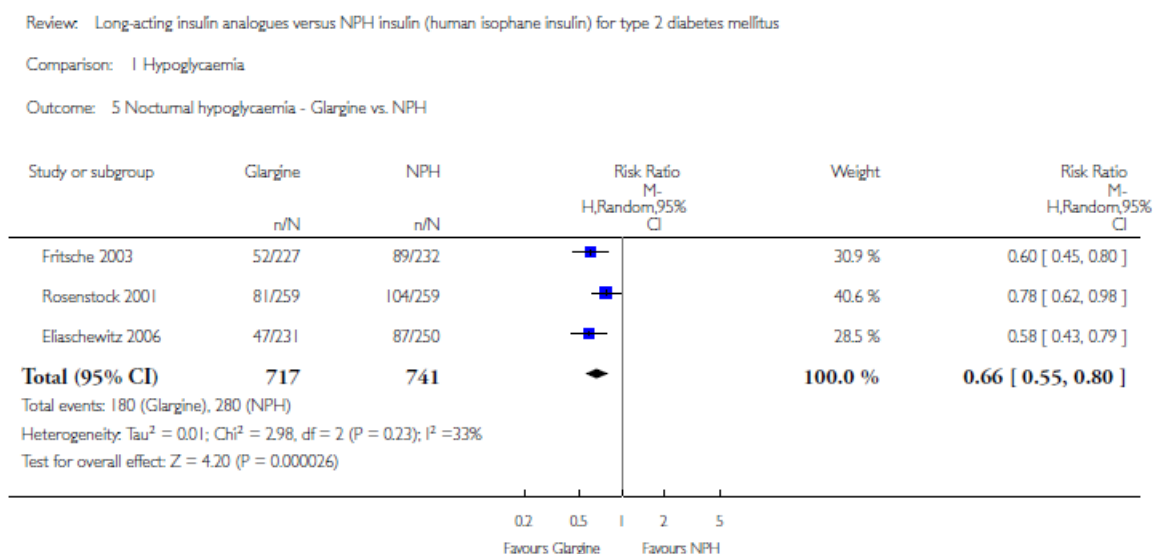
5.1 Long-acting Insulin Analogs versus NPH Insulin

Long-acting insulin analogs (i.e., insulin glargine and insulin detemir) compared to NPH insulin have shown little added benefit with regard to clinically relevant outcomes for type 2 diabetes. A Cochrane review found no differences between either insulin glargine or detemir compared with NPH insulin for glycemic control, changes in body weight, or adverse events, with the exception of a reduction in nonsevere hypoglycemia (i.e., symptomatic or nocturnal events) for insulin analogs. No evidence regarding the differential impact of long-acting insulin analogs vs. NPH insulin on long-term outcomes such as mortality, diabetes-related complications, and health-related quality of life were provided in these RCTs.

A total of eight RCTs were identified in the 2006 Cochrane review comparing NPH insulin to long-acting insulin analogs, with six for insulin glargine and two for insulin detemir (Horvath, 2009). There were no significant between-group differences for HbA1c levels, rates of severe hypoglycemia, or changes in body weight. There was a significant reduction in symptomatic but nonsevere (i.e., with typical symptoms such as palpitations and sweating but without requirement for third-party assistance to restore blood glucose levels) as well as nocturnal hypoglycemia (i.e., recorded nighttime blood glucose ≤ 70 mg/dl but without symptoms) with insulin analogs; rates for nocturnal hypoglycemia are presented in Figures 2 and 3 on the following page. Approximately one-third of patients in the NPH arms had episodes of nocturnal hypoglycemia vs. 18% among those receiving insulin analogs. However, the review also found that all eight RCTs were of relatively poor quality, primarily because of poor reporting of methods of randomization and concealment as well as use of equivalence or noninferiority designs in many of these studies. In addition, no study evaluated the long-term impact of insulin use on diabetes-related complications, mortality, or health-related quality of life. The review concluded that insulin analogs offer a “minor clinical benefit” at best, and suggested a cautious approach to their use in clinical practice.

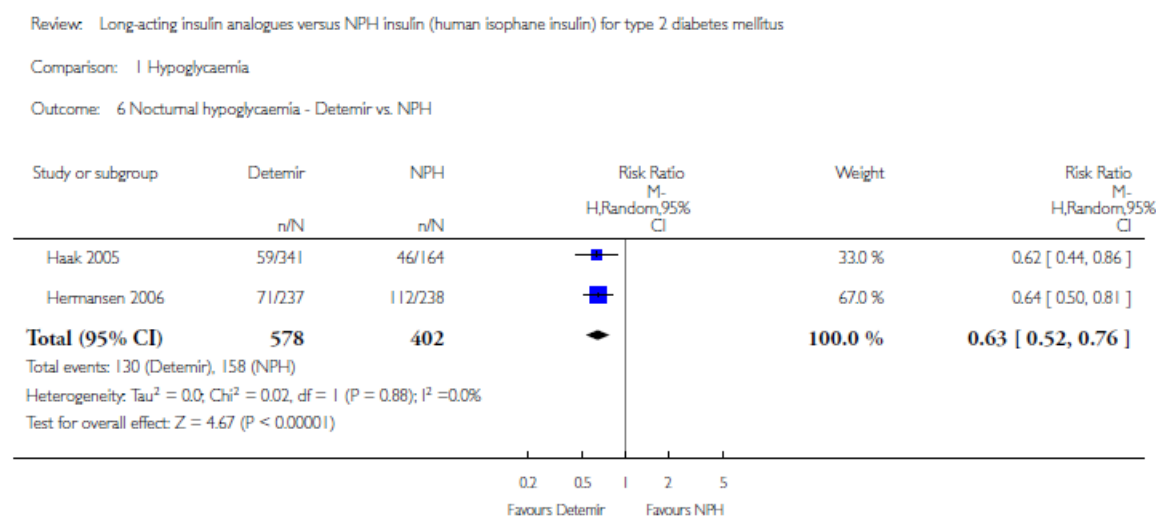
The relative clinical importance of hypoglycemia and the association of hypoglycemic events of varying severity to mortality, cardiovascular risks, and other long-term outcomes remains a topic of intense debate, as studies of intensive glycemic control in patients with cardiovascular disease have suggested a link between episodes of severe hypoglycemia and excess mortality (Frier, 2011). While nonsevere and asymptomatic nocturnal hypoglycemia have generally been felt to be of lower clinical consequence, some studies have suggested that these events may be correlated with lower productivity and fatigue (Brod, 2013). In addition, other studies have recorded instances of QT prolongation and arrhythmia during nocturnal hypoglycemic episodes (Landstedt-Hallin, 1999; Chow, 2014), but these studies have not documented a connection between episodes of arrhythmia and long-term or lasting damage.

Figure 2. Comparison of rates of nocturnal hypoglycemia – glargine vs. NPH.



Source: Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus (human isophane insulin) for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2007;2:CD005613.

Figure 3. Comparison of rates of nocturnal hypoglycemia – detemir vs. NPH.



Source: Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus (human isophane insulin) for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2007;2:CD005613.

We identified an additional six RCTs (three each for insulin glargine and insulin detemir) published after the Cochrane review, as well as a post-hoc analysis of a glargine RCT that was included in the Cochrane review. Major findings are summarized in the sections that follow.

Insulin Glargine vs. NPH

Three small RCTs published after the Cochrane review have produced similar findings to the original review with regard to hypo- and hyperglycemic events. One of these studies (Forst, 2010) randomized 28 insulin-naïve type 2 patients with a mean BMI of 30.7kg/m² and HbA1c of 6.5-8.5% to initiate different formulations of insulin to replace a sulfonylurea as add-on therapy to metformin and found that both HbA1c levels and the rate of hypoglycemia episodes were comparable between NPH and insulin glargine at the end of the three-month study. A cross-over study (De Mattia, 2009) of 20 patients, mean age 59.4 years and a diabetes duration of at least five years, reported statistically-significant reductions in HbA1c from baseline in both arms, but no difference between them; changes in body weight also did not differ between groups. Several cases of hypoglycemia were reported for both groups, but none of the episodes was considered severe.

The third RCT (Wang, 2007), comprising 24 patients, mean age 56 years, with an average diabetes duration of 10 years, found that evening injections of insulin glargine stabilized daily blood glucose fluctuations levels better than NPH insulin and was associated with a decrease in nocturnal hypoglycemic events (6.3% vs. 50.0% for NPH, $p=.028$). No significant differences in HbA1c levels were observed in this study.

Finally, a recently published post-hoc analysis (Vahatalo, 2014) of an RCT included in the Cochrane review randomized 109 insulin-naïve patients with poor glycemic control (mean HbA1c of 9.6% with 90% on sulfonylurea and metformin combination therapy) based on fasting or postprandial (post-meal) hyperglycemia to NPH insulin or insulin glargine and found no significant difference with regard to glycemic control between the two groups; neither was there a difference in weight gain after adjusting for baseline BMI. Although more hypoglycemic events were observed in the NPH group (1.4% vs. 0.6% for glargine, $p=.05$), none of these events was categorized as severe, and the difference in overall events disappeared after three months of treatment.

Insulin Detemir vs. NPH

We identified three post-Cochrane review RCTs comparing insulin detemir to NPH insulin, one of which was a cross-over study. One RCT (Fajardo Montañana, 2008) evaluated six month outcomes of 271 patients with a mean age of 62 and average diabetes duration of 16 years to determine if NPH in morning and evening doses, or detemir following the same regimen, yielded different outcomes. While detemir was associated with significantly less weight gain (0.4 kg vs. 2.0 kg for NPH, $p<0.0001$), changes in HbA1c and the proportion of patients reaching target without hypoglycemia did not statistically differ between groups. Another large RCT (Philis-Tsimikas, 2006) compared a pre-breakfast injection of detemir with an evening injection of detemir or NPH insulin among 504 patients (mean age 58.5 years, mean BMI 30, average diabetes duration of 10 years), who were followed for 20 weeks. No between-group differences with regard to HbA1c changes,

incidence of severe hypoglycemia, or nocturnal hypoglycemia episodes were reported, but weight gain was 1.2kg, 0.7kg, and 1.6 kg for morning detemir, evening detemir, and evening NPH, respectively, with a significant between-group difference for detemir vs. NPH when administered as evening doses ($p=0.005$).

Finally, a small cross-over study (Hendriksen, 2012) in which 24 patients with a mean HbA1c of 7.6% and mean body weight of 93.1kg were initially randomized to treatment with NPH insulin or insulin detemir for 8 weeks and then switched to the opposite treatment for an additional 8 weeks, found significant weight loss for detemir after only one week of treatment compared with NPH insulin ($-0.8 \pm 0.2\text{kg}$ vs. $0.4 \pm 0.2\text{kg}$, $p<0.01$). However, in contrast to the previously described RCTs, HbA1c was significantly higher for detemir after 8 weeks of treatment (8.2% vs. 7.6% for NPH, $p<0.01$).

In summary, evidence from both the original Cochrane review as well as subsequent clinical studies suggest no substantial difference in the clinical benefit of long-acting insulin analogs relative to NPH insulin when used as add-on therapy in patients with type 2 diabetes. Because the true level of harm associated with nocturnal and daytime nonsevere hypoglycemic episodes remains unknown, the overall comparative net health benefit (i.e., effectiveness and harms taken together) of analog vs. human insulin appears comparable or perhaps incremental. The degree of certainty about net benefit is moderate, given that the evidence base of 14 RCTs has produced relatively consistent findings.

5.2 Second-Line Pharmacotherapy

There have been very few head-to-head comparative trials of DPP-4 inhibitors, sulfonylureas, GLP-1 agonists, and insulin as second-line agents for patients with continuing hyperglycemia on metformin. A systematic review by the Canadian Agency for Drugs and Technologies in Health (CADTH) of randomized control trials found no adequately powered trials to assess differences in mortality or the development of diabetes-related complications. The review did note statistically significant reductions in HbA1c vs. placebo across all major drug classes analyzed, with the greatest reductions for GLP-1 agonists and insulin. Although severe hypoglycemic events were uncommon across all treatment combinations (1% or less), the insulins and sulfonylureas were associated with higher rates of severe hypoglycemia. Insulins and sulfonylureas were associated with increases in body weight, whereas GLP-1s and DPP-4 were associated with weight-loss and weight-neutral outcomes, respectively. Subsequently published studies have produced similar findings.

An original 2010 CADTH review of second-line pharmacotherapy as well as a 2013 update (CADTH, 2013a) identified a total of 72 placebo- or active-control RCTs involving the agents of interest for this evaluation. Findings from a network meta-analysis of these trials for mean change in HbA1c, change in body weight, and rate of overall hypoglycemia can be found in Figure 4 on page 37. The

review found no adequately powered RCTs to assess the impact of second-line pharmacotherapy on diabetes-related complications or mortality.

All drug combinations produced statistically-significant reductions in mean HbA1c levels relative to control therapy. Among the drug classes of interest for this evaluation, GLP-1 agonists (mean change: -0.96%; 95% CI: -1.13%, -0.80%) and basal insulin (-0.91%; 95% CI: -1.16%, -0.67%) produced the greatest reductions, although sulfonylureas and DPP-4 inhibitors also produced substantial average reductions (-0.79% and -0.69%, respectively). Sulfonylureas and basal insulins were associated with the largest levels of weight gain (means of 2.1 and 1.7 kg, respectively), while use of DPP-4s did not result in statistically-significant change in weight and GLP-1 agonists were associated with a statistically-significant reduction in body weight (mean: -1.8 kg; 95% CI: -2.9, -0.8).

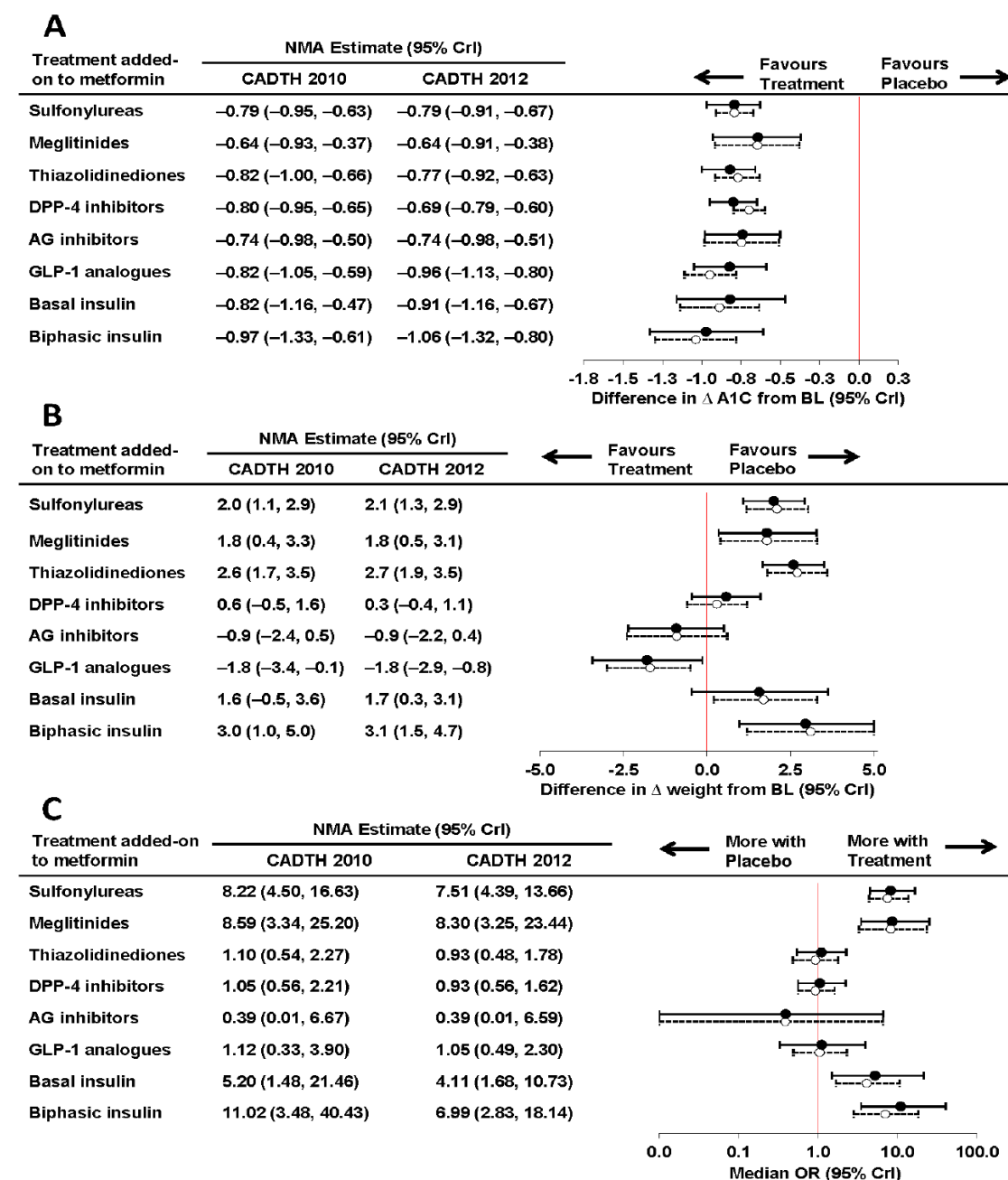
As noted in Figure 4 on the following page, both sulfonylureas and basal insulins were associated with a statistically-significant increase in the rate of overall hypoglycemia (i.e., of any severity), with odds ratios of 7.5 and 4.1 respectively. However, when hypoglycemia events were restricted to those categorized as severe (i.e., requiring medical intervention), the absolute rates were low (1% or less) for all drug classes. In fact, network meta-analysis was not feasible because severe hypoglycemia events were too infrequent. Nevertheless, pairwise comparisons suggested an increased risk for sulfonylureas vs. placebo and DPP-4 inhibitors (odds ratios of 2.2 and 12.2, respectively) and a reduced risk for GLP-1 agonists vs. placebo and basal insulins (odds ratios of 0.3 for both comparisons). Data were insufficient for any other pairwise comparison.

Findings from more recent studies are summarized in the sections that follow, organized by pharmacologic agent.

DPP-4 Inhibitors

We identified one RCT directly comparing two newer second-line agents, an investigational agent in the DPP-4 inhibitor class and a GLP-1 agonist (Bergenstal, 2012). A total of 666 type 2 diabetes patients inadequately controlled on metformin with a mean HbA1c value of 8.0% and average weight of 92.4 kg were allocated to three add-on treatment groups; 10mg of the GLP-1 taspoglutide once weekly (QW); 20mg of GLP-1 therapy QW; 100mg of the DPP-4 sitagliptin once daily (QD); or placebo. There was a significant reduction in HbA1c for both GLP-1 groups compared to DPP-4 (-1.03% and -1.18% vs. -0.66% for DPP-4, $p < 0.001$), as well as a reduction in body weight (-1.6kg and -2.4kg vs. -0.5 for DPP-4, $p < 0.001$) after 52 weeks. However, discontinuation of GLP-1 therapy due to adverse events (i.e., nausea, vomiting, diarrhea, and upper abdominal pain) was high in this study (21-28% in the two GLP-1 groups vs. 7 and 11% for DPP-4 and placebo, respectively). There were no cases of severe hypoglycemia reported.

Figure 4. Forest plot of all antidiabetic drugs added as second-line pharmacotherapy.



Δ = change; A1C = glycated hemoglobin; AG = alpha-glucosidase; BL = baseline; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; NMA = network meta-analysis; OR = odds ratio.

Note: Forest plots comparing the results of the original (●) and updated (○) CADTH network meta-analyses for change from baseline in A1C (A), change from baseline in body weight (B), and overall hypoglycemia (C).

CADTH 2010 (●) and Updated Network Meta-Analyses (○) for A1C (%) (A),
Weight (kg) (B), and Overall Hypoglycemia (C)

Source: Canadian Agency for Drugs and Technologies in Health. Second-line pharmacotherapy for type 2 diabetes – Update. Ottawa: The Agency;2013.

Several studies comparing a DPP-4 to a sulfonylurea have also been published since the most recent CADTH review. One study (Gallwitz, 2012a) randomized 1,519 overweight patients (54% male; mean baseline HbA1c 7.7%) to a DPP-4 inhibitor (linagliptin) or a sulfonylurea (glimepiride) plus metformin. The study found that the sulfonylurea was associated with a statistically significant but clinically modest mean reduction in HbA1c relative to DPP-4 therapy, but an increased risk of severe hypoglycemia vs. the DPP-4. Most importantly, however, DPP-4 patients experienced fewer cardiovascular events over two years of active treatment (12 vs. 26 for sulfonylurea; relative risk 0.46, 95% CI 0.23–0.91, $p=0.0213$); these events were primarily nonfatal MI and nonfatal stroke. The authors acknowledge that the study duration was too short for a comprehensive assessment of the impact of treatment on cardiovascular risks, and that the study was not powered to detect differences in these events. They suggest that possible protective vascular effects of DPP-4 inhibitors as well as the potential for increased cardiovascular risk with sulfonylureas might both be at play in this outcome.

A smaller RCT comparing the DPP-4 sitagliptin to a sulfonylurea (glimepiride) in 33 patients (Kim, 2013) found comparable reductions in HbA1c between groups and no statistical differences in the rate of hypoglycemia; the study was underpowered to detect differences in adverse events, however.

Similar outcomes were found in a retrospective comparative cohort (Gitt, 2013). Subjects in this analysis were identified from a registry of 884 patients who were at least 40 years old and divided into two subgroups – one taking a DPP-4 and one taking a sulfonylurea, both added to metformin. Although DPP-4s were associated with a similar reduction in HbA1c compared to sulfonylurea, at the end of the 12-month study there were fewer hypoglycemic events for DPP-4s (OR 0.32, 95% CI 0.19-0.54, $p=0.05$) relative to sulfonylureas, as well as significantly fewer non-fatal cardiovascular events, including stroke and transitory ischemic attacks (0.2 vs. 2.0%; $p<0.05$).

GLP-1 Agonists

In addition to the above-described direct comparison of GLP-1 and DPP-4 therapy (Bergenstal, 2012), we identified one additional RCT (Gallwitz, 2012b) assessing the comparative effectiveness of the GLP-1 agonist exenatide plus metformin versus a sulfonylurea (glimepiride) added to metformin for patients with inadequate glucose control on metformin alone. A total of 1,029 patients with a mean age of 56 and mean HbA1c of 7.5% were followed for an average of two years. Patients in the GLP-1 group were more successful in reducing their HbA1c to less than 7% compared to those receiving sulfonylurea therapy (31% vs. 7%, $p<0.0001$) and there was a statistically-significantly greater reduction in body weight for patients on GLP-1 after four weeks, a difference that was maintained for the study duration ($-3.32\text{kg} \pm 5.45\text{kg}$ vs. $1.15\text{kg} \pm 4.18$ for sulfonylurea, $p<0.0001$). More study participants discontinued therapy in the GLP-1 group than in the sulfonylurea group because of adverse events (9.6% vs. 3.3%; $p=0.001$); however, the difference was only significant

between groups in the first six months of treatment. One case of severe hypoglycemia was reported in the GLP-1 group but the between-group difference was not significant.

Insulin

We identified two RCTs published subsequent to the latest CADTH review that compared insulin to an oral antidiabetic agent as add-on to metformin. One RCT (Aschner, 2012) assigned subjects with mean uncontrolled HbA1c of 8.5% to receive either insulin glargine or a DPP-4 and found that the mean reduction in HbA1c was significantly greater for patients on insulin after 24 weeks of treatment (-1.72% vs. -1.13% for the DPP-4, $p < 0.0001$); however, the DPP-4 group had a reduction in BMI while those on insulin had an increase (-1.08kg/m² vs. 0.44kg/m², 95% CI 0.93–2.09, $p < 0.0001$). Another RCT (Moon, 2013) assessed patients on metformin with mean BMI 34.3 and HbA1c 8.8% who received insulin glargine or a sulfonylurea and found a between-group difference for changes in body weight in favor of the sulfonylurea (1.7kg vs. 0.0kg for sulfonylurea, $p = 0.02$), though there was no significant difference between the two groups with respect to reduction in HbA1c.

In addition to the available RCTs, we identified a large retrospective comparative cohort study (Roumie, 2014) that assessed long-term outcomes for nearly 15,000 veterans with type 2 diabetes who added any type of insulin (long-acting, premixed, or short/fast-acting) or a sulfonylurea (glyburide, glipizide, or glimepiride) to metformin over a median follow-up of 14 months. After propensity matching to control for differences in demographic and clinical characteristics between groups, insulin combination therapy was associated with a significantly greater risk of all-cause mortality (33.7 vs. 22.7 per 1000 person-years, HR 1.44, 95% CI 1.15-1.79, $p = 0.001$), as well as an increased risk of a composite of nonfatal MI, stroke-related hospitalization, or death from any cause (42.7 vs. 32.8 per 1000 person-years, HR 1.30, 95% CI 1.07-1.58, $p = 0.009$). Because this was a retrospective study based on datasets with limited clinical information, the authors allow for the possibility that there might have been residual confounding for which they could not control. For example, patients receiving insulin might have had greater frailty or increased diabetes severity in ways that are difficult to measure. However, they also noted that these findings are consistent with those from UKPDS and trials of intensive glycemic control (e.g., ACCORD) that failed to show reduced rates of macrovascular complications with insulin vs. oral agents and in some cases, increased risk.

In summary, the evidence suggests that second-line pharmacotherapy with metformin and GLP-1 agonists provides an incremental comparative net health benefit relative to the combination of metformin and sulfonylureas, based on greater reductions in HbA1c levels, favorable impact on body weight, and very low risk of severe hypoglycemia, balanced against a higher rate of discontinuation due to gastrointestinal side effects. DPP-4 inhibitors also carry a low risk of severe hypoglycemia and have little impact on body weight, but appear to have a less pronounced impact

on HbA1c, all of which suggests a comparable net health benefit relative to sulfonylureas. Finally, basal insulin with either NPH or insulin analogs appears to lower HbA1c more than sulfonylureas but has similar impacts on body weight and hypoglycemia risk, suggesting a comparable or incremental comparative net health benefit. We consider the level of certainty moderate for all of these comparisons, however, as despite numerous placebo-controlled trials there remains a paucity of head-to-head evidence and, while observational studies suggest differences in cardiovascular and mortality risks with certain treatment strategies in patients inadequately controlled on metformin, such evidence cannot yet be considered conclusive.

5.3 Third-Line Pharmacotherapy

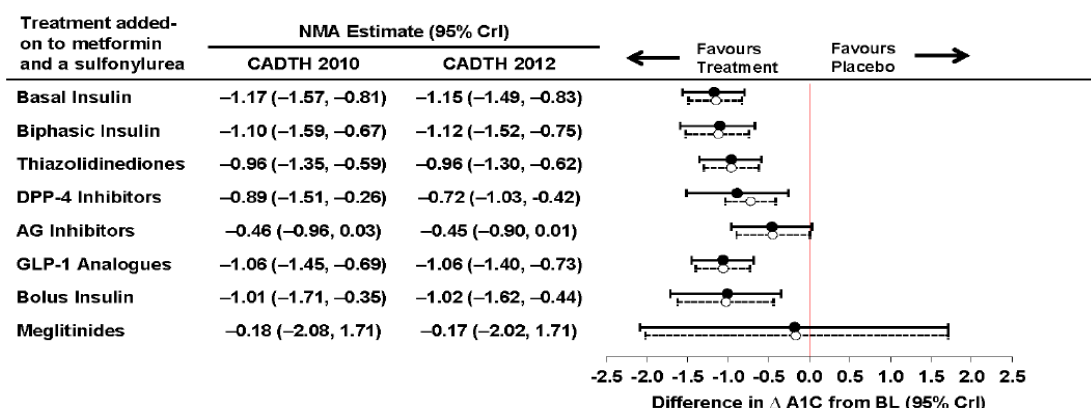
Another CADTH systematic review of randomized control trials comparing third-line pharmacotherapy added to metformin and a sulfonylurea for type 2 diabetes found statistically significant reductions in HbA1c across all drug combinations, with the most significant reduction with insulins. The addition of GLP-1s was associated with reductions in HbA1c similar to those of basal insulin, but with significant weight loss compared to other combination therapies. Basal insulin and DPP-4 inhibitors were associated with a significant excess risk of overall hypoglycemia relative to placebo. However, as with second-line pharmacotherapy, severe hypoglycemia was relatively rare even for three-drug combinations (<2% in most circumstances), and many comparisons could not be made due to a lack of events in one or both study arms.

The literature search conducted by CADTH comparing the addition of a third-line medication to metformin and sulfonylurea combination therapy yielded a total of 3 RCTs for DPP-4s, 7 for GLP-1s, and 21 for basal insulin (CADTH, 2013b). There were no significant differences between the classes as add-on to metformin and sulfonylurea; all drugs produced significant reductions in HbA1c, with basal insulin producing the greatest effect (-1.15%, 95% CI -1.49% to 0.83%) (See Figure 5 on the following page). Basal insulin was associated with a significant increase in body weight (1.9kg, 95% CI 0.7 to 3.0) while DPP-4s were not associated with any statistically-significant changes in body weight and GLP-1s produced significant weight loss (-1.6kg, 95% CI -2.8 to -0.4). The incidence of long-term diabetes-related complications were not reported in any included study.

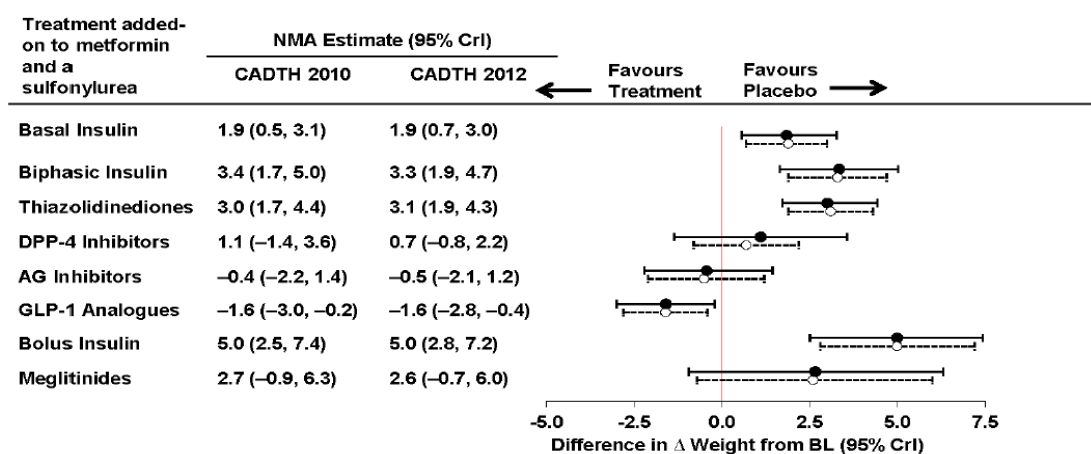
Figure 5. Forest plot of all antidiabetic drugs added as third-line pharmacotherapy.

CADTH 2010 (●) and Updated Network Meta-Analyses (○) for A1C (%) (A), Weight (kg) (B)

A



B



A1C = glycated hemoglobin; AGI = alpha-glucosidase inhibitor; BL = baseline; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptid-1e; NMA = network meta-analysis.
 Note: Forest plots comparing the results of the original (●) and updated (○) CADTH network meta-analyses for change from baseline in A1C (A) and change from baseline in body weight (B).

Source: Canadian Agency for Drugs and Technologies in Health. Third-line pharmacotherapy for type 2 diabetes – Update. Ottawa: The Agency;2013.

We identified only one additional comparative study published after the CADTH review that focused on the agents of interest as third-line pharmacotherapy. This was a placebo-controlled RCT (Moses, 2013) of the DPP-4 inhibitor saxagliptin added on to metformin and a sulfonylurea in 257 overweight type 2 patients with a mean weight of 81.5kg (BMI 29.2) and a baseline HbA1c of 8.3%.

The DPP-4 produced a statistically-significantly greater reduction in HbA1c from baseline over 24 weeks relative to placebo (between-group difference: -0.66%, 95% CI -0.86% to -0.47%). Those on the DPP-4 gained a small amount of weight while those on placebo had a small weight loss (mean 0.2kg vs. -0.6kg for placebo, $p=0.0272$). No severe hypoglycemic events occurred in either group.

In summary, as with second-line pharmacotherapy, the use of GLP-1s in combination with metformin and a sulfonylurea provides a comparable reduction in HbA1c relative to the combination of metformin, a sulfonylurea, and basal insulin, but has a favorable impact on body weight and hypoglycemia risk, suggesting an incremental net comparative health benefit. In contrast, DPP-4 inhibitor-based combinations produce slightly inferior reductions in HbA1c and have similar effects on hypoglycemia risk relative to a third-line combination with basal insulin; although DPP-4s do not significantly change body weight (while insulin results in a ~2 kg increase on average), the overall net benefit appears comparable. The level of certainty in these judgments of benefit should be considered moderate due to a lack of evidence on the impact of these combinations on long-term outcomes such as diabetes-related complications and mortality.

5.4 Insulin Pump Therapy and Multiple Daily Injections

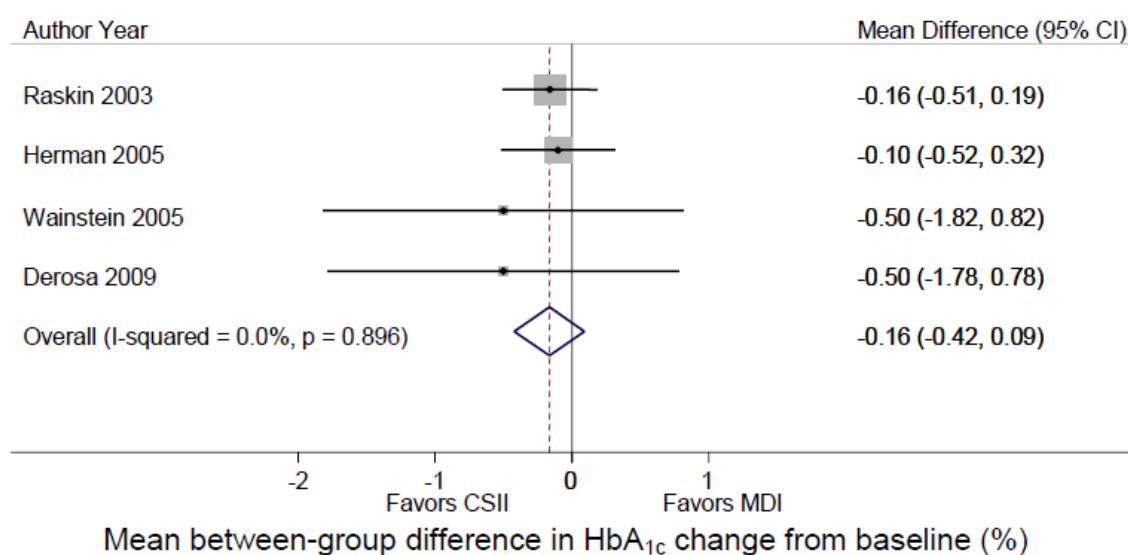
Few clinical trials have evaluated the use of insulin pumps compared to multiple daily injections for type 2 diabetes patients on insulin treatment. A recent systematic review and meta-analysis conducted by the Agency for Healthcare Research and Quality (AHRQ) found no differences in glycemic control or weight gain between insulin delivery approaches, and insufficient evidence on the impact of pumps vs. multiple daily injections on hypoglycemic events as well as mortality and other clinical outcomes. Although recent trials have provided some evidence of clinical benefit, these have suffered from methodological concerns and use of nonstandard outcomes.

Four RCTs, one of which was a crossover study, were assessed in the AHRQ review comparing insulin pumps with multiple daily injections (MDI) (Golden, 2012). The review concluded that there was moderate evidence of no significant difference in glycemic control between insulin delivery approaches (see Figure 6 on the next page), a low level of evidence suggesting no differences in weight gain or severe hypoglycemia, and insufficient evidence to determine differences in outcome with regard to nocturnal hypoglycemia, diabetes-related complications, or mortality.

We identified four additional RCTs evaluating the use of insulin pumps compared to multiple daily injections, as well as a large case series, since the publication of the AHRQ study. The most recently published RCT (Reznik, 2014) was an open-label study that included 495 patients, mean age 56 years with an average diabetes duration of 15 years, who were inadequately controlled on multiple daily injections of high doses of insulin (on average, four injections daily, up to 220 IU per day). The study found a significant between-group difference for reduction in HbA1c in favor of pump

treatment (-0.7%, 95% CI -0.9 to -0.4, $p < 0.0001$). There was no significant difference in changes in body weight between groups, and only one case of severe hypoglycemia, which occurred in the multiple-injections group. Mean total daily insulin dose for this group was significantly higher than among insulin pump users (112 IU vs. 97 IU, $p < 0.0001$). These results should be viewed with caution, however, as this study was subject to several important limitations. For one, there was substantial study dropout during the pre-randomization “run-in” phase (164 patients) as well as post-randomization (23 patients). In addition, one study center was dropped due to repeated protocol violations. Finally, patients in the multiple-injections group tested their blood glucose less frequently than those in the pump group, suggesting that knowledge of treatment assignment may have affected patients’ interest in maintaining glycemic control (Choudhary, 2014). In addition, in both groups, the average number of daily tests (3.1-3.8) was below the standard of care for patients injecting multiple times daily, which may have also affected study results (Reznik, 2014).

Figure 6. Between-group differences in changes in HbA_{1c} for insulin pumps vs. MDI among adults with type 2 diabetes.



Source: Golden SH et al. Methods for insulin delivery and glucose monitoring: comparative effectiveness. AHRQ Publication No. 12-EHC036-EF.

Reduction in HbA_{1c} and weight gain were not reported in the remaining RCTs; time to reach HbA_{1c} goal and mean daily insulin dose were assessed as primary outcomes in two studies, however. One RCT (Lv, 2013) observed 119 patients, mean age 61 years with an average diabetes duration of 10.5 years who were assigned to either one of two multiple-injection groups (insulin glargine and detemir) or a pump group and found that the multiple-injection groups took 2-3 days longer to reach their HbA_{1c} target (7.48 ± 2.51 days and 6.85 ± 2.28 days vs. 4.20 ± 1.34 days for pump, $p < 0.05$). Another RCT (Lian, 2013) randomized 150 subjects with an average age of 54 years and average diabetes duration of 9 years to insulin pump or multiple daily injections and found that

both short-term (use of pump until glycemic control achieved) and long-term (use after control achieved) insulin pump therapy was associated with less time to achieve glycemic control compared to intensive insulin treatment with multiple injections (3.8-3.9 days vs. 6.1-9.1 days for multiple injections, $p<0.05$). Both studies reported that insulin was administered at lower daily doses for pump groups, although the difference was only significant in one study. No cases of severe hypoglycemia were observed in either trial.

The final RCT (Luo, 2013) of 60 type 2 patients with a mean diabetes duration of 10.2 years and baseline HbA1c of 9% compared a sensor-augmented insulin pump (pump with integrated continuous glucose monitor) to conventional insulin pump therapy and multiple daily injections over six days. Although the sensor-augmented pump group saw a significant decrease in mean daily blood glucose after four days, the conventional pump and multiple-injection groups – including daily injections with basal, prandial, and biphasic insulin – had similar outcomes with regard to total daily insulin dose and mean daily glucose levels. No severe hypoglycemic events occurred during the study.

In addition to the available RCTs, we identified a retrospective case series (Choi, 2013) that selected 521 Korean patients with uncontrolled diabetes ($\geq 7\%$ HbA1c) and mean diabetes duration of 10 years enrolled in a diabetes center who were switched to insulin pump therapy from multiple daily injections and followed for one year. Median HbA1c decreased after 6 months of therapy and was maintained between 6.3%-6.5% for the remainder of the study ($p<0.0001$), with no reported cases of hypoglycemia. However, BMI significantly and continuously increased at a steady rate over the course of study follow-up (25.7 kg vs. 23.6 kg at baseline, $p<0.0001$).

Findings from the evidence base of eight RCTs suggests a moderate level of certainty that insulin pumps provide a comparable net health benefit to multiple daily injections in patients with type 2 diabetes, with similar effects on glycemic control, body weight, and hypoglycemia. While newer RCTs suggest better glucose-control performance with pumps, methodological concerns as well as use of short-term, nonstandard outcomes makes comparisons with older RCTs problematic.

5.5 Continuous Glucose Monitors versus Self-Monitoring of Blood Glucose

Data are extremely limited with regard to the potential added benefits from real-time continuous glucose monitors compared to traditional self-monitoring of blood glucose in patients with type 2 diabetes. A recent systematic review published by the Agency for Healthcare Research and Quality (AHRQ) reported no studies comparing these monitoring strategies in a type 2 population using insulin. We did not identify any subsequent studies in type 2 patients taking insulin, but did identify one industry-sponsored RCT in a population not taking insulin, which is provided for context.

The one RCT of real-time continuous glucose monitoring in a type 2 population (Vigersky, 2012) followed 100 military health beneficiaries with type 2 diabetes not using insulin (mean age 58 years, mean HbA1C 8.3%) to either real-time continuous glucose monitors (rt-CGM) or self-monitoring of blood glucose (SMBG) for 12 weeks; all patients were then followed for an additional 40 weeks at the end of the active monitoring period. There was a significant and consistent difference between the two groups in changes in HbA1c at 12, 24, 38, and 52 weeks, respectively (-1.0, -1.2, -0.8, and -0.8% vs. -0.5, -0.5, -0.5, and -0.2% in the SMBG group, $p=0.04$), with no severe hypoglycemia or significant between-group differences in body weight reported. Improvement was greatest among patients using the rt-CGM device for at least six weeks. A secondary analysis of this RCT (Fonda, 2013) identified five glucose response patterns of those using a rt-CGM and found that patients who viewed their display more frequently had tighter glycemic control than those who only intermittently viewed their device (23 vs. 15 times/day, $p=0.05$), suggesting that adherence to monitoring plays a factor into whether HbA1c levels improve.

Given that neither the original AHRQ review nor our subsequent search identified any comparative studies of continuous vs. conventional glucose monitoring in type 2 diabetes patients who are taking insulin, the evidence appears insufficient to determine whether continuous monitoring provides added clinical benefit for these patients.

6. Economic Evaluation

6.1 Previously Published Economic Studies

The published literature on the economic impact and potential cost-effectiveness of interventions for type 2 diabetes is vast; our initial search for economic evaluations yielded over 3,500 citations. The availability of long-term epidemiologic data on diabetes from cohorts such as the Framingham Heart Study has also allowed for the development and validation of models to simulate the outcomes and costs of type 2 diabetes management on a lifetime basis. These models have proliferated to such an extent that their ability to predict the development of diabetes-related complications and other events has been explicitly compared on multiple occasions (Palmer, 2013). For most measures, these models appear to perform (a) well when compared with robust external data, and (b) similarly when explicitly compared with each other (Hornberger, 2013). We summarize selected evaluations below, focusing on those sponsored by government agencies or independent academic efforts.

Pharmacotherapy

We did identify economic evaluations specific to the comparisons of interest in our analysis. The CADTH reviews of second- and third-line pharmacotherapy for type 2 diabetes each featured an economic evaluation based on the validated U.K. Prospective Diabetes Study (UKPDS) Outcomes Model (CADTH, 2013 [a]; CADTH, 2013 [b]); costs in both analyses were estimated in 2012 Canadian dollars. The evaluation of second-line treatment options found that sulfonylureas were a cost-effective addition for patients not achieving glycemic control on metformin alone (~\$8,500 per quality-adjusted life year [QALY] gained) (CADTH 2013 [a]). However, the model results showed that both DPP-4 inhibitors and all forms of basal insulin (human and analog) were less effective when added to metformin than metformin-sulfonylurea combination therapy, as well as more expensive. While the combination of metformin and GLP-1 agonists produced the greatest number of QALYs in the evaluation, its greater expense yielded a very high incremental cost-effectiveness ratio in comparison to metformin+sulfonylureas (~\$560,000 per QALY gained). Findings for the newer agents were similar in the evaluation of third-line treatment options: the combination of metformin+sulfonylurea+DPP-4 inhibitor was less effective and more costly in comparison to metformin+sulfonylurea+basal insulin, and while the GLP-1 agonist combination was slightly more effective than the insulin combination, the increased costs were substantial (\$1.8 million per QALY gained).

An earlier evaluation of second-line therapy conducted by the Veteran's Administration and based on a validated lifetime model from the CDC involved a comparison of the sulfonylurea glyburide, the DPP-4 inhibitor sitagliptin, and the GLP-1 agonist exenatide (Sinha, 2010). All three agents were found to have comparable effects on long-term diabetes-related complications, but a favorable impact on body weight and hypoglycemia led to greater QALYs for the newer agents (about one month of additional quality-adjusted life expectancy vs. the sulfonylurea strategy). The substantial costs of both new agents led to relatively high cost-effectiveness ratios, however (~\$170,000 and ~\$280,000 per QALY gained for the DPP-4 and GLP-1 agents vs. glyburide, respectively, in 2008 U.S. dollars).

Finally, a recent publication of a joint AHRQ-National Science Foundation-funded effort to develop a new Markov model summarized a comparison of sulfonylureas, DPP-4, GLP-1, and insulin strategies for second-line therapy (Zhang, 2014). As with other evaluations, the sulfonylurea strategy generated the lowest lifetime costs. In contrast with other analyses, however, the sulfonylurea strategy was also the most effective (i.e., "dominant"), as expressed by a modest gain in QALYs and longest duration of time before third-line insulin was required. As with other analyses, greater risks and disutility were assumed for sulfonylureas relative to hypoglycemia and weight gain, but improvement in HbA1c levels, which was estimated based on observed "real world" changes from a linked health care claims-laboratory dataset, was greater among sulfonylurea recipients than among those treated with the other second-line medications of interest.

Insulin Choice

There are many economic evaluations comparing long-acting insulin analogs to NPH insulin and other oral therapies, the overwhelming majority of which are industry-sponsored. A recent exception was an evaluation by the U.K.'s National Institute for Health Research (NIHR) to support the updating of a clinical guideline for the National Institute for Health and Care Excellence (NICE) (Waugh, 2010). In the analysis, both insulin glargine and insulin detemir were associated with very slight gains in quality-adjusted life expectancy vs. NPH insulin (2-5 days), and approximately \$3,000-\$4,000 in excess costs (2008 dollars, converted from GBP), yielding cost-effectiveness ratios of \$300,000-\$500,000 per QALY gained. As a result, NICE decided to preserve NPH as the insulin of first choice in type 2 patients who require such therapy (NICE, 2009).

Findings from an earlier CADTH-based evaluation of both short- and long-acting insulin analogs were generated using another validated lifetime model (the CORE Diabetes Model) and involved comparisons of both glargine and detemir to NPH (Cameron, 2009). In this analysis, detemir was found to be clinically inferior to NPH and more costly, while glargine produced 3 additional days of quality-adjusted life expectancy on a lifetime basis with a cost-effectiveness ratio of over \$600,000 per QALY gained (2007 Canadian dollars). Overall, insulin analogs were found to produce no to minimal clinical benefit but substantial additional costs relative to NPH insulin.

Insulin Delivery

We identified only one economic evaluation of insulin pump delivery vs. multiple daily injections in type 2 diabetes, another NIHR-based evidence review and economic evaluation to support the updating of a NICE technology appraisal (Cummins, 2010). The study found only weak observational evidence to support the use of the pump in type 2 patients, and so declined to formally model the cost-effectiveness of the pump in this population. The review does note that patients can expect to pay over \$2,500 more per year to use the pump vs. multiple daily injections of insulin analogs, driven primarily by the cost of the pump itself as well as disposable equipment.

Continuous Glucose Monitoring

We did not identify any studies evaluating the costs and/or cost-effectiveness of continuous glucose monitoring systems in patients with type 2 diabetes.

6.2 ICER Models

We did not attempt to model the economic impact of either insulin pumps or continuous glucose monitors given the acknowledged dearth of evidence in patients with type 2 diabetes. However, while findings from previous evaluations with respect to second- and third-line pharmacotherapy as well as insulin choice have been quite consistent, we nevertheless felt it important to assess the comparative value of these different management options with a focus on the realities of treatment in the U.S. setting. We conducted a formal cost-effectiveness analysis of second- and third-line pharmacotherapy using a published, validated outcomes model. Because there are no clear clinical differences between insulin analogs and NPH, however, our approach was to simply document the budgetary impact of use of varying distributions of analog vs. human insulins in New England. Methods and results for the comparative value analyses are described in detail in the sections that follow. Our approach for the budgetary impact analysis is described beginning on page 59.

6.3 Cost-Effectiveness Model: Methods

Overview

We used the UKPDS Outcomes Model, version 1.3 (Clarke, 2004) to estimate the lifetime clinical and economic effects of type 2 diabetes and its treatment. While the model is based on data collected entirely in the U.K., predictive equations from the study have been extensively validated against U.S.-based studies such as the Framingham Heart Study and the Wisconsin Epidemiology

Study of Diabetic Retinopathy (Kothari, 2002). The model was developed in Microsoft Excel® (Microsoft Corp., Redmond, WA), and generates estimates of the incidence of major diabetes-related complications based on risk equations specific to certain demographic (e.g., age, race/ethnicity, BMI) and clinical (e.g., duration of diabetes, HbA1c, cholesterol) characteristics. Outcomes of interest in the model include:

- Ischemic heart disease
- Fatal and nonfatal myocardial infarction
- Congestive heart failure (CHF)
- Fatal and nonfatal stroke
- Lower-extremity amputation
- Blindness
- Renal failure
- Diabetes-related and all-cause mortality
- Life expectancy and quality-adjusted life expectancy

Costs incorporated in the model include those of treatment, management of diabetes in the absence of complications, and the initial as well as subsequent annual costs of managing complications. The UKPDS is publicly-available to noncommercial researchers and has been well-validated through comparison to epidemiologic studies and large clinical trials (Palmer, 2013).

The model generates stable estimates of clinical outcomes and costs for a given cohort through the use of multiple “Monte Carlo iterations,” or repeated random samplings of the baseline data for the cohorts. We chose to use 1,000 iterations for our analyses based on the recommendations of the UKPDS developer. The model also generates confidence intervals around each estimate using a bootstrapping technique – we chose 500 iterations for bootstrapping, again based on the developer’s recommendations.

Target Population

Consistent with the approach to the evidence review, the target populations of interest included patients with type 2 diabetes whose blood glucose was (a) inadequately controlled by metformin alone (for second-line therapy); or (b) inadequately controlled by the combination of metformin and a sulfonylurea alone (for third-line therapy). A cohort of 100 patients was assumed in each case; baseline characteristics of each cohort were adapted from the CADTH reviews of second- and third-line therapy, which also used the UKPDS model (CADTH 2013 [a], CADTH 2013 [b]). Characteristics for each analysis can be found in Table 5 on page 51.

Treatment Strategies

We considered multiple treatment strategies for this evaluation, consistent with the scope of the evidence review. For second-line pharmacotherapy, medications added to metformin included sulfonylureas, DPP-4 inhibitors, GLP-1 agonists, long-acting insulin analogs, and NPH insulin. Consistent with the approach taken in the evidence review, we assumed that individual drugs within a given class would have identical treatment effects. Given the generic availability of both metformin and sulfonylureas, this combination was considered the “referent,” and all other combinations were compared to it.

For third-line pharmacotherapy, the combination of metformin, a sulfonylurea, and NPH insulin served as the referent management option. This was compared to metformin-sulfonylurea combinations with DPP-4s, GLP-1s, and insulin analogs added.

Perspective

Consistent with the policy context around CEPAC deliberations, analyses were conducted from the perspective of a state Medicaid agency. As such, cost estimates were limited to direct medical costs only (i.e., costs of drug treatment or insulin, routine diabetes management, and treating diabetes-related complications).

Table 5. Baseline characteristics for hypothetical cohorts of patients with type 2 diabetes who are candidates for second- or third-line pharmacotherapy.

Characteristic	2 nd -Line Estimate	3 rd -Line Estimate
Mean age (years)	56.1	57.7
Duration of diabetes (years)	6.7	9.5
Weight (kg)	89.0	89.0
Height (m)	1.7	1.7
BMI	31.2	31.2
Sex (% male)	54.0	57.0
Ethnicity (% Caucasian)	98.0	94.0
HbA1c (%)	8.30	8.61
Smoking status (%)	Current: 16 Past: 49 Never: 35	Current: 16 Past: 49 Never: 35
Cholesterol (mmol/L)	4.50	4.50
LDL (mmol/L)	3.30	3.30
HDL (mmol/L)	1.20	1.20
Systolic BP (mmHg)	139	139
History of (%):		
Ischemic heart disease	9.0	11.0
Congestive heart failure	5.0	7.0
Amputation	0.0	1.0
Blindness	0.0	1.0
Renal failure	0.0	1.0
Stroke	4.0	5.0
Myocardial infarction	9.0	9.0
Atrial fibrillation	4.0	4.0
Peripheral vascular disease	3.0	3.0

Sources: CADTH 2013a, CADTH 2013b

Treatment Effects

The effects of each treatment combination were estimated with respect to reductions in HbA1c levels and changes in body weight. We obtained data on these changes from the network meta-analyses conducted as part of the CADTH reviews (see Table 6 on the following page).

Table 6. Key model inputs.

Parameter	Estimate		Source(s)
<i>Clinical Impact of Treatment</i>	HbA1c (%)	Weight (kg)	
<u>Second-Line</u>			CADTH 2013 (a)
Metformin/Sulfonylurea	-0.79	+2.1	
Metformin/GLP-1	-0.96	-1.8	
Metformin/DPP-4	-0.69	+0.3	
Metformin/NPH or Insulin Analog	-0.91	+1.7	
<u>Third-Line</u>			CADTH 2013 (b)
Metformin/Sulfonylurea/GLP-1	-1.06	-1.6	
Metformin/Sulfonylurea/DPP-4	-0.72	+0.7	
Metformin/Sulfonylurea/NPH or Insulin Analog	-1.15	+1.9	
<i>Utility Values</i>			
Type 2 diabetes	0.785		Clarke, 2004
Ischemic heart disease	-0.090		
Myocardial infarction	-0.055		
Congestive heart failure	-0.108		
Stroke	-0.164		
Amputation	-0.280		
Blindness	-0.074		
Renal failure	-0.263		
<i>Disutility of Obesity (Sensitivity Analysis Only)</i>			
<u>Second-Line</u>			CADTH Reviews Hunger, 2012
Metformin/Sulfonylurea	-0.0047		
Metformin/GLP-1	+0.0041		
Metformin/DPP-4	-0.0007		
Metformin/NPH or Insulin Analog	-0.0038		
<u>Third-Line</u>			
Metformin/Sulfonylurea/GLP-1	+0.0036		
Metformin/Sulfonylurea/DPP-4	-0.0016		
Metformin/Sulfonylurea/NPH or Insulin Analog	-0.0043		
<i>Annual Drug Costs (2013\$):</i>			
Metformin	981		Zhang, 2014
Sulfonylureas	658		"

GLP-1 agonists	3,912			“
DPP-4 inhibitors	2,794			“
Insulin Analogs	2,661			Redbook, 2014
NPH Insulin	986			Redbook, 2014
<i>Complication Costs (2013\$):</i>	Fatal	Nonfatal	Annual	
No complications	---	---	1,000	Assumption
Ischemic heart disease	---	8,672	2,241	Zhuo, 2013
Myocardial infarction	25,015	43,712	2,416	“
Congestive heart failure	---	11,492	3,935	Heidenreich/Pfuntner 2013
Stroke	60,199	60,199	20,084	Zhuo, 2013
Amputation	78,480	57,032	10,000	“, assumption (annual)
Blindness	---	1,850	6,101	Zhuo, 2013
Renal failure	80,735	80,735	80,735	Zhuo, 2013

Importantly, the UKPDS model does not currently have the ability to estimate the impact of severe hypoglycemic episodes on mortality, costs, or other outcomes. While we did not model this impact explicitly, we report the observed rates of these events by treatment combination as documented in the CADTH reviews to provide further context.

Costs

Costs included those of treatment, management of diabetes in the absence of the complications of interest, and the costs of initial treatment and subsequent management of diabetes-related complications. All costs were estimated in 2013 US dollars; we adjusted these when necessary using the medical care component of the U.S. Consumer Price Index (U.S. Bureau of Labor Statistics, 2014). Treatment costs were estimated based on average wholesale prices (Redbook, 2014) as well as from a recent cost-effectiveness analysis that included median generic and branded prices for certain medications (Zhang, 2014). We assumed daily dosing of NPH or insulin analog therapy at 0.3 units per kg of body weight, consistent with recommended dosing levels for add-on therapy. We also assumed an annual cost of diabetes management in the absence of complications of \$1,000 for office visits, HbA1c and other laboratory testing, eye exams, and other resources. Complication costs were estimated from multiple sources, the most prominent of which involved use of the CDC simulation model to estimate event-based and subsequent management costs for ischemic heart disease, MI, stroke, amputation, blindness, and renal failure (Zhuo, 2013). In the absence of data, we assumed that follow-on costs post-amputation would be approximately half of those post-stroke (\$10,000 per year). Costs of initial and subsequent management of CHF were

obtained from a population-based simulation (Heidenreich, 2013) and hospital database analysis (Pfundner, 2013).

Valuing Patient Outcomes

In addition to rates of diabetes-related complications and mortality, the model expresses effectiveness in terms of the quality-adjusted life year (QALY), which captures both the quality and quantity of life. Utility levels that range between 0 (death) and 1 (perfect health) are used to represent the decrement in quality of life that is associated with any given outcome. We used utility levels from the original paper on the UKPDS Outcomes Model (Clarke, 2004), which were derived from the EuroQoL EQ-5D instrument. Patients with type 2 diabetes were assumed to have a utility of 0.785. Decrements in utility associated with each diabetes-related complication are presented in Table 6, and ranged from -0.055 for MI to -0.280 for amputation.

While BMI is an explicit risk factor in the UKPDS model, it primarily affects CHF risk. To allow for the possibility that treatment-induced weight gain might also adversely affect quality of life, we conducted a sensitivity analysis in which data from a population-based study correlating BMI changes with utility decrements on the EQ-5D were applied (Hunger, 2012). Each single-unit increase in BMI was associated with a -0.006 decrement in utility, which was then multiplied by the change in BMI from baseline for each treatment strategy evaluated. Resulting utility decrements are presented in Table 6 above.

Key Model Assumptions

We made several key assumptions for this analysis. First, we assumed that all clinical outcomes were associated with the initial treatment strategy only; we did not assume switching between strategies, although we acknowledge that patients evaluated over such a long time horizon will likely modify their treatment regimen multiple times. The relative effects of each regimen were assumed to be constant over time, although the absolute effects differed because the UKPDS model accounts for progression of risk factors over time (e.g., HbA1c). Finally, in the absence of any clear evidence of clinical benefit for insulin analogs over NPH insulin, we assumed clinical equivalence (but different costs) for these therapeutic options.

6.4 Cost-Effectiveness Model: Results

Second-Line Pharmacotherapy

All modeled regimens had comparable effects on the rate of diabetes-related complications, although the addition of GLP-1 agonists to metformin resulted in a lower rate of heart failure than the other alternatives. This combination also resulted in the greatest gains in both unadjusted and

quality-adjusted life expectancy, but was also by far the most costly, resulting in cost-effectiveness estimates of over \$20 million per diabetes death averted and nearly \$700,000 per QALY gained vs. metformin+sulfonylurea. The addition of DPP-4 inhibitors to metformin resulted in lower effectiveness and higher costs relative to metformin+sulfonylurea. Clinical gains with metformin+basal insulin were modest; the difference in treatment costs by insulin type resulted in vastly different cost-effectiveness estimates, however (e.g., \$160,000 vs. \$1 million per QALY gained for NPH insulin and insulin analogs, respectively).

Clinical findings for second-line pharmacotherapy among type 2 diabetes patients can be found in Table 7 below. All regimens were associated with reductions in clinical event rates relative to metformin alone, including approximately one fewer diabetes-related death per 100 patients treated. However, rates of most events were quite comparable across combination regimens. The one exception was congestive heart failure, where the combination of metformin and a GLP-1 agonist resulted in an incidence rate of 11.1% (vs. 11.8-12.4% for other regimens), due to the decrease in body weight associated with GLP-1 therapy.

Table 7. Cumulative lifetime incidence of diabetes-related complications, by second-line treatment option.

Event Type	Regimen				
	MET Alone (Reference)	MET+SULF	MET+GLP-1	MET+DPP-4	MET+Insulin
	Incidence (%)				
Ischemic heart disease	8.6	7.9	8.1	8.0	8.2
Myocardial infarction	29.2	27.9	27.4	28.4	27.6
Congestive heart failure	12.4	12.2	11.1	11.8	12.2
Stroke	14.2	13.1	13.0	13.1	13.1
Amputation	3.9	3.3	3.2	3.3	3.2
Blindness	7.2	6.3	6.5	6.5	6.3
Renal failure	2.3	2.3	2.2	2.3	2.3
Diabetes-related death	21.5	20.5	20.3	20.8	20.4

MET: Metformin; SULF: Sulfonylurea; GLP-1: Glucagon-like peptide-1 agonist; DPP-4: Dipeptidyl peptidase-4 inhibitor

The cost-effectiveness of second-line pharmacotherapy combinations is presented in Table 8 on the following page. The combination of metformin and GLP-1 agonists produced the greatest life expectancy and QALYs relative to other combinations, and there were also no severe hypoglycemic events observed in available placebo- or active-controlled RCTs of this combination. Lifetime costs for the metformin and GLP-1 combination were substantially higher than those for metformin+sulfonylurea (~\$117,000 vs. \$77,000, respectively). The incremental cost per diabetes death averted for metformin+GLP-1 vs. metformin+sulfonylurea was over \$20 million, driven by a

modest difference in this outcome (0.2%). The cost per QALY gained was estimated to be nearly \$700,000, as the difference in quality-adjusted life expectancy between these two combinations was only about 20 days. Combination therapy with the other newer agent (DPP-4s) resulted in slightly lower effectiveness and higher cost relative to the metformin+sulfonylurea combination, as the modeled impact on HbA1c was greater for the latter.

As noted previously, we assumed equivalent effectiveness of NPH insulin and insulin analogs for this evaluation. When given with metformin, both insulins produced slightly more QALYs than metformin+sulfonylurea (8.45 vs. 8.43, respectively), but an increased cost. Costs were about \$4,000 higher for the NPH strategy vs. the sulfonylurea combination, yielding an incremental cost-effectiveness ratio of approximately \$160,000 per QALY gained. The wider difference in lifetime costs for the insulin analog strategy (\$102,000 vs. \$77,000 for the sulfonylurea strategy) yielded a cost-effectiveness estimate of over \$1 million per QALY gained.

Table 8. Cost-effectiveness of second-line treatments added to metformin for type 2 diabetes.

Regimen	Life Expectancy (years)	QALYs	Diabetes Death (%)	Severe Hypoglycemia (%)*	Total Costs	vs. MET+SULF	
						Cost per Death Averted	Cost per QALY Gained
MET Alone (Ref)	11.01	8.33	21.5	N/A	\$ 70,494	---	---
MET+SULF	11.11	8.43	20.5	1.0	\$ 76,956	---	---
MET+GLP-1	11.17	8.49	20.3	No events	\$ 117,184	\$ 20,114,146	\$ 689,850
MET+DPP-4	11.10	8.42	20.8	<0.1	\$ 104,026	‡	‡
MET+Insulin Analog	11.13	8.45	20.4	0.9	\$ 101,839	\$ 24,883,051	\$ 1,020,313
MET+NPH Insulin	11.13	8.45	20.4	0.9	\$ 80,817	\$ 3,861,003	\$ 158,318

*Not from model; pooled findings from RCTs in CADTH review

‡Less effective, more expensive

MET: Metformin; SULF: Sulfonylurea; GLP-1: Glucacon-like peptide-1 agonist; DPP-4: Dipeptidyl peptidase-4 inhibitor

Third-Line Pharmacotherapy

As with second-line pharmacotherapy, third-line combinations had comparable impacts on development of all diabetes-related complications with the exception of heart failure, where lower rates were generated for the combination of metformin, a sulfonylurea, and a GLP-1 agonist. In comparison to the referent combination of metformin+sulfonylurea+NPH insulin, the GLP-1 combination averted 6 diabetes-related deaths per 1,000 treated and resulted in a slight improvement in quality-adjusted life expectancy (6 days). Costs were significantly higher, however, resulting in incremental costs per diabetes death averted and per QALY gained of approximately \$5 million and \$1.8 million, respectively. Cost-effectiveness ratios could not be generated for DPP-4- or insulin analog-based regimens due to equivalent or lower effectiveness and higher cost.

Clinical results for third-line pharmacotherapy combinations can be found in Table 9 below. As with second-line combinations, all regimens of interest improved clinical outcome relative to metformin+sulfonylurea alone, and prevented 1-2 diabetes-related deaths per 100 persons treated. Consistent with findings from the second-line model, differences between third-line combinations in clinical event rates were modest, with the exception of congestive heart failure. Incidence with the GLP-1 combination was 10.6%, vs. 11.5% and 11.6% for the DPP-4- and insulin-based regimens, respectively.

Table 9. Cumulative lifetime incidence of diabetes-related complications, by third-line treatment option.

Event Type	<i>Regimen</i>			
	MET+SULF (Reference)	MET+SULF +GLP-1	MET+SULF +DPP-4	MET+SULF +Insulin
	Incidence (%)			
Ischemic heart disease	7.2	7.0	6.8	6.8
Myocardial infarction	27.9	26.3	26.7	26.3
Congestive heart failure	12.4	10.6	11.5	11.6
Stroke	13.4	12.0	12.5	12.1
Amputation	3.9	2.5	3.1	2.5
Blindness	6.4	5.6	5.9	5.4
Renal failure	1.9	1.9	1.9	2.0
Diabetes-related death	24.6	23.0	23.8	23.6

MET: Metformin; SULF: Sulfonylurea; GLP-1: Glucagon-like peptide-1 agonist; DPP-4: Dipeptidyl peptidase-4 inhibitor

Cost-effectiveness findings can be found in Table 10 on the following page. In this analysis, the GLP-1- and insulin-based combinations were essentially equally effective, producing approximately seven years of quality-adjusted life expectancy. In contrast to findings for second-line pharmacotherapy, rates of severe hypoglycemia (1.1-1.5%) were similar across all treatment strategies, in all likelihood because sulfonylureas are included in every combination. The one exception was the DPP-4 combination (2.6%). This finding should be interpreted with great caution, however, as only two RCTs of third-line therapy with DPP-4 inhibitors were identified in the CADTH review, and severe hypoglycemic events were observed in only one.

Cost-effectiveness ratios could not be generated for the DPP-4- and insulin analog-based combinations, as the former was less effective and more expensive than the NPH insulin-based combination, and the latter was equally effective and more expensive. The cost per diabetes death averted for metformin+sulfonylurea+GLP-1 was approximately \$5.2 million relative to metformin+sulfonylurea+NPH insulin. The cost-effectiveness of this combination relative to the

NPH-based referent combination was approximately \$1.8 million per QALY gained, as lifetime costs were over \$30,000 greater and the difference in QALYs was slightly more than 0.01, or about six days of quality-adjusted life expectancy.

Table 10. Cost-effectiveness of third-line treatments added to metformin+sulfonylurea for type 2 diabetes.

Regimen	Life Expectancy (years)	QALYs	Diabetes Death (%)	Severe Hypoglycemia (%)*	Total Costs	vs. MET+SULF+NPH	
						Cost per Death Averted	Cost per QALY Gained
MET+SULF (Ref)	9.02	6.82	24.6	N/A	\$ 81,773	---	---
MET+SULF+NPH							
Insulin	9.21	7.00	23.6	1.1	\$ 91,025	---	---
MET+SULF+GLP-1	9.23	7.01	23.0	1.5	\$ 122,181	\$ 5,192,565	\$ 1,771,354
MET+SULF+DPP-4	9.13	6.92	23.8	2.6	\$ 111,048	‡	‡
MET+SULF+Insulin Analog	9.21	7.00	23.6	1.1	\$ 108,717	¤	¤

*Not from model; pooled findings from RCTs in CADTH review

‡Less effective, more expensive

¤Equally effective, more expensive

MET: Metformin; SULF: Sulfonylurea; GLP-1: Glucagon-like peptide-1 agonist; DPP-4: Dipeptidyl peptidase-4 inhibitor

Obesity-Related Sensitivity Analysis

The results of our sensitivity analysis, in which we applied a change in utility to correspond with treatment-induced changes in body weight, can be found in Appendix B. For second-line therapy, the gap in effectiveness widened between the combination of metformin and GLP-1 therapy vs. metformin+sulfonylurea (8.53 vs. 8.38 QALYs). However, the increased costs of the GLP-1 combination still resulted in a cost-effectiveness ratio of over \$250,000 per QALY gained. Cost-effectiveness was also improved with DPP-4- and insulin analog-based regimens, as these resulted in less weight gain than the referent combination, but incremental cost-effectiveness ratios were still over \$700,000 per QALY gained. The cost-effectiveness of the NPH-based regimen was also improved somewhat, to approximately \$110,000 per QALY gained.

In analyses of third-line pharmacotherapy, the addition of a GLP-1 agonist to metformin and sulfonylurea also improved outcome relative to the NPH insulin-based referent combination (7.05 vs. 6.96 QALYs, respectively), resulting in a cost-effectiveness ratio of approximately \$350,000 per QALY gained. However, as in primary analyses, cost-effectiveness ratios could not be generated for DPP-4 inhibitor-based treatment or insulin analogs given equivalent or lower effectiveness in relation to the NPH referent and higher costs in both instances.

6.5 Budget Impact Analysis: Methods

As described at the beginning of this section, our intent was to document the one-year budgetary impact of changes in the distribution of NPH insulin vs. insulin analogs in type 2 patients using insulin as add-on therapy to other antidiabetic drugs. In keeping with assumptions made for the cost-effectiveness analysis, we assumed no difference in major clinical outcomes by insulin type; we do present estimates of the numbers of patients who would experience nocturnal hypoglycemia at different distributions, however. While the clinical significance of this outcome remains uncertain, it was the one variable that differed materially in head-to-head RCTs of NPH and insulin analogs. Annual costs of NPH and insulin analogs were estimated as in the cost-effectiveness analysis, based on typical add-on dosing (0.3 u/kg) for an individual weighing 89 kg.

The prevalence of type 2 diabetes in New England was estimated based on age-specific prevalence estimates from the Centers for Disease Control. Estimates were 4.1%, 16.2%, and 25.9% for persons age 18-44, 45-64, and 65 years and older, respectively. We assumed that 95% of these individuals would have type 2 disease. The proportion of type 2 patients using insulin was estimated to be approximately 15% from an analysis of a large insurer health claims database (Lipska, 2014). That same analysis described the current prevalent levels of insulin glargine (64%) and detemir (16%) use among type 2 diabetics, a pattern that has been shown to be similar in other settings. Our baseline for insulin analog vs. NPH insulin use was therefore 80% and 20%, respectively.

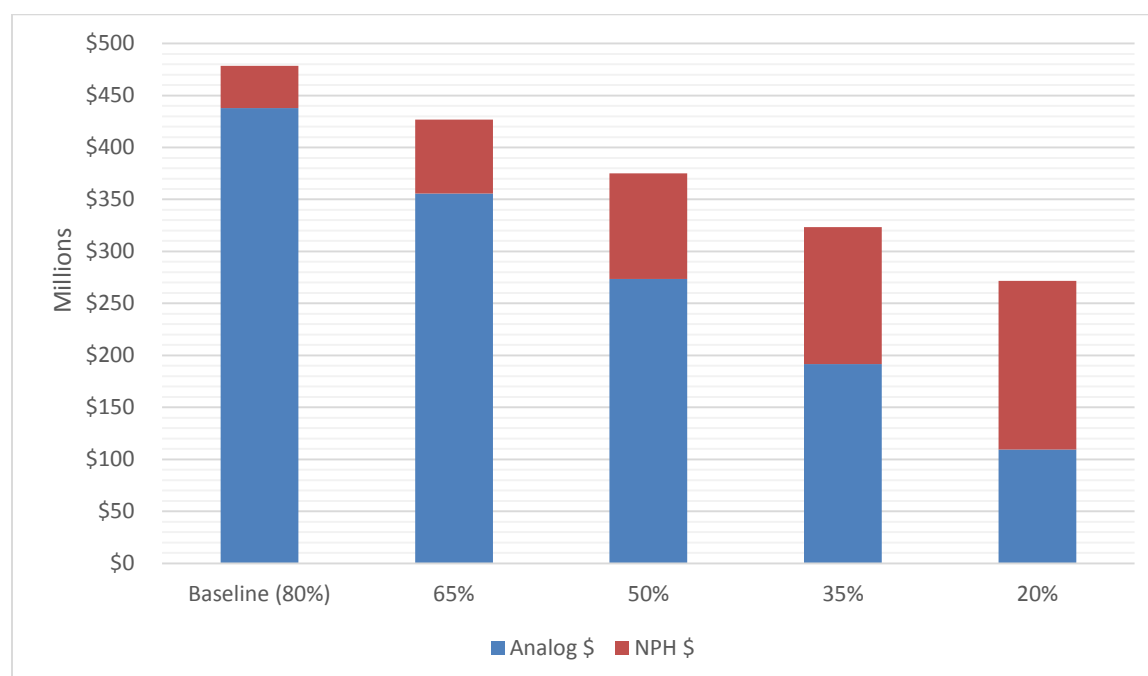
6.6 Budget Impact Analysis: Results

Based on our estimates, of the 11 million adults currently residing in New England, approximately 1.4 million (12%) have type 2 diabetes. Of these individuals, slightly more than 200,000 are currently using insulin to help manage their condition.

At baseline, the number of patients experiencing nocturnal hypoglycemia is estimated to total 209 per 1,000 patients treated. Reductions in the proportion of individuals receiving insulin analogs would increase the number experiencing nocturnal hypoglycemia, as the rate of these events with NPH insulin is nearly double that of insulin analogs. If 65% of patients were receiving insulin analogs, an additional 18 patients per 1,000 treated would experience nocturnal hypoglycemia (an increase of 9%). If this distribution were to be reversed (i.e., 65% of patients receiving NPH insulin), the number would grow by an additional 56 patients over baseline (a 27% increase). As mentioned previously, there is great uncertainty regarding the clinical significance of nocturnal hypoglycemia, but these data provide context for considerations of the type of insulin used in the region.

In contrast, the impact of changes in the distribution of insulin type on insulin-related expenditures is quite clear. As shown in Figure 7 below, the high percentage of insulin analog recipients, coupled with prices that are approximately threefold higher for insulin analogs vs. NPH (i.e., \$2,661 vs. \$986 annually) results in annual expenditures in the region of nearly \$500 million, 92% of which is driven by insulin analog costs. Reducing the percentage of patients using insulin analogs to 65% from 80% would result in \$52 million in savings (11%). A further reduction to 50% would increase these savings to over \$100 million (21.6%). If 80% of insulin use were NPH-based, cost savings would exceed \$200 million. Simply put, for every 1,000 patients treated with insulin, a switch from insulin analogs to NPH insulin would result in approximately \$1.7 million in cost savings.

Figure 7. Budgetary impact of shifts in the distribution of insulin analog vs. NPH insulin use in New England.



6.7 Limitations

We note some limitations of our analyses. First, while the UKPDS Outcomes Model has been extensively tested and externally validated, we cannot rule out the possibility that small differences in clinical benefit could have been the result of sampling error during model simulations. In addition, as previously noted, we were not able to explicitly model the clinical impact and cost of severe hypoglycemia. Nevertheless, while estimates differ somewhat, our findings are congruent with all of the independently-conducted economic evaluations highlighted at the beginning of this section, including at least one that suggests somewhat better “real world” effectiveness for generic

sulfonylureas (Zhang, 2014). While we await the publication of the impact of these treatment alternatives on long-term outcomes from the Mini-Sentinel and other initiatives, we nevertheless take comfort in the knowledge that the direction of our model findings is similar to those of other efforts that have used independently-validated simulation models.

We also did not model the contribution of changes in weight gain to clinical outcomes and costs other than for congestive heart failure, a link already established in the UKPDS. We did conduct sensitivity analyses exploring the impact of assuming changes in utility that correspond with treatment-induced weight gain or loss, however. While incremental gains in effectiveness and differential costs did change somewhat in these analyses, our conclusions did not—namely, the least expensive second- and third-line pharmacotherapy options offer good value for money.

6.8 Summary

The results of our cost-effectiveness analysis of second-line pharmacotherapy suggest that, given the best available knowledge of current clinical evidence, use of a treatment regimen of metformin and a sulfonylurea in patients inadequately controlled on metformin alone produces outcomes nearly as good as with newer agents at a much lower cost. While GLP-1 agonists produced the best overall clinical outcomes, including consideration of weight gain, hypoglycemia, and blood sugar control, among all available combinations, gains in total quality-adjusted life expectancy were small, while costs were over 50% higher, yielding a cost-effectiveness ratio of nearly \$700,000 per QALY gained. Findings were similar for insulin analogs, but a combination of metformin and less expensive NPH insulin produced a more reasonable cost-effectiveness ratio (~\$160,000 per QALY gained).

Similar results were seen in analyses of third-line pharmacotherapy options. Again, the least expensive treatment option (metformin+sulfonylurea+NPH insulin) was nearly as effective as the GLP-1-based combination, which resulted in a very high cost-effectiveness ratio (~\$1.8 million per QALY gained) for the latter.

Our budget impact analysis is also illustrative. Without clear evidence favoring insulin analogs over NPH insulin in type 2 patients, our results suggest that payers in New England may be overspending by as much as \$200 million per year for more expensive analogs. While we do acknowledge that many other regions and systems are encountering the same phenomenon, we note that this is not universally true. For example, a recent comparison of insulin use among Veteran's Affairs and Medicare Part D patients showed that only a little more than a quarter (27%) of type 2 diabetes patients on insulin in the VA system were using insulin analogs for their treatment (Gellad, 2013).

In summary, the current state of the evidence suggests that the use of newer oral antidiabetic

agents and insulin analogs may offer small clinical improvements over generic sulfonylureas and human insulin in patients with type 2 diabetes who are inadequately controlled on metformin, but the high costs of these agents call their potential cost-effectiveness into question. In contrast, the less expensive agents appear to provide good value for those patients who would be considered good candidates for such therapy.

7. Questions and Discussion

Following the public CEPAC meeting on October 29, 2014, this section will be completed to capture the discussion of the Council members regarding the evidence, specifically around the Questions to Guide Discussion (questions for deliberation are posted for public comment at cepac.icer-review.org).

CEPAC Conflict of Interest Policy

CEPAC members, excluding ex-officio members, cannot work for any of the New England state agencies or regional private payers. CEPAC members, excluding ex-officio members, are expected to be free from financial conflicts of interest, and all members will be required to disclose financial ties to any private health care organization. While issues of financial influence will be handled on a case-by-case basis, as a guideline, CEPAC members, excluding ex-officio members, may not have substantial financial interests in the health care industry, defined as the following:

- A specific financial association, such as individual health care stock ownership (including those held by spouse or minor child) in excess of \$25,000 during the previous year from any one health care manufacturer or insurer (e.g., \$25,000 holdings in XYZ healthcare manufacturer or \$25,000 consultancy income from ABC health insurer).
- Financial association, such as individual health care stock ownership (including those held by spouse or minor child) in excess of \$50,000 in aggregate during the previous year from health care manufacturers or insurers (e.g., \$15,000 holdings in XYZ healthcare manufacturer, \$15,000 in speaking fees from ABC health insurer, and \$20,000 in consultancy income from 123 health insurer).

Recusal

Any Council member with a potential influence on judgment, including but not limited to, a personal experience with a particular technology or condition, or a political consideration, shall recuse themselves from voting at a CEPAC meeting. Any Council member with a direct financial association with the particular product or service being evaluated at a CEPAC meeting shall also recuse themselves from voting at that CEPAC meeting. “Direct financial association” is defined as individual health care stock ownership (including those held by spouse or minor child) in or health care consultancy income from the manufacturer of the product being evaluated in excess of \$5,000 during the previous year. Their presence will count towards establishing a quorum, but they will not be able to vote.

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Appendix A: Literature Search and Synthesis Strategy

Type 2 Diabetes Management – Literature Search and Synthesis Strategy

- Separate searches will be conducted for each domain in MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials

1. Insulin choice: ***neutral protamine Hagedorn (NPH) insulin vs. long-acting insulin analogs***

Data Source:	Long-acting insulin analogs vs. NPH insulin (Horvath [Cochrane]; 2009)
Date Range:	September 2006 – August 2014
Population Type:	Adult T2D patients requiring basal insulin treatment
Interventions/Comparators:	NPH insulin vs. insulin detemir or glargine
Included Studies:	RCTs, comparative cohorts, single-arm studies of ≥50 patients

2. Second-line medication options: metformin two-drug combination therapy with ***sulfonylureas vs. DPP-4 inhibitors vs. GLP-1 agonists vs. insulin***

Data Source:	Second-line pharmacotherapy for type 2 diabetes (CADTH; 2013)
Date Range:	February 2012 – August 2014
Population Type:	Adult T2D patients inadequately controlled on metformin monotherapy
Interventions/Comparators:	Metformin <i>plus</i> one of the following: sulfonylurea, GLP-1 agonist, DPP-4 inhibitor, or basal insulin
Included Studies:	RCTs, comparative cohorts, single-arm studies of ≥50 patients

3. Third-line medication options: metformin three-drug combination therapy with sulfonylurea and ***DPP-4 inhibitors vs. GLP-1 agonists vs. insulin***

Data Source:	Third-line pharmacotherapy for type 2 diabetes (CADTH; 2013)
Date Range:	February 2012 – August 2014
Population Type:	Adult T2D patients inadequately controlled on metformin and sulfonylurea combination therapy
Interventions/Comparators:	Metformin and sulfonylurea <i>plus</i> one of the following: GLP-1 agonist, DPP-4 inhibitor, or basal insulin
Included Studies:	RCTs, comparative cohorts, single-arm studies of ≥50 patients

4. Intensive insulin administration strategies: ***multiple daily injections (MDI)*** vs. ***continuous subcutaneous insulin infusion (CSII)***

Data Source:	Methods for insulin delivery and glucose monitoring (Golden [AHRQ]; 2012)
Date Range:	April 2011 – August 2014
Population Type:	Adult T2D patients on insulin treatment
Interventions/Comparators:	Multiple daily injections vs. insulin pump therapy
Included Studies:	RCTs, comparative cohorts, single-arm studies of ≥50 patients

5. Intensive glucose monitoring strategies: ***continuous glucose monitors (CGM)*** vs. ***self-monitoring of blood glucose (SMBG)***

Data Source:	Methods for insulin delivery and glucose monitoring (Golden [AHRQ]; 2012)
Date Range:	April 2011 – August 2014
Population Type:	Adult T2D patients on insulin treatment
Interventions/Comparators:	Continuous glucose monitoring vs. conventional blood glucose monitoring
Included Studies:	RCTs, comparative cohorts, single-arm studies of ≥50 patients

Appendix B: Results of Obesity-Related Sensitivity Analyses

Table B1. Cost-effectiveness of second-line treatments added to metformin for type 2 diabetes, with consideration of obesity-related utility values.

Regimen	Life Expectancy (years)	QALYs	Diabetes Death (%)	Severe Hypoglycemia (%)*	Total Costs	vs. MET+SULF	
						Cost per Death Averted	Cost per QALY Gained
MET Alone (Ref)	11.01	8.33	21.5	N/A	\$ 70,494	---	---
MET+SULF	11.11	8.38	20.5	1.0	\$ 76,956	---	---
MET+GLP-1	11.17	8.53	20.3	No events	\$ 117,184	\$ 20,114,146	\$ 257,379
MET+DPP-4	11.10	8.41	20.8	<0.1	\$ 104,026	‡	\$ 753,617
MET+Insulin Analog	11.13	8.41	20.4	0.9	\$ 101,839	\$ 24,883,051	\$ 725,972
MET+NPH Insulin	11.13	8.41	20.4	0.9	\$ 80,817	\$ 3,861,003	\$ 112,646

*Not from model; pooled findings from RCTs in CADTH review

‡Less effective, more expensive

MET: Metformin; SULF: Sulfonylurea; GLP-1: Glucagon-like peptide-1 agonist; DPP-4: Dipeptidyl peptidase-4 inhibitor

Table B2. Cost-effectiveness of third-line treatments added to metformin+sulfonylurea for type 2 diabetes, with consideration of obesity-related utility values.

Regimen	Life Expectancy (years)	QALYs	Diabetes Death (%)	Severe Hypoglycemia (%)*	Total Costs	vs. MET+SULF+NPH	
						Cost per Death Averted	Cost per QALY Gained
MET+SULF (Ref)	9.02	6.82	24.6	N/A	\$ 81,773	---	---
MET+SULF+NPH							
Insulin	9.21	6.96	23.6	1.1	\$ 91,025	---	---
MET+SULF+GLP-1	9.23	7.05	23.0	1.5	\$ 122,181	\$ 5,192,565	\$ 344,517
MET+SULF+DPP-4	9.13	6.91	23.8	2.6	\$ 111,048	‡	‡
MET+SULF+Insulin							
Analog	9.21	6.96	23.6	1.1	\$ 108,717	¤	¤

*Not from model; pooled findings from RCTs in CADTH review

‡Less effective, more expensive

¤Equally effective, more expensive

MET: Metformin; SULF: Sulfonylurea; GLP-1: Glucagon-like peptide-1 agonist; DPP-4: Dipeptidyl peptidase-4 inhibitor